SEPARATION OF ENANTIOMERS OF BACLOFEN

by

Alexander Franciscus Wildervanck

A Thesis submitted for the degree of

MASTER OF SCIENCE

in the Department of Chemistry

Faculty of Science

UNIVERSITY OF CAPE TOWN

March 1996

Acknowledgements

The following people gave me tremendous support during this research period:

Professor M.R. Caira has shown enormous concern and interest in the progress of this project. I thank him for his tireless assistance and excellent standards he set.

Professor L-(*R*)-Nassimbeni for his encouragement and proving to me how indispensable models are in absolute configuration assignments.

Dr. J.L. Scott. I owe Janet many thanks for her excellent ideas and practical advice. I also thank her for kindly rendering to me her crystal structure solution of the Tartaric acid complex.

Rainer Clauss for sharing all his organic chemistry knowledge and experience that proved to be vital for finally obtaining the enantiopure drug.

Publications

"Resolution of optical isomers of 4-amino-*p*-chlorobutyric acid lactam by co-crystallisation", M. R. Caira, L.R. Nassimbeni, J. L. Scott, and A.F. Wildervanck, *J. Chem. Crystallogr.*, in press. (ref. no. JCCA418).

Conferences

33rd Convention of the South African Chemical Institute, 29 Jan. - 2 Feb. 1996. "Separation of Enantiomers of Baclofen", M.R. Caira, R. Clauss, B.R.D. Easter, L.R. Nassimbeni, J.L. Scott, and A.F. Wildervanck.

Patents

South African provisional patent. *Application no.* 95/10844, *Filed* 20/12/1995. *Applicant*: S.A. Druggists Limited. *Inventors*: A.F. Wildervanck, M.R. Caira, J.L. Scott, L.R. Nassimbeni, R. Clauss, and B.R.D. Easter. *Title of Invention*: process. (Resolution of 3-(p-chlorophenyl)glutaramic acid with S-(-)-α-Methylbenzylamine).

Abstract

β-(Aminomethyl)-4-chlorobenzenepropanoic acid (Baclofen), 3-(*p*-chlorophenyl)-pyrrolidone (Baclofen lactam) and 3-(*p*-Chlorophenyl)glutaramide (baclofen's synthetic precursor) were individually used as substrates in co-crystallisation experiments with several resolving agents. Experiments were conducted in the solid state and in solution. The (-) enantiomer of the lactam and the (+) enantiomer of the glutaramide were found to co-crystallise selectively with (2*R*,3*R*)-(+)-tartaric acid and (*S*)-(-)-α-Methylbenzylamine respectively. Both these *dissociable diastereomers* were analysed by X-ray crystallography. HPLC analysis of the lactam retrieved from the former co-crystals indicated only partial separation of its (+) and (-) enantiomers. X-ray crystallographic, thermal, and polarimetric analyses were performed on the (+)- *and* (-)-salts of the latter co-crystals. The solubilities of these salts in methanol were found to differ by a factor of 4. A solubility diagram was established showing the phase equilibria of various ratios of these two salts in methanol. The (+) enantiomer of the glutaramide was separated from the methylbenzylamine in the (+) salt by treatment with HCl. This enantiomer was converted to (*R*)-(-)-Baclofen by means of a Hofmann Rearrangement with an overall yield of 40%. The enantiomeric excess of (*R*)-(-)-Baclofen was 99.7%.

Author's Note

There are three systems by which the absolute configuration of enantiomers are designated:

1. *Fischer Projection:* This is the oldest system by which the absolute configuration of a particular enantiomer is designated **D** or **L** (as indirectly related to the enantiomers of glyceraldehyde). Today this system is no longer used, except for certain groups of compounds such as carbohydrates and amino acids.

2. *Cahn-Ingold-Prelog System:* This has replaced the DL system. The four groups on an asymmetric carbon are ranked according to a set of sequence rules. The asymmetric centre is then designated **R** or **S** accordingly.

3. *Optical rotation:* A practical method of referring to particular enantiomers of chiral compounds is by assignment of the letters ***d*** or ***l***. This simply refers to the direction in which the enantiomers rotate the plane of polarized light. The ***d***extro isomer rotates the plane clockwise and is designated (+), while the ***l***evo isomer rotates the plane counterclockwise and is designated (-).

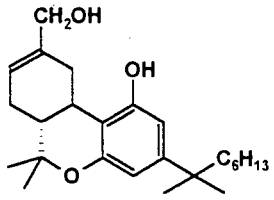
The Author is aware that the three systems are in no way interrelated. In this thesis the absolute configuration of particular enantiomers are designated in accordance with the publications reporting their resolutions or other related studies. The enantiomers resolved in this study are designated by means of the second system.

Contents

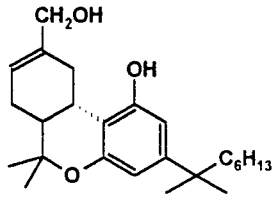
1. INTRODUCTION

1.1 Chiral Drugs

The biological activity of drug racemic mixtures rests in most cases on one of the two antipodal isomers (enantiomers), and the other is an undesired commodity. Chiral drugs are therefore of growing interest, due to their higher selectivity in biological action and greater potency than the corresponding racemic mixtures[1]. Pharmaceutical industries are accepting the dogmas that racemic mixtures should first be resolved and only the active enantiomer be further investigated. Enantiomers display different pharmacokinetics, are metabolised differently by enzymes, and have quite different toxicities. The Thalidomide disaster in the early 1960's is perhaps the most vivid example of the importance of stereochemistry in drug molecules[2]. (*S*)-(-)-Thalidomide is a powerful tranquilliser whereas (*R*)-(+)-Thalidomide can disrupt fetal development, causing severe handicap. Developed by the West German firm of Chemie-Gruenenthal just after World War II, the drug was finally withdrawn from the market in December 1961. By then, as a consequence of specific recommendations by the makers that Thalidomide be used in pregnant women, some 8 - 9000 babies were born with horrible deformities. Preparation and testing of both enantiomers, although costly, is therefore vital. This form of careful research may lead to two medically useful agents such as the antipodes of the optically active Tetrahydrocannabinols HU-210 and HU-211.



HU-210

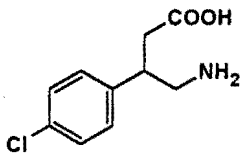


HU-211

The former shows potent psychotropic activity, while the latter is an antiemetic[3].

It therefore suffices to mention that a wide variety of examples of differing medicinal uses of enantiomorphous antipodes exist, and that single enantiomeric drugs constitute 20% of the world's 95 best selling drugs[4]. Kooreman of International Biosynthesis in the Netherlands predicted that more than 50% of the manufactured drugs would be chiral by the end of the century[1].

This leads to the drug under investigation in this project, viz. Baclofen (β-(Aminomethyl)-4-chlorobenzenepropanoic acid, hereinafter BC).



BC

Sold under the trade name Lioresal, the drug is presently still marketed as the racemate. The biological activity and physical properties of the racemic drug are well documented in the literature[5,6]. Further extensive pharmacological tests have concluded that the biological activity of this skeletal muscle relaxant resides with the *l*-enantiomer[7]. Later studies by Hill and Bowery confirmed that this enantiomer was indeed 100 times more active than the *d*-enantiomer[8]. Hence there is a need for an effective and simple resolution method.

1.2 Resolution Methods.

There are two broad categories of methods for enantiomeric purification: *Resolution*, and *stereoselective synthesis*. Although previous enantiomeric purifications of baclofen have made use of the latter method (see section 1.3.1), our present survey will only be dealing with the former category. By definition, a resolution is the separation of a racemate into its enantiomer constituents. In resolution methods, the point of departure is the racemate implying that a maximum yield of only 50% can be attained. Under this broad category, several resolution methods are now widely used:

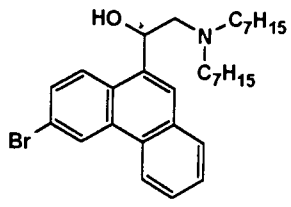
The oldest resolution method is the direct crystallisation of enantiomers from solutions of racemates in the absence of resolving agents. This may be enhanced by seeding the supersaturated solutions of the racemates to initiate *preferential crystallisation*. The theory thereof is well established[9] and forms a fascinating yet simple resolution technique. The major prerequisite (and therefore restriction) is that the racemate must be a conglomerate under the conditions of crystallisation. An industrial scale resolution of the Chloramphenicol base (Sect 3.1 compound **20**) developed by Amiard and co-workers[10] uses this method. The racemate is seeded with the (-) enantiomer causing conglomerates of this enantiomer to crystallise out preferentially. Further resolution methods are the following: Resolution via the formation of Dissociable or Covalent Diastereomers, Resolution via Chiral Liquid or Gas Chromatography , Kinetic Resolutions and Resolutions via Host-Guest Chemistry.

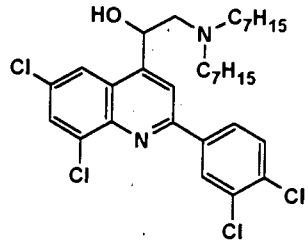
1.2.1 Dissociable Diastereomers.

The largest number of recorded resolutions have been effected by conversion of a racemate to a mixture of diastereomers. In this type of reaction the substrate that is to be resolved is treated with one enantiomer of a chiral substance.

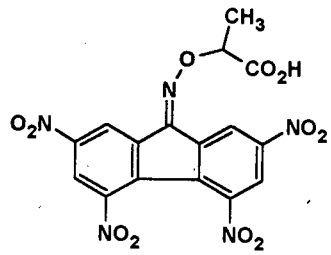
1.2.1.1 Diastereomeric Complexes.

Although less common, diverse addition compounds do exist and have in common their ease of usage. Examples of dissociable crystalline combinations are Lewis acid-base complexes, inclusion compounds and quasi-racemates. Resolution of compounds devoid of acidic or basic functionality can in principle be resolved by this method. Aromatic amines whose chirality resides in the side chain, such as the examples given below,

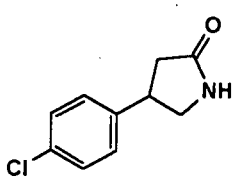




have been resolved by the formation of π-complexes with α-(2,4,5,7 - Tetranitrofluorenylideneaminooxy)propionic acid[11] also shown below.



BC, when heated above 180^{0}C degrades to form a Lactam (3-(4-chlorophenyl)pyrrolidinone) hereinafter BC-Lac[12].



BC-Lac

This compound, being a substrate similarly devoid of both strong acidic or basic moieties, can therefore in theory only really be separated by means of the above discussed interaction, if a suitable resolving agent were to be used.

1.2.1.2 Diastereomeric Salts

Resolution via diastereomeric salt formation is widely used industrially and in particular furnishes a large proportion of those optically active drugs which are not derived from natural products[13]. A study conducted in a representative group of such drugs showed that 65% owe their optical activity to this classical resolution method[14]. An excellent review exists, provided by Wilen *et al* [15], describing systematic strategies in optical resolution via diastereomeric salt formation. Despite the technique being sometimes viewed as owing too much to empiricism to be worthy of serious consideration, this review provides a rational approach for resolving organic compounds bearing acidic or basic functional groups.

The method utilising the formation of a salt between a racemic acid and an optically active base was discovered by Pasteur in 1853[16]. The process may be summarised by the following scheme (symbols **A** and **B** represent an acid and base respectively).

$$\underset{\text{racemate}}{dl\text{-}\mathbf{A}} + \underset{\text{resolving agent}}{l\text{-}\mathbf{B}} \rightarrow \underset{\text{n-salt*}}{d\text{-}\mathbf{A}.l\text{-}\mathbf{B}} + \underset{\text{p-salt*}}{l\text{-}\mathbf{A}.l\text{-}\mathbf{B}}$$

The salts formed are diastereomers with differing physical properties and may be separated in a number of ways, for example by chromatography. The most efficient way of separating such salts is by crystallisation. The latter method relies on the differing solubilities of the two diastereomeric salts and is the key that governs their separation. The greater the solubility difference of the two diastereomers, the greater the ease with which resolution can be effected. Solubility differences can be substantial. Some examples follow in Table 1.1:

Table 1.1: (Solubilities are in g/100g solution)

Acid	Base	Solubility		Solvent	T(^{0}C)	ref.
		p salt	n salt			
2,2'-dihydroxybinaphthyl-3,3'-dicarboxylic acid	Leucine	0.44	101	Methanol	28.5	18
6,6'-Dinitrodiphenic acid	α-Methylbenzylamine	0.61	13.0	Acetone	30	19
Mandelic Acid	Ephedrine	6.0	77.48	Water	25	20
Mandelic Acid	α-Methylbenzylamine	23	4.0	Ethanol	10	21
Mandelic Acid	α-Methylbenzylamine	18	4.9	Water	30	22
Hydratropic Acid	α-Methylbenzylamine	4.8	6.4	Ethanol	10	21
Mandelic Acid	Propadrine	6.08	7.70	Water	25	20

* This convenient nomenclature derives from a proposal made by Ugi[17] where p refers to the salt in which substrate and resolving agent are of like sign and n to the salt in which substrate and resolving agent are of unlike sign.

Among the physical properties of Diastereomeric salts, such as crystal structure (to be discussed in more detail in Chapter 4), density, melting points and enthalpy of fusion, the above listed solubility differences are perhaps the most indicative of separation effectiveness. Salts such as the 2,2'-dihydroxybinaphthyl-3,3'-dicarboxylic acid / Leucine diastereomers show such considerable solubility differences between the p and n salts, that primary enrichment may easily be effected by "washing off" the more soluble n salt with methanol. Where the solubilities differ to a lesser extent, optimal crystallisation conditions for diastereomerically pure recoveries (such as temperature and concentration), are more difficult to establish. The solubilities of a three component system (two diastereomers and a solvent) may be rationalised in terms of a ternary phase diagram.

Solubility Diagrams of Diastereomeric Salt Mixtures:

Leclercq *et al.* [21] provide one of the few experimentally determined solubility diagrams. Particularly in the case of industrial resolutions where optimisation is economically justifiable, such investigations may lead to the desired improvement.

A solubility diagram (Figure 1.1) describes the solubility of each diastereomer in pure solvent (points a and b) and of diastereomer mixtures in the same solvent (isotherms ae and be). For many organic mixtures the eutectic composition (point c) is practically independent of temperature[23]. This implies that at lower temperatures, parallel isotherms (a'e' and b'e') similarly yield the composition of the saturated solutions of all possible mixtures of P and N salts. Assuming the salts to be unsolvated, four significant regions in the phase diagram can be defined:

D: P and N salts both unsaturated.

A: Pure P is in equilibrium with solvent containing dissolved P and N in proportion described by the ae isotherm.

B: Pure N is in equilibrium with solvent containing dissolved P and N in proportion described by the be isotherm.

C: Saturated solution of fixed composition (composition c) in equilibrium with solid P and solid N.

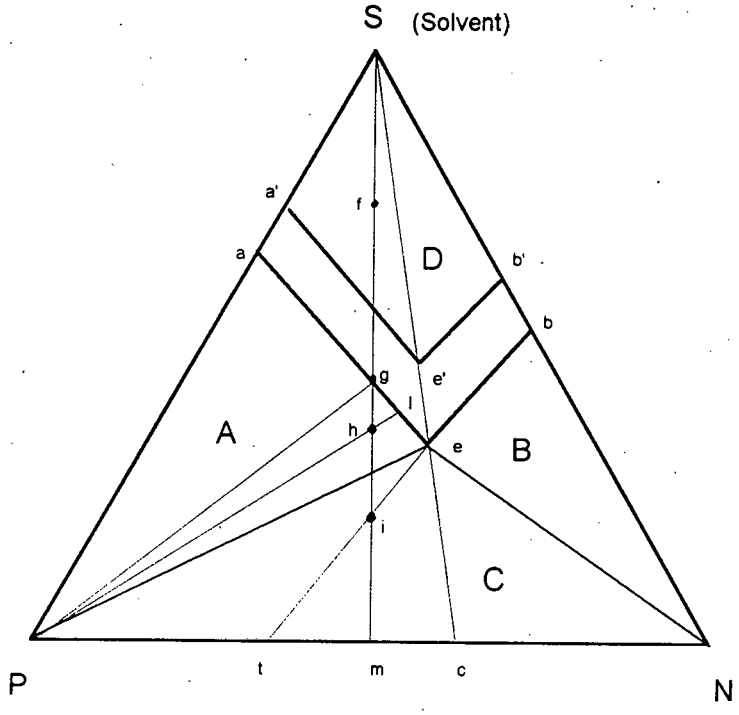


Figure 1.1: Ternary phase diagram of unsolvated salts.

A typical separation experiment will therefore start with an unsaturated solution of composition m (i.e. 1:1 n:p ratio) which would be represented on the diagram by point f. As the solvent evaporates and the solution is concentrated, point f descends along the tie line to point g where the less soluble P salt becomes saturated and crystallisation of pure P commences. Further evaporation (point h) will still yield pure crystalline P in equilibrium with the mother liquor of composition l. Below tie line Pe the more soluble N salt commences to crystallise. "Overshooting" the crystallisation to point i would therefore yield a mixture of crystalline P and N salts in equilibrium with a mother liquor of eutectic composition.

These Phase Diagrams are somewhat complicated by the following:

(a) Formation of solvated salts. This usually causes isotherms ae and eb to deviate from linearity.

(b) Formation of solid solutions. The purity of the diastereomer obtained in such a separation process depends upon the possible existence of a solid solution at the extremities of the diagram and upon their relative importance. (Figure 1.2).

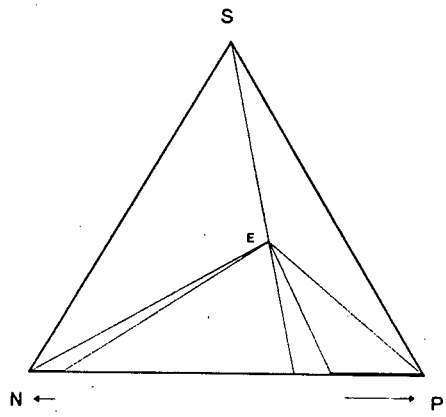


Figure 1.2: Solid solutions at the extremities P and N of the diagram

(c) Formation of double salts. Partial resolution is still possible when double salts [p_x , n_y] form where $x \neq y$. However, the optical purity attainable cannot exceed that which may be deduced from the stoichiometry of the salts.

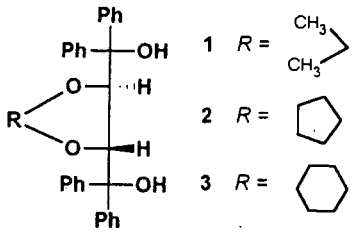
Generally, the further away point c (eutectic composition) lies from point m (racemic solution), (Figure 1.1), the greater the ease of separation and the higher the yield per crystallisation.

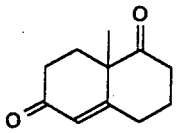
1.2.2 Host-Guest Chemistry

1.2.2.1 In solution

This resolution methodology is particularly useful for those compounds devoid of any conventional functionality (e.g., chiral alkenes and arenes, sulfoxides and phosphines). Inclusion of molecules within others is a widespread phenomenon and is finding increasing application in resolutions. Some excellent reviews cover this growing topic[24,25]. With the host compounds being chiral, preferential inclusion of one substrate enantiomer can occur as a result of selective hydrogen bonding and van der Waals attraction between guest and host molecules. Subsequent separation of the diastereomeric inclusion compound may involve melting, dissolution, or extraction of the enantiomerically enriched guest. Resolution therefore depends on differential solubility or stability. A limitation of this technique is that the relative size and shape of the guest molecule must match the size and shape of the chiral cavity created by the host molecule (resolving agent). The *cavitates* are large host compounds, such as cyclodextrins, and have cavities that may partially or entirely envelop the resolution substrate. Similar cavities can result from the assemblance of several chiral host molecules forming a cage or channel. These are often called *clathrates*. More often than not these chiral hosts

require resolution prior to their use in resolutions. To circumvent this problem in this study, a host was chosen that itself derives from enantiopure diethyl (*2R,3R*)-tartrate (made from natural tartaric acid), viz. *trans* bis(hydroxydiphenylmethyl)-2,2-dimethyl-1,3-dioxycyclopentane **1** and similar derivatives **2** and **3**.



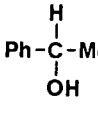


4

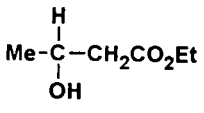
1 has been effectively applied to the resolution of racemates such as the Wieland-Miescher ketone **4**[26].Compounds **1** - **3** are extremely effective in resolving some neutral compounds that are otherwise difficult to resolve.

1.2.2.2 In the Solid State.

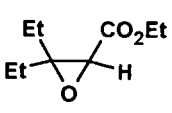
Alternatively, the host-guest complexes can be formed by grinding together solid guest and host reaction partners. Often, the physical conditions needed for the latter reactions to take place, i.e. high temperatures and pressures, are generally too insensitive and uncontrolled to allow for effective solid state chiral discrimination. Despite this, bypassing the slow process of crystallisation from solution and alleviating the often confronted problem of included solvents seemed important enough to undertake particular solid state experiments with the drug in question. Supportive of this novel technique are recent indications in the literature that crystalline hosts such as **1** and **2**, when suspended in hexane or water, form the same inclusion compounds with chiral guests as in solution[27,28]. This suspension technique is more selective and effective than the initially developed solution technique. Racemic alcohols, β-hydroxy esters, epoxy esters and epoxy ketones, such as compounds **5** - **8**, were stirred for a few hours with appropriate hosts (suspensions of **1, 2** and **3**) and formed 1:1 complexes that could be isolated in yields > 85% and with ee* values > 97%. Thus a crystal/liquid reaction occurs. This is probable because the solid-state inclusion complexation has been proven to occur by simple shaking of a mixture of powdered host and guest compounds[29].



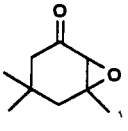
5



6



7



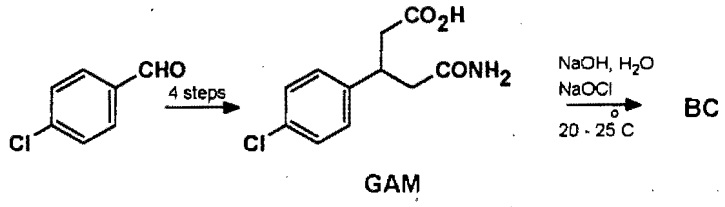
8

* Where a racemic compound is resolved into its R and S enantiomers, we define the percent enantiomeric excess (ee) as ([R] - [S])/([R] + [S]) x 100 = %R - %S.

Extending these possibilities to solid-solid reactions between host and guest (resolving agent and substrate) therefore seemed an exciting prospect in the present study, especially in view of recent successful solid-solid reactions discovered in our own laboratory[30]. Concerning the current project, preliminary interests were therefore merely to test whether any diastereomeric association could result from co-grinding a powdered resolving agent with a powdered racemic drug. This in itself proves to be a unique field of research, since the intricate processes involved in co-operative hydrogen bonding arrangements and solid state phase transformations are as yet poorly understood.

1.3 Baclofen.

Baclofen is synthesised from 4-chlorobenzaldehyde as indicated in the scheme below:



The drug's synthetic precursor, 3-(p-Chlorophenyl)glutaramide (hereinafter GAM), is converted to baclofen by means of a Hofmann Rearrangement. The reaction proceeds under relatively mild conditions and absolute configuration is retained during the reaction[31]. The preparation route is covered by two separate patents.[32,33]

Baclofen is used clinically for the treatment of spasticity of spinal and cerebral origin[34]. It was synthesised as a possible γ-aminobutyric acid (GABA)-mimetic which could readily gain access to the brain after oral administration. The drug appears to have stereospecific actions on the peripheral and central nervous systems. As previously mentioned, the enantiomers of this compound differ in their pharmacodynamic and toxicological properties; the (-) enantiomer is much more active but also more toxic than the (+) enantiomer. The R configuration was assigned to the more active enantiomer on the basis of X-ray crystallography[35].

1.3.1 Previous Resolutions

The above mentioned selective activities led to extensive research concerning methods of separating the optical isomers of Baclofen. Several methods of resolution have since appeared in the literature. These are mainly *Chromatographic separations*, making use of either bonded chiral stationary phases, or mobile phases with chiral modifiers. Other methods include

Asymmetric syntheses as well as a *Chemoenzymatic synthesis.* Here follows a brief chronological account of the more interesting separations reported in the literature thus far:

Chromatographic separations.

i) Analytical

(1) An HPLC (reverse-phase) enantioselective determination of the drug by making use of pre-column derivatisation with an *o*-phthaldialdehyde - N-acetyl-L-cysteine (OPA-NAC) reagent[36].

(2) Separation of baclofen's corresponding Lactam, **BC-Lac,** by Chiral Liquid Chromatography using immobilised bovine serum albumin as the stationary phase. Baclofen showed little retention and no resolution[37].

(3) An enantioselective crown ether HPLC column was used to separate Baclofen and analogues. Perchloric acid with methanol as organic modifier was used as mobile phase. The best results were obtained with Baclofen ($\alpha = 1.48$; $R_S = 8.07$)[38].

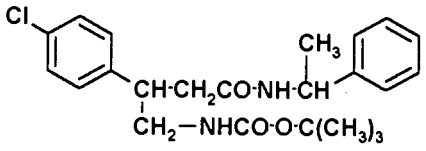
(4) Separation on a β- or a γ-cyclodextrin-bonded silica column after pre-column fluorescence derivatisation with *o*-phthalaldehyde or 2,3-naphthalenedialdehyde in the presence of thiols or cyanide[39].

Other variations of analytical procedures for the detection of R and S enantiomers in different environments exist. An example is the detection of the enantiomers in blood plasma and urine by gas chromatography using a chiral fused-silica capillary column and an electron-capture detector[40].

ii) Preparative

(5) A three-step separation involving a reverse-phase (C18) HPLC column using a chiral mobile phase of aqueous copper (II) acetate and N,N-di-*n*-propyl-L-alanine (DPA) diluted with acetonitrile. Subsequent breaking of the copper-DPA-baclofen complex was performed by retention of copper ions on a cation-exchange column. Baclofen was separated from DPA by reverse-phase HPLC using 70% MeOH/water as the mobile phase[41].

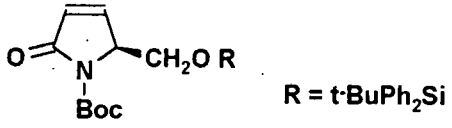
(6) A diastereomeric mixture separation of Baclofen after derivatisation by protection of the amino group with di-*tert*-butyl carbonate and reaction with (*S*)-α-methylbenzylamine. The RS and SS diastereomers 9 were successfully resolved by Chromatography carried out on silica gel employing *n*-hexane-ethyl acetate as eluent[42].



9

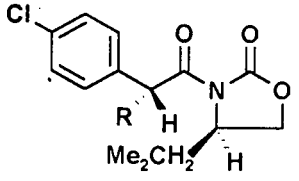
Asymmetric synthesis:

(7) Facile access to (*R*)-Baclofen was provided in a five-step synthesis starting from (*S*)-pyroglutamic acid derivative **10** with an overall yield of 16%[43]. This synthesis was subsequently optimised and patented by using a different Grignard reagent in the 1,4-conjugate addition to **10**[44].



10

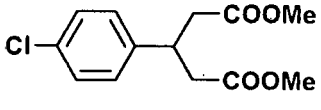
(8) The Chiral Imide **11** (R = H) was alkylated via its imide enolate with $BrCH_2CO_2CMe_3$. Removal of the chiral auxiliary from intermediate **11** (R = $CH_2CO_2CMe_3$) provided a lactone. This was transformed to give the Lactam (BC-Lac) which yielded (*R*)-Baclofen after acidic hydrolysis[45].



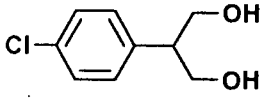
11

Chemoenzymatic synthesis:

(9) Two approaches are used in the enantioselective syntheses of Baclofen based on the distinction between enantiotropic ester groups in compounds bearing a prochiral centre. The first involved the key step of highly stereoselective enzymatic hydrolysis of **12** by Chymotrypsin. In the second, the key step was the enzyme-catalysed esterification of **13** by acetic anhydride in the presence of a lipase[46].



12



13

1.4 Resolving Agents.

Today, numerous enantiomerically pure compounds are commercially available that may be useful as asymmetric building blocks, for use as chiral auxiliaries or as resolving agents. No attempt shall be made to present an exhaustive list of resolving agents and their specific fields of application. A variety of optically pure amino acids, hydroxy acids, carbohydrates and their derivatives, terpenes and alkaloids are now readily available. The choice of resolving agent relating to the formation of diastereomeric salts and subsequent crystallisation is not trivial. Looking at any of the molecules such as GAM, BC or BC-Lac, one could in theory choose suitable acids or bases, according to the substrate's functionality, with which to commence experimentation in a suitable solvent. One searches for:

(1) diastereomeric salts that crystallise well and show suitable differential solubility between the diastereomeric pairs.

(2) Ease of salt formation and subsequent recovery of the individual components.

(3) Inexpensive resolving agents.

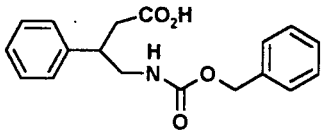
(4) Resolving agents that are available in optically pure form.

(5) Substrates and resolving agents whose chiral centres are not too remote from the functionality with which salt formation is to be effected.

(6) Chemically stable agents that do not racemise.

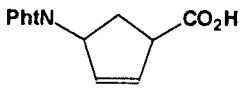
(7) The availability of both enantiomers of the agent.

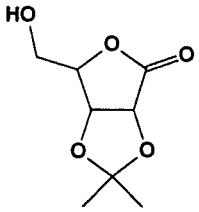
With the above considerations and bearing in mind the aforementioned functional groups present in our substrates, the literature provides some encouraging information. Amino acids are most often resolved in "protected" form, mainly via derivatisation of the amino group to yield for example N-acetyl or N-benzyloxycarbonyl compounds that may be resolved with an optically active base[47]. α-Methylbenzylamine (MBA) is a common basic (pK_b = 4.5) resolving agent easily regenerated and purified after use via its sulphate[48]. MBA was found useful in the separation of a GABA analogue β-Phenyl-γ-aminobutyric acid. This drug, differing from Baclofen in the absence of the *p*-chloro substituent is used as a mood elevator and tranquilliser[49]. The resolution was effected by fractional crystallisation of the N-carbobenzyloxy-protected racemate **14** with MBA[50] or Cinchonidine[51]. Protection of the primary amine yielded an exposed acidic moiety, similar to the functionality of GAM, with which salt formation could be effected.

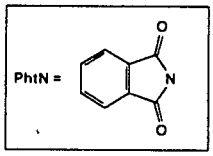


14

Further protection by diastereomeric ester formation has been applied to the resolution of the *N*-phthalimido derivatives of GABA analogues (**15**) by using the alcohol protected sugar Ribonolactone **16**[52].

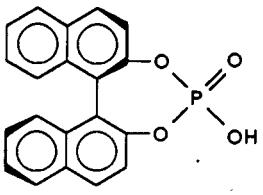






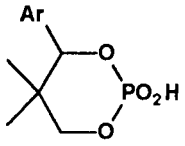
15 **16**

The *trans*-(+)-(1*R*,4*R*)-phthalimido ester was crystallised out of a solution of pyridine and tetrahydrofuran. The direct resolution of *free* amino acids is obviously a more attractive process than that involving prior introduction and subsequent cleavage of a protection group. Strong acidic resolving agents are sometimes capable of forming , with neutral, unprotected amino acids, nicely crystalline salts that are analogous in nature to amino acid hydrochlorides. DL-phenylglycine[53] and Terleucine[54] have been efficiently resolved with 10-Camphorsulphonic acid (CSA), and *o*-tyrosine[55] and Homomethionine[56] with the phosphoric acids (**17**) and (**18**) respectively.



17

2,2'-(1,1'-binaphthyl)-phosphoric acid **17** is a strongly acidic resolving agent ($pK_a = 2.50$). The racemate of **17** is resolved with cinchonine to afford pure (*S*)-(+)-**17**, and with cinchonidine to afford pure (*R*)-(-)-**17**[57]. The enantiomers of this acid form well crystallised salts with a wide variety of organic bases, and therefore represent a useful tool for the resolution of amines[58,59]. The subsequently designed anologue (**18**) has also proved to be useful for the separation of amines and amino acids[60].



18

Among the natural optically pure resolving agents, tartaric acid probably has the longest history within organic stereochemistry. Industrially it finds its use mainly as a resolving agent rather than as a chiral building block. Being a "bi-acid" it is effective in resolving diamines for example[61]. The acid's abundance and availability make it an attractive agent for experimentation. Several resolving agents are derivatised from the acid, such as compounds **1-3**, di-*p*-toluoltartaric acid and *O,O*-dibenzoyltartaric acid. This latter derivative, for example, was used in resolving the methyl ester of Terleucine ($(CH_3)_3CCH(NH_2)COOH$)[62].

Numerous other possible agents could be discussed in speculating what may be the correct choice of resolving agent for the resolution of Baclofen. The objective of this project was to produce optically pure (*R*)-(-)-Baclofen by either resolving the racemic drug itself, by resolving its synthetic precursor GAM, or even by trying to separate the BC-Lac and hydrolysing the enantiopure Lactam with HCl to give the desired product[63].

1.5 References:

1. A. Brossi, *Medicinal Research Reviews,* **14** (6), (1994), 665.
2. P.I. Folb, *The Thalidomide Disaster, and its Impact on Modern Medicine,* Inaugural Lecture 8, Sept. 1977, University of Cape Town.
3. J.J. Feigenbaum, S.A. Richmond, Y. Weissman, R. Mechoula, *Eur. J. Pharmacol.*, **169**, (1989), 159.
4. S.C. Stinson, *C&EN*, Sept. 19, (1994), 38.
5. R.N. Brogden, T.M. Speight, G.S. Avery, *Drugs,* **8,** (1974), 1.
6. S. Ahuja in *Analytical Profiles of Drug Substances*,**vol. 14**, K. Florey, Ed. (Acedemic Press, New York, (1985), 527.
7. H.R. Olpe, H. Demiéville, V. Baltzer, W.L. Bencze, W.P. Koella, P. Wolf, H.L. Haas, *Eur. J. Pharmacol.,* **52**, (1978), 133.
8. D.R. Hill, N. G. Bowery, *Nature,* **290**, (1981), 149.
9. A. Collet, M. Brienne, J. Jacques, *Chem. Rev.* **80** (3), (1980), 215.
10. L. Velluz, G. Amiard, R. Joly, *Bull. Soc. Chim. Fr.,* (1953), 342.
11. F.I.Carrol, B. Berrang, C.P. Linn, *Chem. Ind.*(London), 1975, 477, *J. Med. Chem,* **21**, (1978), 326.
12. L. Borka, *Acta Pharm. Suec.*,**16**, (1979), 345.
13. A.N. Collins, G.N. Sheldrake, J. Crosby, *Chirality in Industry.* John Wiley & Sons, New York, 1994.
14. H.J. Roth, A. Kleeman, T. Beisswenger, *Pharmaceutical Chemistry,* Ellis Horwood, Chichester, **1**, (1988).
15. S.H. Wilen, A. Collet, J. Jacques, *Tetrahedron,* **33**, (1977), 2725.
16. L. Pasteur, *C.R.Acad. Sci..***37**, (1853), 162.
17. I. Ugi, *Z. Naturforsch.*, **20B**, (1965), 405.
18. R. Kuhn, K. Vogler, *Z. Naturforsch,* **6b**, (1951), 232.
19. A.W. Ingersoll, J.R. Little, *J. Am. Chem. Soc.*, **56,** (1934), 2123.
20. C. Jarowski, W.H. Hartung, *J.Org. Chem.*, **8**, (1943), 564.
21. M. Leclercq, J. Jacques, *Bull. Soc. Chim. Fr.*, (1975), 2052.
22. A.W. Ingersoll, S.H. Babcock, F.B. Burns, *J. Am. Chem. Soc.*, **55**, (1933), 411.
23. J. Jacques, J. Gabard, *Bull. Soc. Chim.Fr.*, (1972), 342.
24. F. Toda, "Isolation and Optical Resolution of Materials Utilizing Inclusion Crystallization," *Top. Curr. Chem.*, **140,** (1987), 43.

25. D. Worsch, F. Vögtle, "Separation of Enantiomers by Clathrate Formation." *Top. Curr. Chem.*. **140,** (1987), 21.

26. F. Toda, K. Tanaka, *Tetrahedron Lett.*, **29**, (1988), 551.

27. G Kaupp, *Angew. Chem. Int. Ed. Engl.* **33(7)**, (1994), 728.

28. F. Toda, Y. Tohi, *J. Chem. Soc. Chem. Commun.*, (1993), 1238.

29. F. Toda, K. Tanaka, A. Sekikawe, *J. Chem. Soc. Chem. Commun.*, (1987), 279.

30. M R. Caira, L. R. Nassimbeni, A. F. Wildervanck, *J. Chem. Soc. Perkin Trans, 2,* (1995), 2213.

31. J. March, *Advanced Organic Chemistry,* John Wiley (New York) 4th Ed., (1992), 1090.

32. CIBA Ltd. **Neth. Appl. 6,407,755** (Cl. C07*c*), Jan. 11, 1965.

33. K. Rudnick, K. Bochow, (VEB Berlin-Chemie) **Ger. (East) DD 234,162** (Cl. C07C101/10), 26 March 1986.

34. P. Hudgson, D. Weigtmann, *Brit. Med. J.*, **4**, (1971), 15.

35. C.H. Chang, D.S.C. Yang, C.Y. Chung, W. Bi-Cheng, J. Pletcher, M. Sax, C.F. Terrence, *Acta Crystallogr. Sect. B.*. **B38**, (1982), 2065.

36. E.W. Wuis, E.W.J. Beneken Kolmer, L.E.C. van Beijsterveld, R.C.M. Burgers, T.B. Vree, E. van der Kleyn, *J. Chromatogr.*, **451**, (1987), 419.

37. S. Allenmark, S. Andersson, *Chirality.*, 1:**154**, (1989), 160.

38. C. Vaccher, P. Berthelot, M. Debaert, *J. Chromatogr.*, **645** (1), (1993), 95.

39. A. Sano, S. Takitani, H. Nakamura, *Kuromaogurafi,* **15** (4), (1994), 234.

40. A. Sioufi, G. Kaiser, L. Leroux, J.P. Dubois, *J. Chromatogr.*, **450**, (1988), 222.

41. R.P. Weatherby, R.D. Allen, G.A.R. Johnston, *J Neurosci. Methods.* **10**, (1984), 23.

42. C. Vaccher, P. Berthelot, N. Flouquet, M. Debaert, *J. Chromatogr.*, **542**, (1991), 502.

43. C. Herdies, H.P. Hubmann, *Tetrahedron:Asymmetry,* **3** (9), (1992), 1213.

44. H. P. Hubmann, C. Herdies **DE 4,224,342** / 27 Jan. 1994.

45. A. Shoenfelder, A. Mann, S. Le Coz, *Synlett*, **1**, (1993), 63.

46. R. Chênevert, M. Desjardins, *Can. J. Chem.*, **72**, (1994), 2312.

47. Examples are the optical resolution of terleucine with bases such as cinchonine and quinine, T. Tanabe, S. Yajima, M. Imaida, *Chem. Pharm. Bull.*. **41**, (1968), 2178, and T. Miyazawa, K. Takashima, Y. Mitsuda, T. Yamada, S. Kuwaka, H. Watanabe, *Bull. Chem. Soc. Jpn.*, **52,** (1979), 1539.

48. W. Markwald, R. Meth, *Ber.*, **38**, (1905), 801.

49. I. S. Sytinsky, A.T. Soldatenkov, *Prog. in Neurobiol.*. **10**, (1978), 89.

50. N.A. Sivov, R.A. Gracheva, V.M. Potapov, L.G. Polevoi, I.P. Neumyvakin, *Otkrytiya, Izobret., Prom. Obraztsy, Tovarnye Znaki,* **17**, (1981), 88. (**U.S.S.R 827480**/ 7 May (1981).

51. M. Sobocinska, G. Kupryszewski, M.M. Zobaczewa, *Rocz. Chem.* **48**, (1974), 461.

52. R.D. Allan, J. Fong, *Aust. J. Chem.* **39**, (1986), 855.

53. A.W. Ingersoll, *J. Am. Chem. Soc.*, **47**, (1925), 1168.

54. J. Viret, H. Patzelt, A. Collet, *Tetrahedron Lett.* **27**, (1986), 5865.

55. A. Garnier-Suillerot, J.P. Albertini, A. Collet, L. Faury, J-M. Pastor, L. Tosi, *J. Chem. Soc. Dalton Trans.*, (1981) 2544.

56. B.K. Vriesema, W. ten Hoeve, H. Wynberg, R.M. Kellog, *Tetrahedron Lett.*, **27**, (1986), 4045.

57. J. Jacques, C. Fouquey, *Organic Synthesis,* **67**, (1989), 1.

58. J. Jacques, C. Fouquey, R. Viterbo, *Tetrahedron Lett.*, **48**, (1971), 4617.

59. S. Wilen, J.Z. Qi, *J. Org. Chem.*, **56** (1991), 485.

60. W. ten Hoeve, H. Wynberg, *J. Org. Chem.*, **50**, (1985), 4508.

61. See for example O.F. Williams, J.C. Bailar *J. Am. Chem. Soc.*, **81**, (1959), 4464, and H. Suda, M. Motoi, M. Fujii, S. Kanoh, H. Yoshida, *Tetrahedron Lett.* (1979) 4565.

62. H. Pracejus, S. Winter, *Chem. Ber.*, **104**, (1971), 687.

63. R.D. Allan, H. Tran, *Aust. J. Chem.*, **34**, (1981), 2641.

2. METHODS AND MATERIALS

2.1 Starting Materials.

2.1.1 Substrates.

Both BC and GAM were kindly supplied by Fine Chemicals Corporation, Eppindust, South Africa. BC-Lac was synthesised by simple cyclodehydration of BC. Several synthetic methods optimise lactam production from γ- or δ-amino acids[1] A simplistic approach is to keep BC at the melting temperature (205^{0}C) for a few minutes[2]. Upon cooling, instant resolidification occurs. Completion of the thermal decomposition or rearrangement to the γ-lactam may be checked by TLC (precoated silica gel 60 F 254 plates. Mobile phase: isopropanol: acetic acid: water (70: 15: 15)). The lactam is then purified by two recrystallisations from toluene:hexane (90:10) (m.p. 118^{0}C).

This method was subsequently improved by refluxing in toluene / acetic acid. 30 ml acetic acid was added to a stirred suspension of 8.230g BC in 300 ml toluene and refluxed for *ca* two hours. The progress of the reaction was followed by TLC (chloroform: ethyl acetate 70:30 on silica). The reaction mixture becomes clear with time as the lactam is soluble in this solvent mixture. The solution was filtered to remove any unreacted BC and the solvent removed by using a rotary evaporator. The remaining acetic acid was removed by redissolving the product in 100 ml toluene and the solvent again removed under vacuum.

2.1.2 Resolving Agents.

The following resolving agents were at our disposal for experimentation with the drug and the analogues as discussed above: (abbreviations used hereafter follow in parentheses)

Acids

L-(+)-Tartaric Acid	(TA)
L-(+)-Tartaric Acid Dimethyl Ester	(DMT)
L-(-)-Tartaric Acid 2,3-Dibenzoyl Ester	(DBT)
D-(-)-10-Camphorsulfonic Acid	(CSA)
L-(-)-Mandelic Acid, D-(+)-Mandelic Acid	(L-MA, D-MA)
L-(-)-Malic Acid	(MAL)

Bases

(*R*)-(-)-α-Methylbenzylamine, (*S*)-(+)-α-Methylbenzylamine	((*R*)-MBA, (*S*)-MBA)
L-(-)-Ephedrine	(ED)

Brucine	(BRC)
Cinchonidine, Cinchonine	(CIN, CIND)
Quinine, Quinidine	(QIN, QIND)

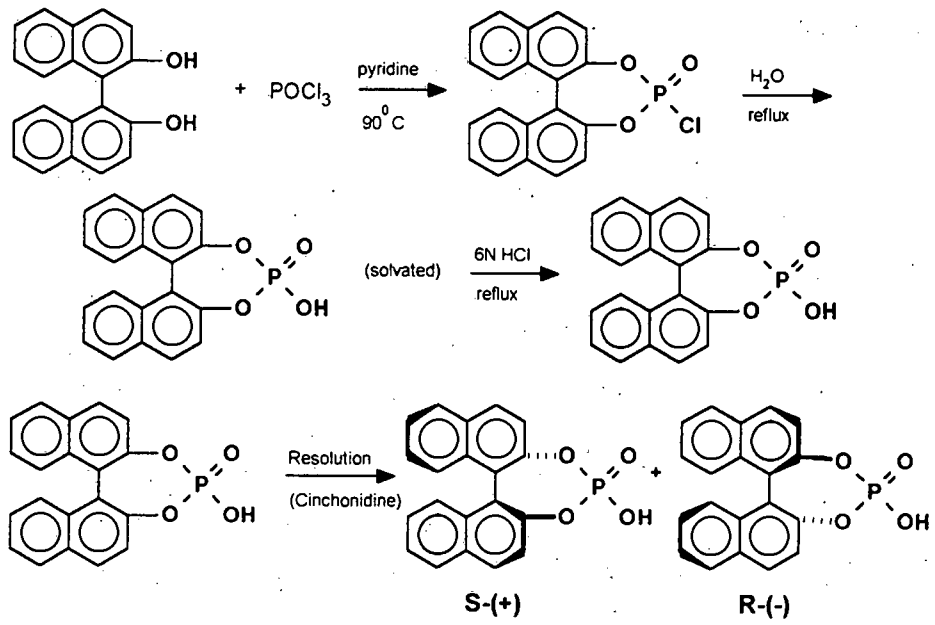
Host Compounds

trans-4,5-bis(hydroxydiphenylmethyl)-2,2-dimethyl-1,3-dioxacyclopentane (HMD3)*
(*R*,*R*)-(-)-*trans*-2,3-bis(hydroxydiphenylmethyl)-1,4-dioxaspiro[4.4]nonane (HMD5)*
(*R*,*R*)-(-)-*trans*-2,3-bis(hydroxydiphenylmethyl)-1,4-dioxaspiro[5.4]decane (HMD6)*

Some of the alkaloids were also available as their sulphate or chloride salts. In the interest of diastereomeric salt formation these were generally avoided.

Synthesis of (R)-(-)-1,1'-Binaphthyl-2,2'-Diyl Hydrogen Phosphate ((R)-(-)-BNP Acid)

Procedures for the synthesis of BNP acid have been reported in the literature[3,4,5,6] . The acid is successfully resolved with either CIND or CIN, but has more recently been resolved with (*R*)-(-)-2-aminobutanol[7]. The general procedures (shown in the scheme below) of Jacques and Fouquey were adopted and modified[4]. Subsequent literature values quoted for optical rotational values etc. refer to the latter reference:



To a stirred suspension of 4g (14 mmol) (±)-1,1'-bi-2-naphthol in 18 ml pyridine, was added 1.78 ml (19.2 mmol) of freshly distilled phosphorus oxychloride by slow dropwise injection. The

* These hosts are sketched on page 8 of Chapter 1 (compounds 1,2 and 3).

temperature of the solution was allowed to rise to *ca* 80°C to allow for complete dissolution. The solution was cooled to 65°C at which temperature crystallisation occurred. To the stirred suspension was added 2 ml water raising the reaction temperature to 120°C. The solution was allowed to cool to 60°C and was slowly added to 36 ml of 6 M HCl, whilst vigorously stirring. The resulting pyridine solvated BNP acid was collected by suction filtration and the wet cake added to and stirred with 12 ml 6 M HCl. The solid was thoroughly filtered off at the pump, washed with water and air dried to afford 4.32g (90%) of (±)-BNP acid. This product decomposed slowly at about 300°C without melting (as quoted in literature).

4g (±)-BNP (11.3 mmol) acid and 3.37g (11.3 mmol) Cinchonidine were dissolved in 50 ml hot (60°C) methanol. To the hot solution was added *ca* 10 ml hot water dropwise over a period of about 30 min. During this time the solution was stirred and maintained at this temperature. The solution was kept sufficiently dilute in order to prevent fast crystallisation. The diastereomeric salt mixture was then allowed to cool, affording 1.84g of colourless crystals of the p salt [(-)-acid, (-)-base] after *ca* 24 hours, $[\alpha_D]_{589} = -390^0$ (methanol), m.p. 240°C (slow melt).

1.5 g of the above salt was dissolved in 10 ml ethanol by heating to reflux. To this solution was slowly added 11 ml of 6 M hydrochloric acid whilst stirring vigorously and maintaining the temperature at 80°C. Precipitation of the BNP acid commenced immediately upon cooling. The solid was collected and washed with water and air dried to afford 0.72 g of (*R*)-(-)-BNP acid, $[\alpha_D]_{589} = -590^0$ (Lit. -595°). The acid decomposed above 300°C.

2.2 Diastereomeric Salt Formation.

As a consequence of the numerous experiments carried out in attempts to primarily effect some form of association between the drug molecules and one enantiomer of a chiral resolving agent, general procedures of typical resolution experiments are outlined in sections 2.2.1 and 2.2.2. Further details on a few of the more successful experiments will be discussed in Chapter 3.

2.2.1. Salt Formation in Solution.

Approximately 10^{-3} mole (normally of the order of 100 - 150 mg) of the racemic substrate were combined with an equivalent amount of optically active base or acid. These were then dissolved in a quantity of a suitable solvent (*ca* 4 - 5 ml). A statistical analysis of solvents used in over 800 resolutions involving formation and separation of diastereomeric salts showed that alcohols and acetone (anhydrous or aqueous), water, and mixtures of solvents containing an alcohol figure in about 90% of the cases[8]. In our experiments the following solvents were used (this was also subject to the solubility characteristics of the resolving agents):

Substrate	**Solvents**
GAM	Methanol, ethanol with acetone or ethyl acetate as precipitants.
BC-Lac	Same as for GAM as well as benzene or toluene with hexane as precipitant.
BC	The drug is poorly soluble in almost all organic solvents. BC is soluble in acidic or basic solutions. Dissolution in solutions of acidic or basic resolving agents were only partially successful.

Crystallisation experiments were set up in 10 ml vials. Complete dissolution was accomplished by gentle warming to 40 - 60^{0}C (boiling was avoided). Crystallisation was induced by one of the following techniques:

1) *Slow evaporation:* Dilute solutions were allowed to stand for 24 hours (sometimes several days). Should the system lend itself to preferential crystallisation of one diastereomer, this technique avoided overshooting the concentration to that of region C on the phase diagram (Figure 1.1, section 1.2.1.2).
2) *Slow cooling:* In terms of the phase diagram, this technique differs from the latter in that isotherms ae and eb are "lowered" from their equilibrium position such that complete dissolution may take place. Crystallisation is then induced by allowing gradual return ("rising") of the isotherms (i.e. gradual cooling). Concentration is therefore static and must carefully be chosen such that it lies within region A. This was therefore only possible once salt formation was confirmed.
3) *mixed solvents:* Where single solvent systems rendered inadequate solubility differences between diastereomeric pairs, the solvents were modified by the addition of a second (or even a third) solvent, to alter the polarity, density, and viscosity of the system. In effect this may alter

the position of a eutectic or even reverse the relative solubilities of the p and n salts. In the resolution of 2,2-Dimethyl-3-phenylpentanoic acid with quinine for example[9], the (+) enantiomer was retrieved from the less soluble salt when crystallised from ethanol whereas the use of aqueous ethanol rendered the salt containing the (-) enantiomer less soluble due to solvation. Dual solvent systems proved to be imperative where substrate and resolving agent did not have a common solvent. In the latter case combination of the acid base pairs would be effected by separate dissolution of the two components and subsequent combination of two solutions.

Other methods less frequently used were *liquid diffusion* or *vapour diffusion* these being modifications of mixed solvent systems where the second solvent (usually precipitant) is introduced by slow diffusion processes.

2.2.2 Salt Formation in The Solid State.

Equimolar amounts (e.g. 100mg BC and 108.7mg CSA) were weighed and mixed. The mixture was manually ground in a mortar for *ca* 4 min. The 1:1 mixture was then carefully transferred to a 14mm id. X 35 mm stainless steel cylinder with either one 8.34g, 12mm or two 1g, 5mm iron balls. The cylinders were sealed and mounted on a Grindex Ball Grinder. The sample was ground mechanically for several minutes (typically 15 min) during which time the cylinder's temperature was observed to increase to approximately 45^0C. The powder was then removed and analysed for any indication of phase change by measurement of the melting point and recording the solid's X-ray powder pattern.

2.3 Analytical Methods

2.3.1 NMR.

Crystals and powders were dissolved in deuterated chloroform, water or methanol and their ^{1}H NMR spectra recorded at either 200 MHz (Varian VXR200) or 400 MHz (Varian Unity 400) with tetramethylsilane as reference.

2.3.2 Microanalysis

C, H, and N analyses were performed on a Heraeus Universal combustion analyser Model CHN-RAPID.

2.3.3 Thermal Analysis.

Resolving agent-substrate association was analysed by means of Differential Scanning Calorimetry (DSC). A Perkin Elmer PC7 Series thermal analysis system was employed. Indium ($\Delta H = 28.5$ J/g, m.p. = 156.7°C) and Zinc ($\Delta H = 102.1$ J/g, m.p. = 419.6°C) were used for calibrating the instrument. Sample masses ranging between 3 - 8 mg were placed in vented aluminium pans and heated at a constant rate of $10^0C.min^{-1}$. The sample chamber was purged with N_2 gas at a rate of 30 ml/min. Melting points were determined using a Linkam TH600 hot stage with a Linkam CO600 temperature controller. This apparatus was fitted with a Nikon SMZ-10 microscope for viewing melting and desolvation processes.

2.3.4 Polarimetry

A Perkin Elmer 141 Polarimeter was employed to measure absolute rotations of solutions to $\pm 0.001^0$. The instrument was set to zero using the appropriate solvent. Samples were pipetted into a 1 ml tube (l = 1 dm) and measured at λ = 589, 546, 436, and 365 nm. $[\alpha]_\lambda$ values reported were calculated by $[\alpha]_\lambda = 100\alpha/c$ where c = g of solute/100 ml solution.

2.3.5 HPLC

Chromatograms were obtained using a RESOLVOSIL BSA-7 (Bovine Serum Albumin) analytical column with a RESOLVOSIL guard column and a Waters Model 510 dual pump system. A Waters Model 440 absorbance detector set at λ = 254 nm. was used for detection. The mobile phase used was 50m*M* Na_2HPO_4/NaH_2PO_4 buffer at a flow rate of 0.9 - 1.0 ml/min giving a 1000 - 1100 psi. column pressure. Samples for analysis were dissolved in small aliquots of the mobile phase or in mobile phase/EtOH 3:1 v/v. This BSA column resolves BC-Lac. (α = 1.9)[10].

2.3.6 XRD

X-ray powder patterns of the powdered resolving agents, substrates and co-ground products were measured on a PHILIPS PW 1050/80 goniometer with Ni-filtered CuKα radiation (λ = 1.5418Å). Step scans of 0.1^0 2θ over the range $6^0 \leq 2\theta \leq 40^0$, 2s per step, were performed using automatic

divergence and receiving slits. Samples were mounted in a 20 x 14 x 1 mm aluminium holder. These powdered samples were carefully packed in order to minimise preferred orientation effects. Co-grinding conditions ensured particle sizes to be no greater than 100 μm.

2.3.6 X-Ray Crystallography.

1) *Preliminary photography.* Oscillation and Weissenberg photographs were taken using a non-integrating Stoë goniometer. The crystals were irradiated with Ni-filtered CuKα radiation (λ= 1.5418Å) generated by Philips PW1120 and PW1140 X-Ray generators. Approximate cell parameters and space group data were calculated from the photographs.

2) *Intensity Data Collections.* Intensity data were measured on an Enraf-Nonius CAD4 diffractometer at 294K using graphite-monochromated Mo Kα radiation (λ = 0.71069Å). Accurate cell dimensions were obtained by least-squares refinement of 24 accurately measured reflections. Data in the range $1^0 \leq \theta \leq 25^0$ were collected in the ω-2θ mode with a maximum recording time of 40s per reflection. Intensity control was performed every hour by means of 3 reference reflections and orientation control every 200 reflections. Measured intensities were corrected by Lorentz-polarisation factors as well as an empirical absorption correction.[11]

3) *Computation:* The structures were solved by direct methods using the program SHELX-86[12] and refined by using SHELX-93[13]. The latter refinement involved the minimisation of $\Sigma(w(F_o^2 - kF_c^2))$ where F_o and F_c are the observed and calculated structure factors respectively. Agreement between these latter two values were calculated by means of an R1 factor = $\Sigma(|F_0| - |F_c|)/ \Sigma(|F_0|)$ and wR2 = $[\Sigma(w(F_o^2 - kF_c^2)^2/ \Sigma(w(F_0^2)^2)]^{1/2}$ where $w = [\sigma^2(F_0^2) + (aP)^2 + bP]^{-1}$ and $P = [\text{Max}(0,F_0^2) + 2F_c^2]/3$. The values of a and b were chosen such that $\Sigma w(\Delta F)^2$ showed no marked systematic trends with the magnitude of $\sin\theta$ and $(F_o / (F_o)_{max})^{1/2}$. The program uses neutral atom scattering factors, f' and f'' and absorption coefficients from International Tables for Crystallography[14]. Further details on refinement methods follow in section 4.2.5 where the individual crystal structures are discussed. From the refined atomic coordinates, thermal parameters, cell and space group data, X-ray powder diffraction patterns were computed using LAZY PULVERIX[15]. The latter powder patterns were used for comparison of the structure and polymorphic nature of crystals collected from large scale crystallisations with the structure determined by single crystal analysis.

2.4 References

1. See for example, Bladé-Font, *Tetrahedron Lett.*, **21**, (1980), 2443, and R. Pellegata, M. Pinza, G. Pifferi, *Synthesis*, (1978), 614.
2. L. Borka, *Acta Pharm. Suec.*, **16**, (1979), 345.
3. C. Marschalk, *Bull. Soc. Chim.*, **43**, (1928), 1388.
4. J. Jacques, C. Fouquey, *Organic Synthesis*, **67**, (1989), 1.
5. E.P. Kyba, G.W. Gokel, F. de Jong, K. Koga, L.R. Sousa, M.G. Sielgel, L. Kaplan, G. Dotsevi, Y. Sogah, D.J. Cram, *J. Org. Chem.*, **42**(26), (1977), 4173.
6. S. Miyano, M. Tobita, H. Hashimoto, *Bull. Chem. Soc. Jpn.* **54**, (1981), 3522.
7. Y. Tamai, P. Heung-Cho, K. Iizuka, A. Okamura, S. Miyano, *Synthesis*, March 1990, 222.
8. S.H. Wilen in *Tables of Resolving Agents and Optical Resolutions*, E.L. Eliel, Ed., University of Notre Dame Press, Notre Dame, Indiana, 1972.
9. M.J. Brienne, C. Ouannès, J. Jacques, *Bull. Soc. Chim. Fr.*, (1967) 613.
10. S. Allenmark, S. Andersson, *Chirality*, 1:**154**, (1989), 160.
11. A.C.T North, D.C.Philips, F.S. Matthews, *Acta Cryst.*, **A 24**, (1968), 351.
12. G. M Sheldrick, *SHELX 76*. Program for crystal structure determination, University of Cambridge, England, 1976.
13. G. M Sheldrick, *J. Appl. Crystallogr.* In preparation.
14. International Tables for Crystallography, Volume C (1992), Ed. A.J.C. Wilson , Kluwer Academic Publishers, Doordrecht.
15. K. Yvon, W. Jeitschko, E. Parthé, *J. Appl. Crystallogr.*, 1977, **10**, 73.

3. RESULTS AND DISCUSSION

3.1 Experiments in solution

Within slight variations, the results from cocrystallisation experiments were categorised into three main groups:

a) A non-crystalline cocrystallisation product, mostly an oil or thick paste.

b) A crystalline product but resolving agent and substrate in separate crystals.

c) Positively identified complexes (co-crystals).

Thermal analyses of many of the crystalline products indicated undefined melting points or complex thermograms and ambiguous DSC traces implying a mixture of products. Varying degrees of solvation often hampered reproducibility. Added to this was the well known problem that the presence of even a very small impurity can hinder formation and growth of the first nuclei. Solutions left for crystallisation would therefore concentrate to such a degree of supersaturation that eventual precipitation yielded powders composed of too many components to be able to make sensible conclusions from the analyses.

We concern ourselves exclusively with those results that indicated some form of association between resolving agent and substrate. Where this was achieved, ensuing experiments establishing the nature of association and possible selectivity are subsequently outlined for selected experiments.

Table 3.1 : Complexes formed from solution

Components[a]	*Solvent*	*M.P.(°C)*	*Stoichiometry*[b]
BC(210°C) + TA(170°C)	Water	140	1:1
BC-Lac (118°C) + TA[c]	MeOH/Toluene	100	2:1
		126	2:1
BC-Lac + CSA (200°C)	Toluene/Hexane	55	1:1
BC-Lac + DBT (150°C)	Toluene/Hexane	94	1:1
BC-Lac + DMT (60°C)	benzene/heptane	86	1:1
GAM(173°C) + MBA(liq.)[d]	MeOH	187	1:1
GAM + CIND(201°C)	EtOH/EtOAc	91	1:1

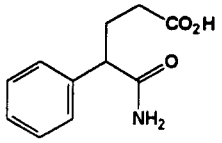
a) Melting points of the pure components follow in parentheses
b) These were established by a combination of CHN and NMR analyses.
c) See sect 3.4, and d) chapter 4 for further details.

BC: In the light of the various unprotected amino acids resolved with strong resolving acids (as mentioned in Sect. 1.4), the failure of any of the acids BNP, MA and CSA to resolve, partially resolve or even form a salt with BC was somewhat surprising. A serious problem in cocrystallising BC with organic resolving acids is the drug's poor solubility in almost all organic solvents (4.3mg/ml in water (pH 7.6) and less than 0.05 mg/ml for all organic solvents (MeOH, EtOH, $CHCl_3$ etc.)). An additional problem is that BC cyclodehydrates readily at low pH to form BC-Lac[1]. Co-crystallising (*R*)-(-)-BNP acid with BC in fact resulted in lactam formation (proven by NMR and m.p.). The co-crystals identified with TA grew after 3 months and were difficult to reproduce. No evidence could be found in the literature of any organic compound, bearing a chiral GABA moiety, resolved as the free amino acid by cocrystallisation with an acidic resolving agent. Both racemates of 2-methyl-GABA[2] and 4 methyl-GABA (4-Aminopentanoic acid)[3], for example, are separated as their N-phthalimido and N-Carbobenzyloxy derivatives respectively. These derivatives are co-crystallised with quinine.

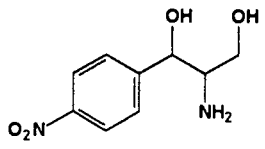
BC-Lac: Co-crystallising BC-Lac with acids in polar solvents led to oily precipitates. Non-polar solvents gave some complexes as indicated in Table 3.1. Given the ionic nature of the salts used in resolutions, one can predict that the best solvents will be polar ones. Solvents such as hexane or benzene sometimes even prevent the formation of salts. Thus the price paid for these more crystalline complexes was their poor selectivity. With the exception of the BC-Lac.TA complex, chiral HPLC (BSA column) analyses of all other BC-Lac complexes indicated approximately equal quantities of R and S isomers.

GAM: The GAM.CIND co-crystals were finely powdered precipitates. NMR, DSC, XRD and microanalysis confirmed phase transformation after co-crystallisation and 1:1 acid:base stoichiometry. In the absence of information detailing chiroptical properties of (+)- and (-)-GAM, as well as any existing chromatographic separation methodology for ee analysis, establishing enantioselectivity was difficult. This was made easier in the GAM.MBA complex, where suitable single crystals could be grown for X-ray analysis to establish absolute configuration (see chapter 4). This was a most interesting result as little evidence concerning separation methodology for analogous glutaric acid monoamides can be traced in the literature. Morlacchi *et al.* in 1975, concerning themselves with the absolute configuration of 2-Phenylpyrrolidine, resolved 4-phenyl-4-

carboxamidobutyric acid (**19**) through salt formation with D(-)-*threo*-(p-nitrophenyl)-2-amino-1,3-propanediol (**20**) in ethanol.[4]



19



20

This Chloramphenicol base (**20**) was not available to us to check its effectiveness with GAM. Various dicarboxylic acids are resolved by this base[5,6] .

3.2 Solid State experiments

Analyses of the co-ground products were similarly categorised to the solution products. Instead of oil formation, we sometimes obtained poorly crystalline material, which was almost amorphous. This type of "damage" inflicted on a crystalline powder was detected in the recorded X-ray powder pattern of the product. These products were devoid of any distinct peaks in the intensity vs. reflection angle plots as shown in Figure 3.1.

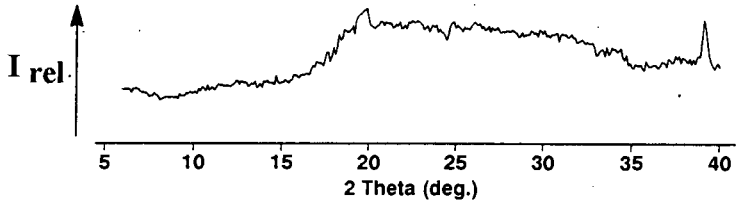


Figure 3.1: XRD powder pattern indicating amorphous structure. This example is the product of co-ground HMD3 + BC powders.

Table 3.2 : New phases identified in solid state co-grinding experiments.

Components	*M.P. (^{0}C)*
BC-Lac(210^{0}C) + TA(170^{0}C)	100
BC-Lac + CSA(200^0)	70
BC-Lac + L-MA(132^{0}C)	45

Had complex formation between a resolving acid and BC succeeded in the solid state, this may have been a suitable bypass to the lactam formation problem. Solid state co-grinding attempts with BC failed. BC-Lac formed some interesting complexes as shown in Table 3.2. The BC-Lac.L-MA

complex (indicated by XRD, microanalysis and melting point) was too unstable to continue experimentation. Interestingly the BC-Lac.CSA complex exhibited different morphology from the crystalline complex grown from solution, and the XRD patterns indicated different phases (see Figure 3.2).

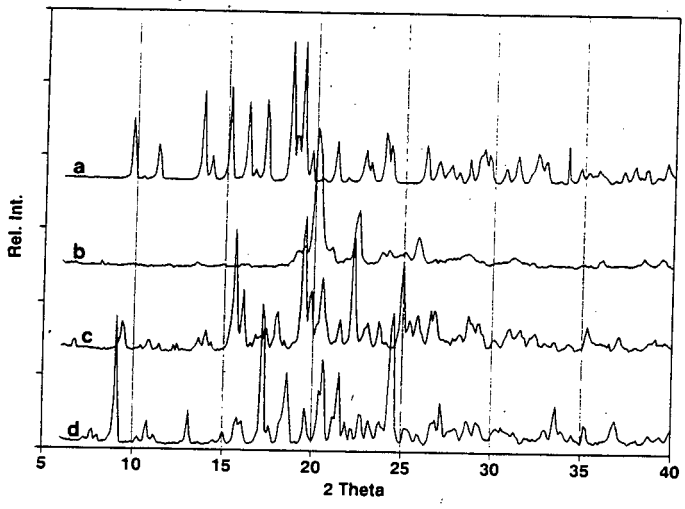


Figure 3.2 : XRD powder patterns of : a) CSA, b) BC-Lac, c) BC-Lac.CSA co-ground powders, and d) BC-Lac.CSA co-crystals grown from Toluene/Hexane solution

Sublimation Experiment: The BC-Lac.TA complex was obtained only after *co-melting* 2.0g BC-Lac with 1.53g TA. Subsequent separation was attempted by fractional sublimation after it was established that BC-Lac sublimes at 80°C under vacuum whereas TA remains a solid at this temperature. This was inspired by the recent reports of Ács *et al.* The Authors developed new methods of optical activation of racemic bases (liquids) based on the selective distribution of the enantiomers between a chiral solid and achiral vapour phases. The chiral solid phase was formed by tartaric acid (and its derivatives) and racemic bases. Upon heating in vacuo these solids released a portion of the bases. Both the distillate and the residue contained an optically enriched base mixture with each containing opposite configurations in excess[7].

The TA.BC-Lac complex melt was cooled and reground to a fine powder. The XRD powder pattern indicated a phase change relative to the summated phases of the two components. The powder was heated to 80°C under vacuum in a BÜCHI TO-51 heating gun (see Figure 3.3) and maintained at this temperature for 12 hours. 0.3g sublimate was collected on a cooler section of the gun; $[\alpha]_D = +5.3^0$ (Lit[8].= $+39^0$ for S-(+)-BC-Lac) giving only a 14% ee.

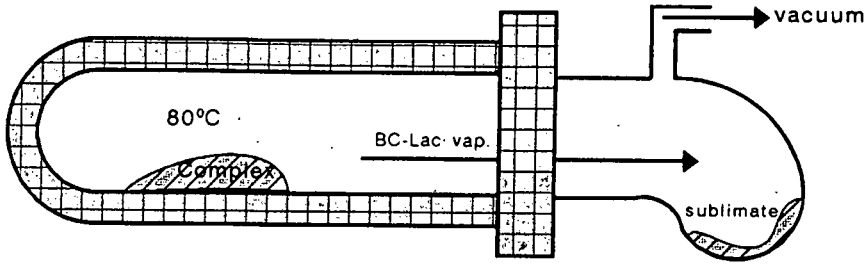


Figure 3.3 : Schematic diagram showing sublimation experiment with TA.BC-Lac complex using a BÜCHI TO-51 heating gun

In the interest of attaining the objective of this project the solid state reactions were not pursued. Purely from a point of view of effecting enantioselective recognition it was clear that fractional crystallisation was the method of choice, since by now resolution trials involving BC-Lac and GAM were proving to be successful. From a mechanistic point of view, however, these solid state experimental results are starting points for further investigations concerning molecular mobilities in solid state phase transformations.

3.3 Host-Guest Chemistry

Attempting to co-crystallise the host compounds HMD3, HMD5, or HMD6 with one of BC, BC-Lac or GAM was not successful. Suspending the host in hexane and allowing for selective inclusion by dissolving the "guest" (drug molecule) in the non-polar solvent was not possible due to the drugs being polar compounds. In the more polar solvents such as CH_3CN, host and guest crystallised out separately. This was detected mainly by the DSC traces of the precipitates showing no new melting points relative to the those of the individual components. The reason for this was not evident in the case of BC-Lac. The host compounds include mainly alcohols, ethers, ketones and esters (as mentioned in chapter 1), and seemingly not the more polar acids such as GAM. Added to this is the previously mentioned sensitivity of a host compound to the size and shape of the molecule it will include. It may simply be a problem of these drug analogues being too large for inclusion.

3.4 BC-Lac with TA[9]

Crystals of a 2:1 BC-Lac:TA complex were grown from a 4:1 molar ratio BC-Lac:TA solution in toluene and dry methanol. The toluene:methanol (85:15) ratio was critical for recovering the desired enantioselective complex with m.p. 126°C. Solutions allowed to crystallise rapidly readily

yielded a different complex of lower melt 100°C. The NMR spectra shown in Figure 3.4 confirm the species present in the high melt complex. Integration of the protons δ_H 2.43(1H, dd, *J* 8.6, 17.0Hz, C*H*CO, BC-Lac) and 4.54(2H, s, C*H*OH, TA) confirmed 2:1 BC-Lac:TA ratio.

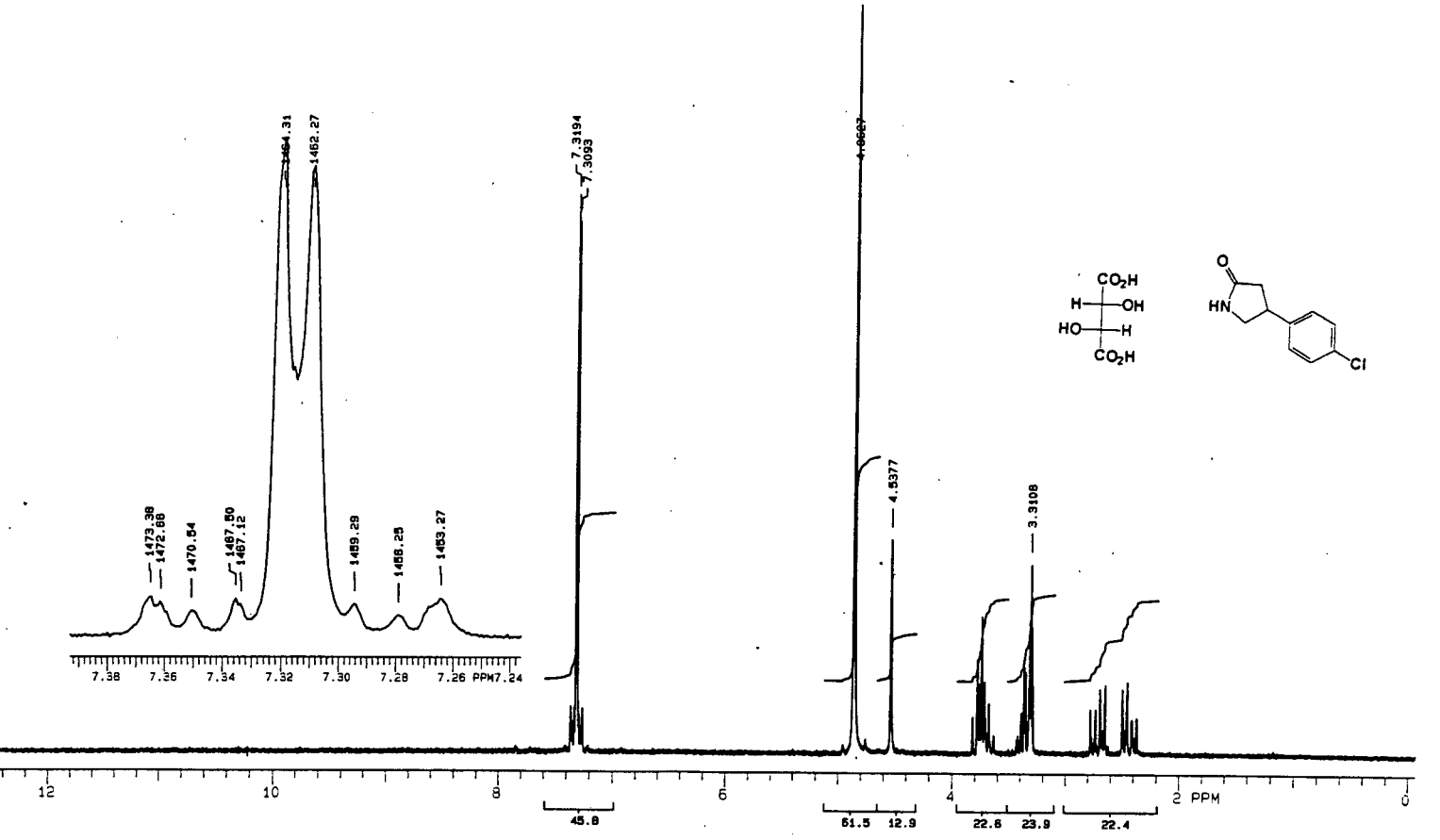


Figure 3.4 : NMR spectrum of BC-Lac.TA complex in CD_3OD.

On analysis of the crystal structure of the high melt complex, two (*R*)-(-)-BC-Lac molecules were found to complex to one (*2R,3R*)-(+)-TA molecule. Unfortunately no single crystals of the low melt complex were suitable for similar analysis. It was therefore not known whether this complex consisted of two (*S*)-(+)- or one (*S*)-(+)- and one (*R*)-(-)-BC-Lac molecule co-crystallising with TA. Crystal data of the high melt complex are given in Table 3.3.

Table 3.3 : Crystal data for BC-Lac.TA high melt complex

Molecular formula	$2(C_{10}H_{10}ONCl).C_4H_6O_6$
Space group	$P2_1$
a(Å)	10.074(2)
b(Å)	10.132(6)
c(Å)	12.238(6)
$\beta(^0)$	99.13(2)
V(Å^3)	1233(1)
Z	2
D_c(g.cm^{-3})	1.458
μ(MoKα) (cm^{-1})	0.32
F(000)	564
R	0.036

The absence of proton transfer distinguished these co-crystals from the diastereomeric salts normally formed between acids and bases. The lactam is too weak a base to be protonated in the presence of TA. It appears that similar problems were encountered in the resolution of 2-Phenylpyrrolidine with TA[4], as the resulting salt was recrystallised 9 times from EtOH until constant rotation was reached. Salt formation was evident though, as the amine was subsequently liberated by addition of NaOH.

In our complex, the selectivity of crystallisation appears to result from the chiral environment created by the TA molecules enveloping the BC-Lac molecules. An interesting hydrogen bonding interaction network was found in this complex. TA is a dicarboxylic acid. Each end of the acid finds itself facing the amido moiety of a lactam molecule and hydrogen bonding to it by means of a typical 8-membered ring $R_2^2(8)$ (graph set notation[10]) interaction. The TA and two distinct (R)-BC-Lac molecules form a "strand" as indicated in Figure 3.5

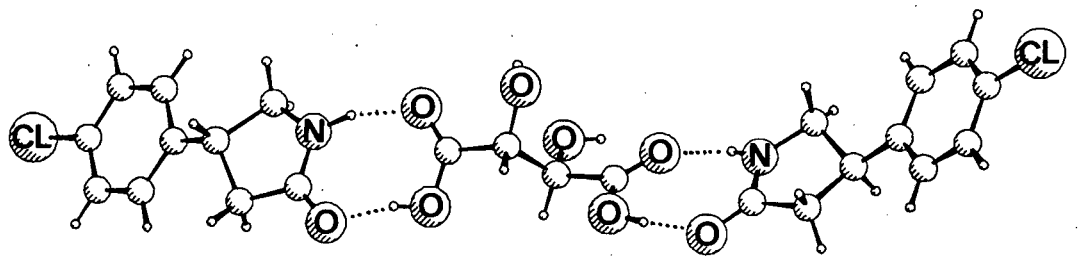


Figure 3.5 : The asymmetric unit in the TA.BC-Lac complex

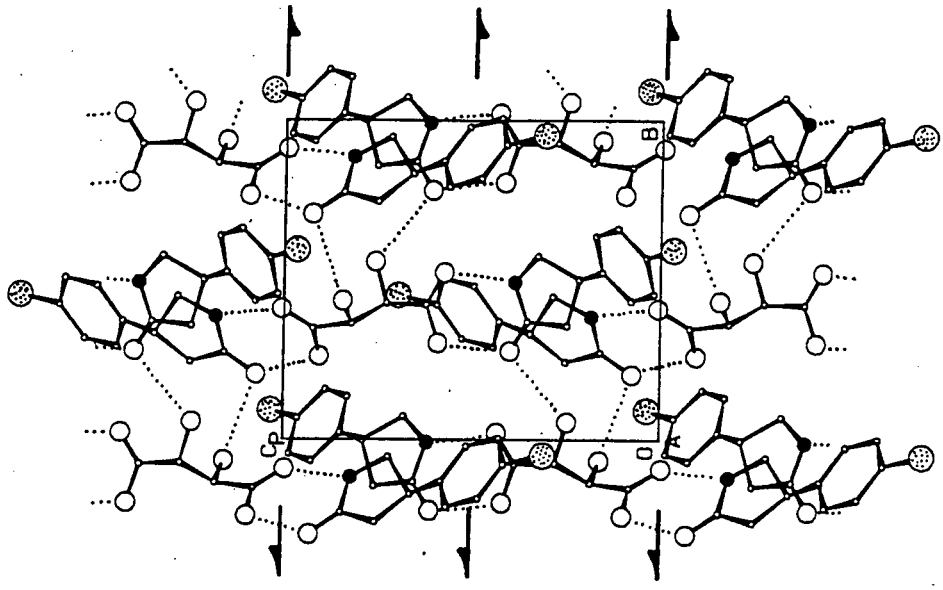


Figure 3.6 : Packing diagram of TA.BC-Lac complex as projected down [100]. Nitrogen and chlorine atoms are represented by solid and dotted circles respectively

These strands are interlinked by secondary hydrogen bonds as shown in Figure 3.6. Together these interactions form a chain of rings running parallel to the polar b axis in helical fashion as depicted in the schematic diagram in Figure 3.7. Two such distinct chains with a $C_2^1(7)$ "backbone" are interspersed throughout the structure

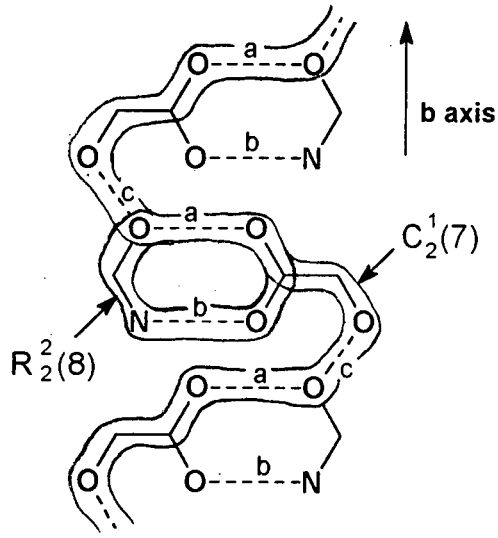


Figure 3.7 : Schematic representation of hydrogen bonding in the TA.BC-Lac complex. Two distinct hydrogen bonding columns are found parallel to the unique axis:

		Column 1:	Column 2
a	O...O	2.619(4)Å	2.559(4)Å
b	N...O	2.886(4)Å	2.992(4)Å
c	O...O	2.972(4)Å	2.935(5)Å

The bonds labelled a,b and c are indicated in the diagram.

Purity:

Enantiomeric purity was determined by using the same chiral BSA column as mentioned previously. The BC-Lac was separated from the complex by dissolving the latter in *n*-butanol and washing with a 1 *M* aqueous sodium bicarbonate solution. The *n*-butanol was then removed under

vacuum affording the pure BC-Lac. Elution times were *ca* 2 and 9 min for the S and R enantiomers respectively. Contamination with the S enantiomer was still detected, even after 3 recrystallisations. Optimisation of this procedure was not pursued as the resolution of BC via its synthetic precursor GAM was proving to be more successful.

3.5 References

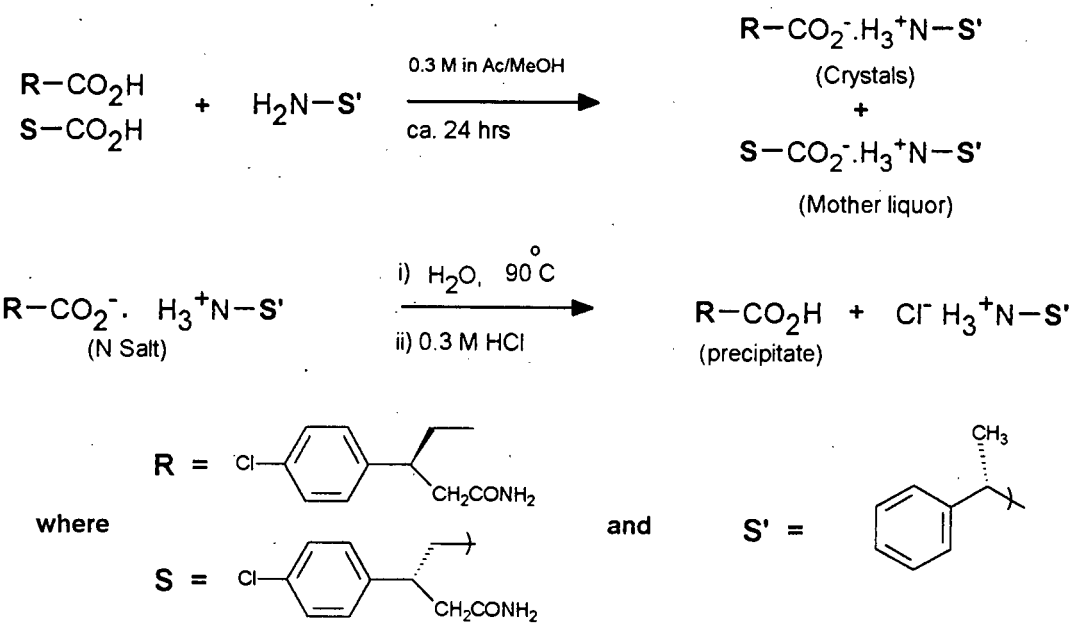
1. S. Ahuja, *Analytical Profiles of Drug Substances,* **vol. 14**, K. Florey, Ed. (Academic Press, New York (1985)), 538.
2. R. Adams, *J. Am. Chem. Soc.*, **81**, (1959), 4946.
3. D.R. Pilpauskas, K.D. Kopple, *Tetrahedron,* **32**, (1976), 2245.
4. F. Morlacchi, V. Losacco, V. Tortorella, *Gazz. Chim. Ital.*, **105**, (1975), 349.
5. Y. Kawanami, Y. Ito, T. Kitagawa, Y. Taniguchi, T. Katsuki, M. Yamaguchi, *Tetrahedron Lett.*, **25**, 857.
6. H.W. Krause, C. Meinicke, *J. Prakt. Chem.*, **327**, (1985), 1023.
7. M. Ács, T. Szili, E. Fogassy, *Tetrahedron Lett.*, **32**, (1991), 7325.
8. A. Shoenfelder, A. Mann, S. Le Coz, *Synlett*, **1**, (1993), 63.
9. This section of the thesis has been accepted for publication: "Resolution of optical isomers of 4-amino-*p*-chlorobutyric acid lactam by co-crystallisation", M.R. Caira, L.R. Nassimbeni, J.L. Scott, A.F. Wildervanck, *J. Chem. Crystallogr.*, in press (ref. no. JCCA418).
10. J. Bernstein, R.E. Davis, L. Shimoni, N. Chang, *Angew. Chem. Int. Ed. Engl.*, **34,** (1995), 1555.

4. RESOLUTION OF GAM WITH MBA

4.1 Experimental Procedures

4.1.1 Resolution of GAM

The following scheme shows the procedures for optical resolution of GAM.



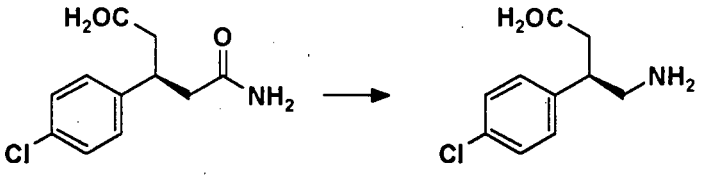
GAM (18g, 74.4mmol) was dissolved in methanol (250ml) and warmed to *ca* 60°C. (*S*)-(-)-MBA (9.48ml, 74.4mmol) was carefully added via a graduated pipette, and the warm solution stirred for a few minutes. The resulting 1:1 GAM.MBA solution was cooled to room temperature and left standing in a dark place* for *ca* 24 hours affording colourless plate-like crystals (9.86g, 73% yield as calculated for one enantiomer). The crystals were isolated by filtration, dried and dissolved in water (200ml) by heating to *ca* 90°C. 3M ** HCl (90.5ml) was added at this temperature after which the solution was allowed to cool to room temperature (or even refrigerated). The precipitate was filtered at the pump, washed with water and vacuum dried to give (*R*)-(+)-GAM (6.23g, 95% yield, 69% overall yield). The mother liquor of the crystallisation was isolated and concentrated further by evaporation. The resulting precipitate was removed from the solution by filtration yielding 12.6g p

* When exposed to light for several hours these solutions appeared to darken.

** The acid concentration can vary. It is important to add 1 molar equivalent.

salt (still contaminated with n salt by a percentage dictated by the eutectic). The p salt was then purified by subsequent recrystallisations from an ethanol / ethyl acetate solution.

4.1.2 Conversion of (*R*)-GAM to (*R*)-baclofen



To a solution of sodium hydroxide (2.8g, 69.4mmol) in water (50ml) was added (*R*)-GAM (6.57g, 27.21mmol) at ca. 20°C. A 10.8% aqueous solution of sodium hypochlorite (28.3g) was then added over 2.5h at 0°C via a dropping funnel. The solution was stirred for a further 12h at room temperature (ca. 20°C) after which time it was carefully neutralised (pH 7.5) with dilute hydrochloric acid. The precipitate was filtered off at the pump, washed with water and acetone. The precipitate was then boiled in methanol to remove the last traces of GAM and filtered to yield pure (*R*)-baclofen (1.3g, 22% yield). The mother liquors were reduced in volume *in vacuo* to yield more product which was boiled in methanol and filtered to give another 2.05g of (*R*)-baclofen (3.35g total, 57.6% yield).

A portion of (*R*)-baclofen was then converted to its hydrochloride salt by treatment with conc. HCl.

4.2 Analyses

4.2.1 NMR

The GAM : MBA ratio was initially established by NMR spectroscopy. The sample was run in CD_3OD (Figure 4.1 (a)). The integration of the two protons bonded to the chiral carbons viz. δ_H 4.4(1H, q, Ph-C*H*(CH_3)NH_2) and 3.5(1H, m, -C*H*(CH_2CONH_2)(CH_2CO_2H)) provided first evidence of a 1:1 ratio. The final product, (*R*)-(+)-GAM, was also characterised by NMR. The spectrum was identical to that of racemic GAM (starting material), proving the product to be the free acid. (Figure 4.1 (b)).

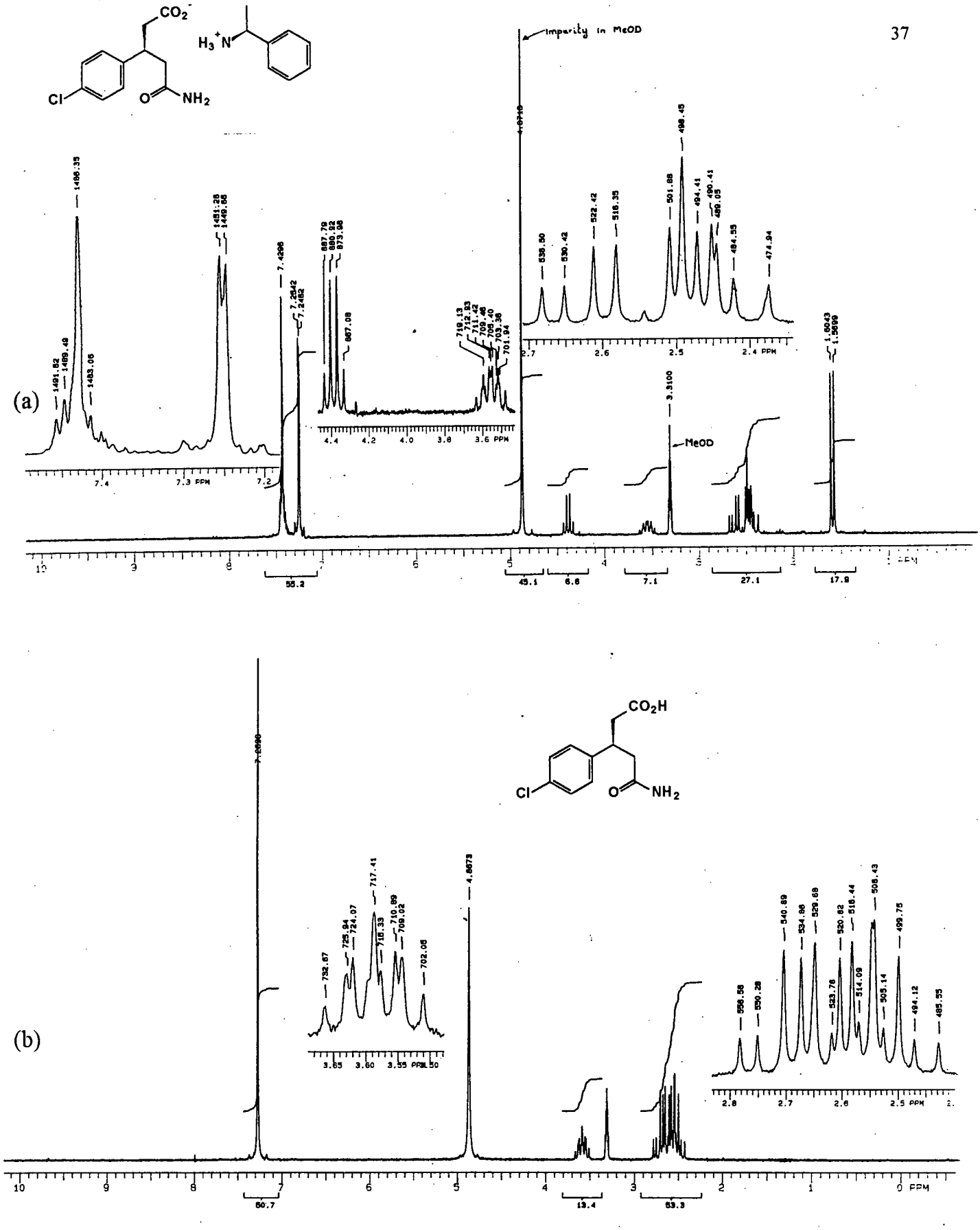


Figure 4.1: NMR spectra of a) n salt b) (*R*)-(+)-GAM

4.2.2 Thermal analysis

Differential Scanning Calorimetry (DSC) showed the *same* melting point for both diastereomeric salts (187^{0}C) by a characteristic broad endotherm (Figure 4.2). The DSC data of 16 conglomerate diastereomeric salt pairs recently analysed by Kozma *et al.* indicated that an efficient resolution can be expected if there is at least a 20^{0}C difference between the melting points of these salts[1]. With a melting range of *ca* 25^{0}C it was difficult to distinguish between the p and n salts by thermal analysis. Figure 4.2 also shows a DSC trace of (-)-GAM.MBA (p salt) mixed with (+)-GAM.MBA (n salt). The approximate ratio of the two salts are 87:13 p:n (corresponding to the subsequently established eutectic composition). Either salt, when contaminated with the opposite diastereomer, exhibited a lowering of the melting point. Attempts at establishing a melting point phase diagram failed due to the aforementioned broad endotherm problem. Both racemic and enantiopure GAM melt at 173^{0}C, and the (*R*)-Baclofen at 205-208^{0}C.

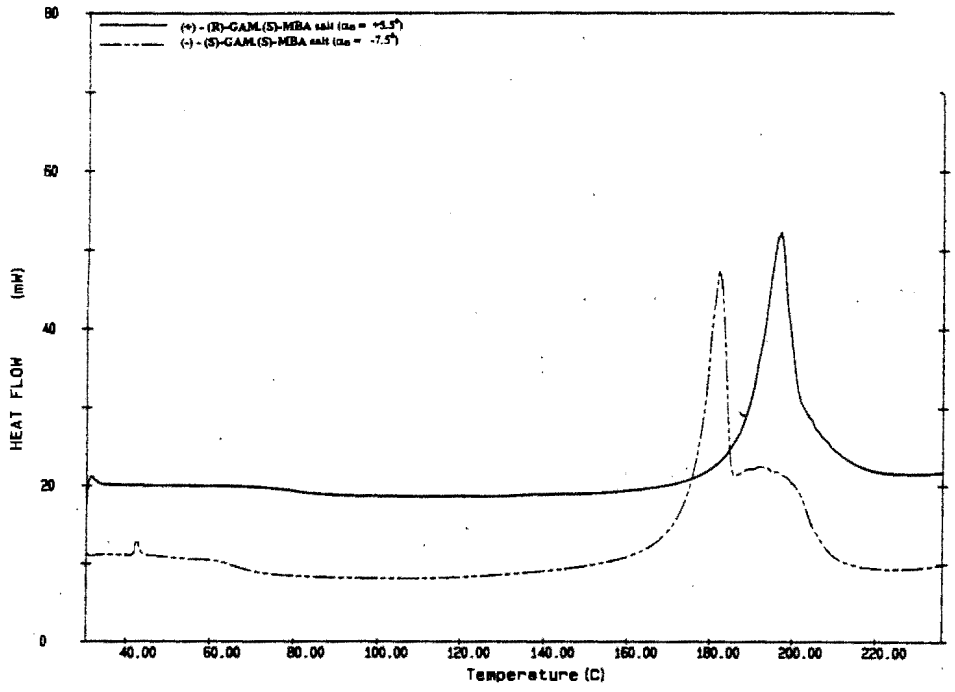


Figure 4.2 : DSC trace of the n salt (solid line) and of the p salt (87%) contaminated with n salt (13%) (dotted line).

4.2.3 Microanalysis

	%C	%H	%N
Calc. for salt :	62.89	6.34	7.72
Found :	62.37	6.40	7.65
Calc. for (*R*)-(+)-GAM	54.67	4.96	5.79
Found :	54.62	4.98	5.72
Calc. for (*R*)-(-)-Baclofen:	56.21	5.66	6.56
Found :	56.30	5.78	6.52

4.2.4 Polarimetry

Optical rotation measurements yielded the results shown in Table 4.1.

Table 4.1 : $[\alpha]_D$ measurements (100mg in 10ml MeOH)

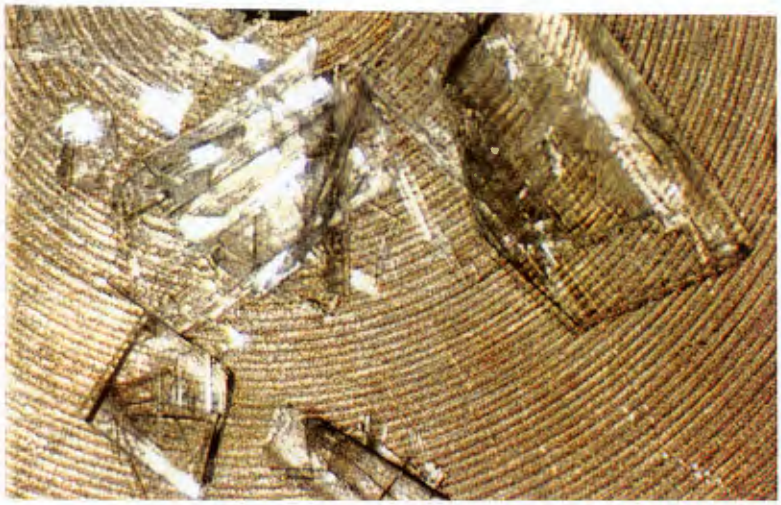
λ(nm.)	*n salt*	*p salt*	*(R)-(+)-GAM*
589	$+5.5^0$	-12.4^0	$+9.5^0$
546	$+6.8^0$	-14.3^0	$+11.0^0$
436	$+11.1^0$	-25.5^0	$+18.8^0$
365	$+16.0^0$	-42.6^0	$+30.4^0$

These values remained constant after further recrystallisations. The error for these low rotational values was 0.5^0.

4.2.5 Crystal structures

Suitable single crystals of the salts were grown by slow evaporation from a methanol solution as described previously. Crystal morphology of the two salts differed markedly (see Figure 4.3). The thin plate-like crystals of the more stable salt contrasted with the long rod-like "fibres" of the more soluble salt. A suitable crystal of each salt was selected, cut to size, and mounted on a glass fibre for Oscillation and Weissenberg photography for preliminary determination of cell parameters and space group data. Single crystals of the p salt proved to be unstable when removed from the mother liquor and were therefore mounted in a 0.3 mm. id. Lindemann capillary tube. The lability and poor crystallinity of the p salt made data collection extremely difficult. Two sets of reflection data were collected from two different crystals and in both attempts less than half the total number of reflections had an intensity $I > 2\sigma(I)$.

(a) 12X



(b) 45X

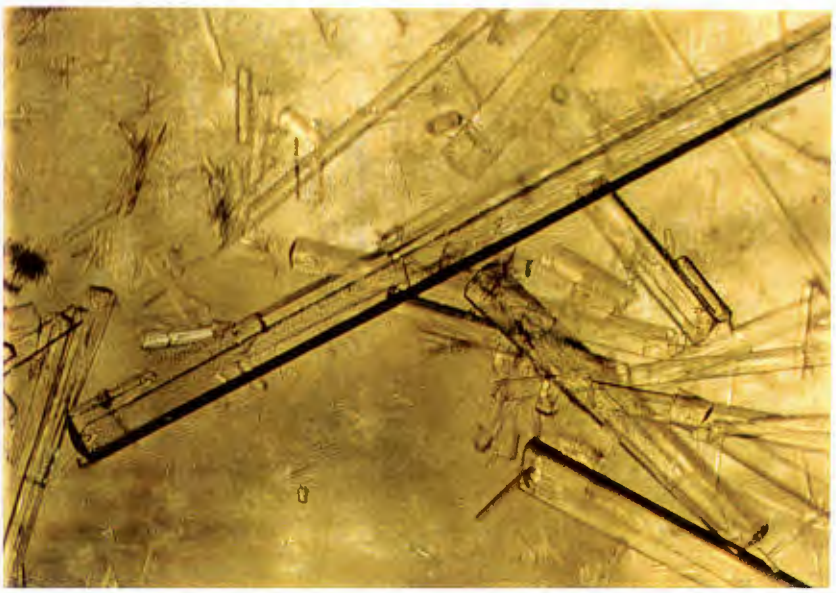


Figure 4.3 : (a) Plate-like crystal of the n salt, (b) long needles of the p salt in mother liquor.

N Salt: The first oscillation photograph of a single crystal of this compound showed no symmetry. Reflections in the zero-level Weissenberg photograph were observed to be mirrored around the mutually perpendicular axes. Together, these photgraphs indicated 2/m Laue symmetry. β was measured from a second zero-level Weissenberg photograph with the crystal remounted along the unique axis. Upper level Weissenberg photography showed no absences amongst the general reflections indicating a primitive lattice. No systematic absences amongst the h 0 l reflections proved

the absence of any glide planes. Thus the only conditions for systematic absences were: 0 k 0, k = 2n + 1, confirming the polar space group $P2_1$.

The structure was solved and refined as previously described (Sect. 2.3.6). In contrast to SHELX-76, the updated refinement program SHELX-93 recognises polar space groups and applies the appropriate polar axis restraints[2]. Anisotropic thermal parameters were assigned to all non-hydrogen atoms. All H atoms were located in difference electron density syntheses and were placed in geometrically generated positions (C-H = 1Å)and refined with positional parameters riding on the parent atom. Variable isotropic thermal parameters were assigned for chemically equivalent groups. The $-NH_3^+$ hydrogen atoms were allowed to refine without restraints.

P Salt: Preliminary space group determination proceeded similarly to the above method described for the n salt. This time the unique axis coincided with the elongated axis of the crystal shown in Figure 4.3. The oscillation photograph showed a mirror plane and subsequent establishment of the crystal system and space group was similar to that of the n salt. Spurious reflections indicating twinned crystals were often observed on photographs. Structure solution proved to be non-trivial. Both refinements using the two different sets of collected data showed disorder in the resolving agent's phenyl ring. All reflections with $I < 2\sigma(I)$ were omitted. No hydrogen atoms could be located, and placing these in geometrically idealised positions increased the R value markedly. Phenyl rings were refined as idealised hexagons with common variable isotropic thermal parameters. Refinement with the carbon atoms of ring A included, gave rise to peaks in the electron density surrounding the phenyl ring suggesting an alternative orientation (ring B) inclined at 72^0 to the plane of ring A. This was modelled by allowing two possible orientations of the phenyl ring whose site occupancy factors were refined to 0.52 and 0.48 for ring A and B respectively.

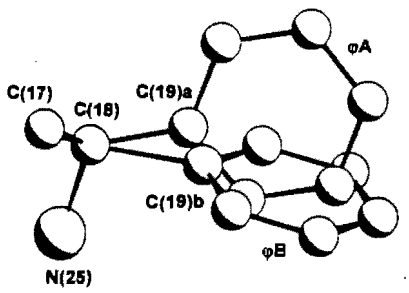


Figure 4.4 : Molecular diagram of (*S*)-(-)-MBA in the p salt showing disorder in the phenyl ring.

Results. Details of the crystal data and structure refinement of the two salts appear in Table 4.2. Fractional atomic co-ordinates, bond lengths, bond angles, selected torsion angles and structure factor data appear in Tables A.1 to A.8 in the Appendix.

Table 4.2: Crystal data and structure refinement for GAM.MBA

	(R)-GAM.(S)-MBA (n salt)	*(S)-GAM.(S)-MBA (p salt)*
Empirical formula	$C_{19}H_{23}ClN_2O_3$	$C_{19}H_{23}ClN_2O_3$
Formula weight	362.84g/mol	362.84g/mol
Temperature	293(2) K	293(2) K
Wavelength	0.71069 Å	0.71069Å
Crystal system	Monoclinic	Monoclinic
Space group	$P2_1$	$P2_1$
Unit cell dimensions	a = 5.728(2) Å	a = 14.344(3)Å
	b = 20.671(3) Å	b = 5.474(1) Å
	c = 8.354(1) Å	c = 14.434(2)Å
	β = 107.39(2)^0	β = 114.75(2)^0
Volume	943.9(4) Å^3	1029.4(3) Å^3
Z	2	2
Density (calculated)	1.277 g.cm^{-3}	1.171 g.cm^{-3}
Density (measured)	1.269 g.cm^{-3}	*
Absorption coefficient	0.222 mm^{-1}	0.204 mm^{-1}
F(000)	384	384
Crystal size	0.4 x 0.5 x 0.3 mm	0.3 x 0.3 x 0.3 mm
Theta range for data collection	1.97^0 to 24.97^0	1.55^0 to 24.99^0
Index ranges	-6 ≤ h ≤ 6	-15 ≤ h ≤ 15
	-24 ≤ k ≤ 0	0 ≤ k ≤ 6
	0 ≤ l ≤ 9	0 ≤ l ≤ 17
Reflections collected	1837	2110
Independent reflections	1703 [R(int) = 0.0301]	2026 [R(int) = 0.0383]
Data / restraints / parameters	1703 / 6 / 253	2026 / 0 / 138
Final R indices [I>2σ(I)]	R1 = 0.0296, wR2 = 0.0938	R1 = 0.1258, wR2 = 0.3111
R indices (all data)	R1 = 0.0387, wR2 = 0.1075	R1 = 0.2244, wR2 = 0.3134
Flack parameter x	-0.12(9)	0.0(5)
Largest diff. peak and hole	0.202 and -0.236 e.Å^{-3}	0.499 and -0.345 e.Å^{-3}

* The density of the p salt was difficult to measure due to the cracking of these crystals once removed from the mother liquor.

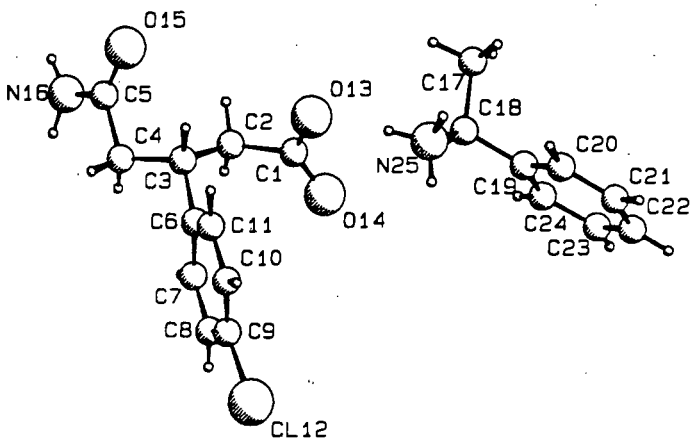


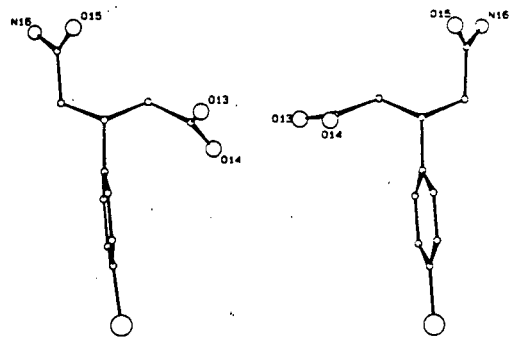
Figure 4.5 Crystal structure diagram of GAM.MBA (n salt) showing numbering scheme.

Absolute configuration:

Knowing the absolute configuration of (*S*)-(-)-MBA, R and S configurations were assigned to dextro- and levorotatory GAM in the n and p salts respectively. Comparison of the Flack absolute structure parameter with its estimated standard deviation (esd), also confirmed the correct assignment as its value was close to zero[3]. Assignment of absolute configuration in the p salt was more difficult due to the high thermal motions of both the amide and carboxylate moieties (see Table A.4). By means of electron density mapping, (*R*)- and (*S*)-GAM, in ionic form, can only be differentiated from one another by the difference in the X-ray scattering powers of an oxygen and nitrogen atom. Assignment was therefore made by means of hydrogen bonding characteristics and supplementary polarimetry experiments. For the GAM isolated from the latter discussed salt, α_D = -9.5^0 (MeOH). This confirmed the two crystalline compounds to be diastereomers (see Table 4.1).

Conformation

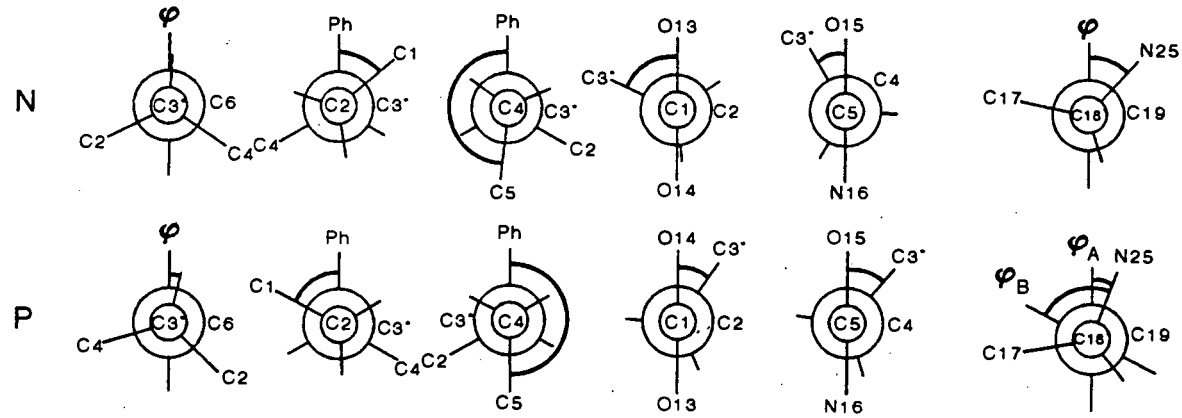
As evident from Figure 4.6 the conformations of GAM's enantiomers in the two diastereomeric salts are essentially similar. Ionisation in the n salt was confirmed by the equidistant C-O bond lengths in the carboxylate moieties and three hydrogens were located in tetrahedral geometry around the nitrogen atom N(25). Proton transfer in the p salt could not be readily justified since the C(1)-O(13) C(1)-O(14) bond lengths, 1.30(2) and 1.22(3)Å respectively, differed significantly. Due to high e.s.d's no conclusion could be drawn. Table 4.3 shows Newman projections of some of the torsion angles defining the molecular shapes.



(*R*)-(+)-GAM (in n salt) (*S*)-(-)-GAM (in p salt)

Figure 4.6 : Conformation of the enantiomers of GAM . Both are viewed down a line perpendicular to the C(3)-C(6) bond. lying in the plane bisecting ∠ C(2)-C(3)-C(4).

Table 4.3 : Newman projections showing representative torsion angles in the diastereomeric salts. (see Fig. 4.5 for atom numbering scheme)



	τ/deg					
N	-3.8(5)	-49.6(3)	174.1(2)	-65.8(3)	-29.8(4)	-42.1(4)
P	-13(1)	62(1)	-179(2)	34(2)	40(4)	A -20(4) B -82(3)

Relative to the C(3)-C(6)...C(9)-Cl(12) axis, bonds C(4)-C(5) and C(1)-C(2) are parallel and oblique respectively, with C(3)*-H bond syn-periplanar to the phenyl ring. This characteristic conformation was similarly found in the crystal structure of the (*R*)-(-)-BC.hydrochloride salt[4]. Comparing the resolving agent's conformation in the two salts is complicated by the disorder found in the amine's aromatic ring carbons. The C(18)-C(19)B bond length (1.72Å) and N(25)-C(18)-C(19)B bond angle

(96.7^0) (Fig. 4.4) make no real chemical sense, and are clearly an artifact of the poor intensity data. Added to this is the fact that the plane of ring B is almost parallel to the polar 5.72Å b axis ($\angle\varphi$B,b axis = 5.5^0) resulting in 3Å carbon...carbon contacts. This phenyl ring was therefore omitted in subsequent packing diagrams to avoid unnecessary confusion. The characteristic torsion angle N(25)-C(18)-C(19)-C(20) shown in Table 4.3 shows a disfavoured syn-periplanar N(25)...φA interaction in this p salt as opposed to the synclinal N(25)...φ interaction in the n salt.

Hydrogen Bonding:

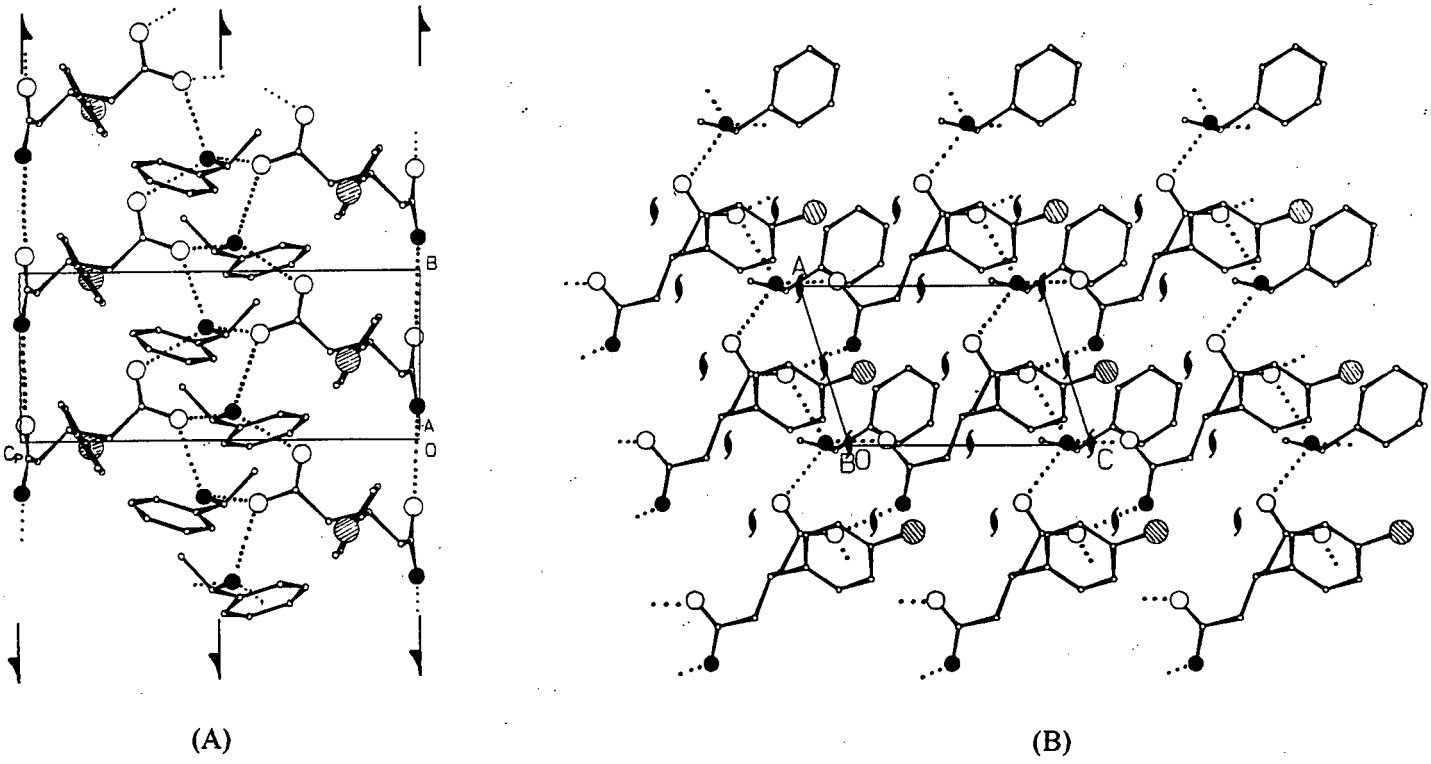
Brianso *et al.* have reported several salt structures involving MBA as resolving agent and have found systems of columns built up of chains of hydrogen bonds wrapped around a helical 2_1 axis[5,6,7]. Studying the two salt structures of MBA with GAM, two quite distinct patterns are observed. Table 4.4 lists the hydrogen bonds found in the two crystal structures and Figure 4.7 shows packing diagrams illustrating these.

Table 4.4 : Hydrogen Bonds

	D-H....A/Å	D-H/Å	D....A/Å	H....A/Å	D-H....A/deg
		N Salt			
a	N(25)-H(253)...O(13)	0.94(3)	2.720(3)	1.79(3)	173(4)
b	N(25)-H(251)...O(14)^{i}	0.96(4)	2.763(3)	1.81(3)	173(3)
c	N(25)-H(252)...O(15)^{ii}	0.95(3)	2.806(4)	1.86(3)	175(3)
d	N(16)-H(161)...O(14)^{iii}	0.84(5)	2.962(4)	2.16(5)	159(4)
		P Salt			
a	N(25)...O(13)		2.71(2)		
b	N(25)...O(13)^{iv}		2.80(1)		
c	N(25)...O(14)^{v}		2.82(2)		
d	N(16)...O(15)^{vi}		2.93(2)		
	N(16)...O(15)^{v}		3.26(6)		

(i) x-1, y, z (ii) x-1, y, z-1 (iii) x+1, y, z+1
(iv) 1-x, y-½, 1-z (v) x, y-1, z (vi) -x, y-½, -z

In both structures the ammonium cation forms three hydrogen bonds to various oxygen atoms of GAM. No hydrogens were located in the p salt so that the ensuing discussion will be in terms of donor....acceptor interactions only (despite having located the hydrogens in the n salt) so that comparisons can be made.



(A) (B)

Figure 4.7 : Packing diagrams of A) p salt viewed as projected down [100] and B) n salt as projected down [010]. Nitrogens are represented as filled circles and Chlorine as shaded circles.

The p salt indeed shows such chains consisting of two chemically distinct hydrogen bonds a and c (see Figure 4.8) linking together the carboxylate anions of vertically (along b) stacked GAM molecules. The two screw-related chains are interlocked by a third hydrogen bond b, altogether composing a "chicken wire" structure: a two-dimensional network of rings that have b in common. Complementing this we find the amide moieties of the GAM molecules facing one another from opposite sides of a 2_1 axis, once again forming a helical chain of hydrogen bonds, d and e.

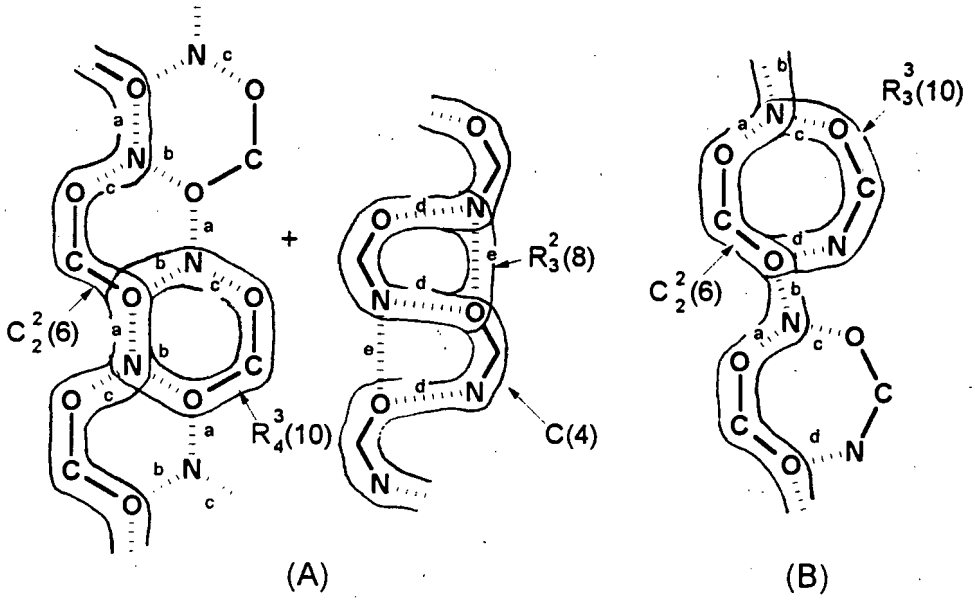


Figure 4.8 : Schematic representation of the hydrogen bonding found in the (A) p salt and (B) n salt. Some of the defining patterns are annotated by graph set notation

In contrast to the crystal's hydrogen bonding network running parallel to the 2_1 axis, the n salt (the more crystalline salt) crystallises in distinct layers, perpendicular to the 2_1 axis, alternately "glued" together by a web of hydrogen bonds forming a "chain of rings". Here the amide and carboxylate moieties are neatly locked around an ammonium cation, the latter in turn interlinking the rings so formed by a fourth N-H...O hydrogen bond. One notes the similarities/differences in the two patterns by means of a graph set notation. On a secondary level notation (i.e. N_2 (ac) and N_2 (ab) for the p and n salts respectively) one can delineate $C_2^2(6)$ patterns for both. At higher level notations when incorporating the characteristic ring-like structures the graph set notations, $R_4^3(10)$ and $R_3^3(10)$ for the p and n salts respectively, differ. To summarise: the n salt has ring structured carboxylate...ammonium...amide interactions whereas the p salt has separate ring structured carboxylate...ammonium...carboxylate and amide...amide interactions.

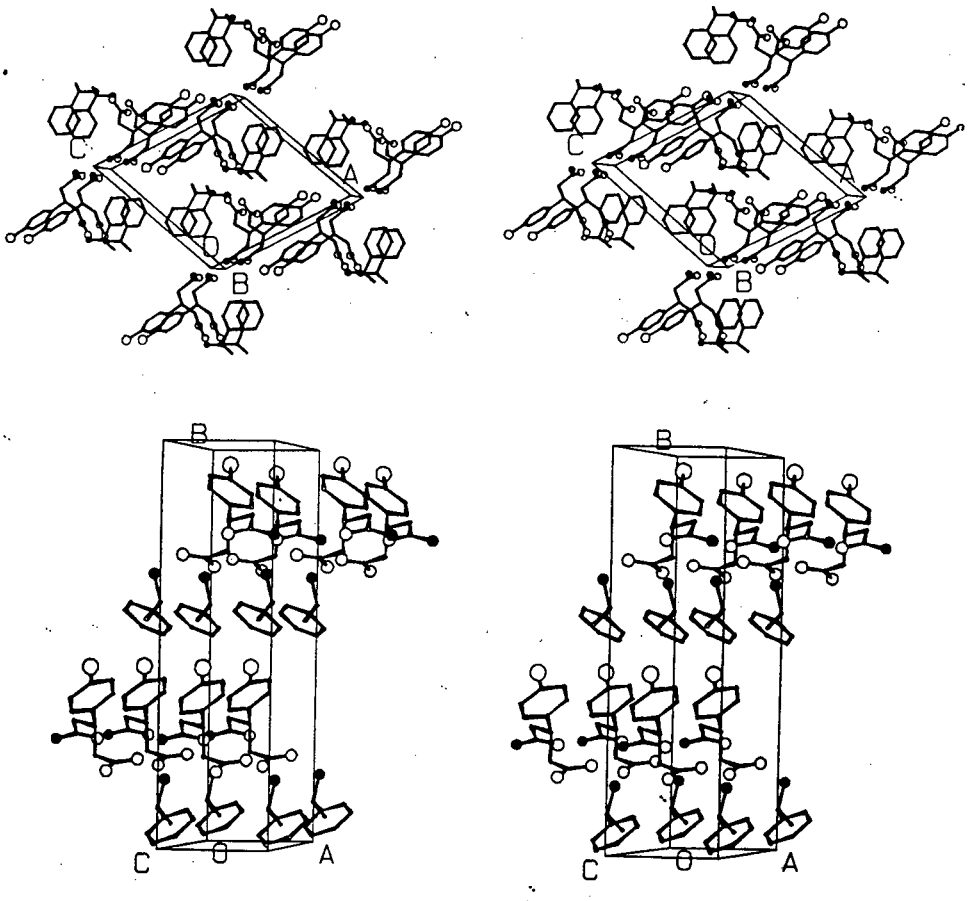


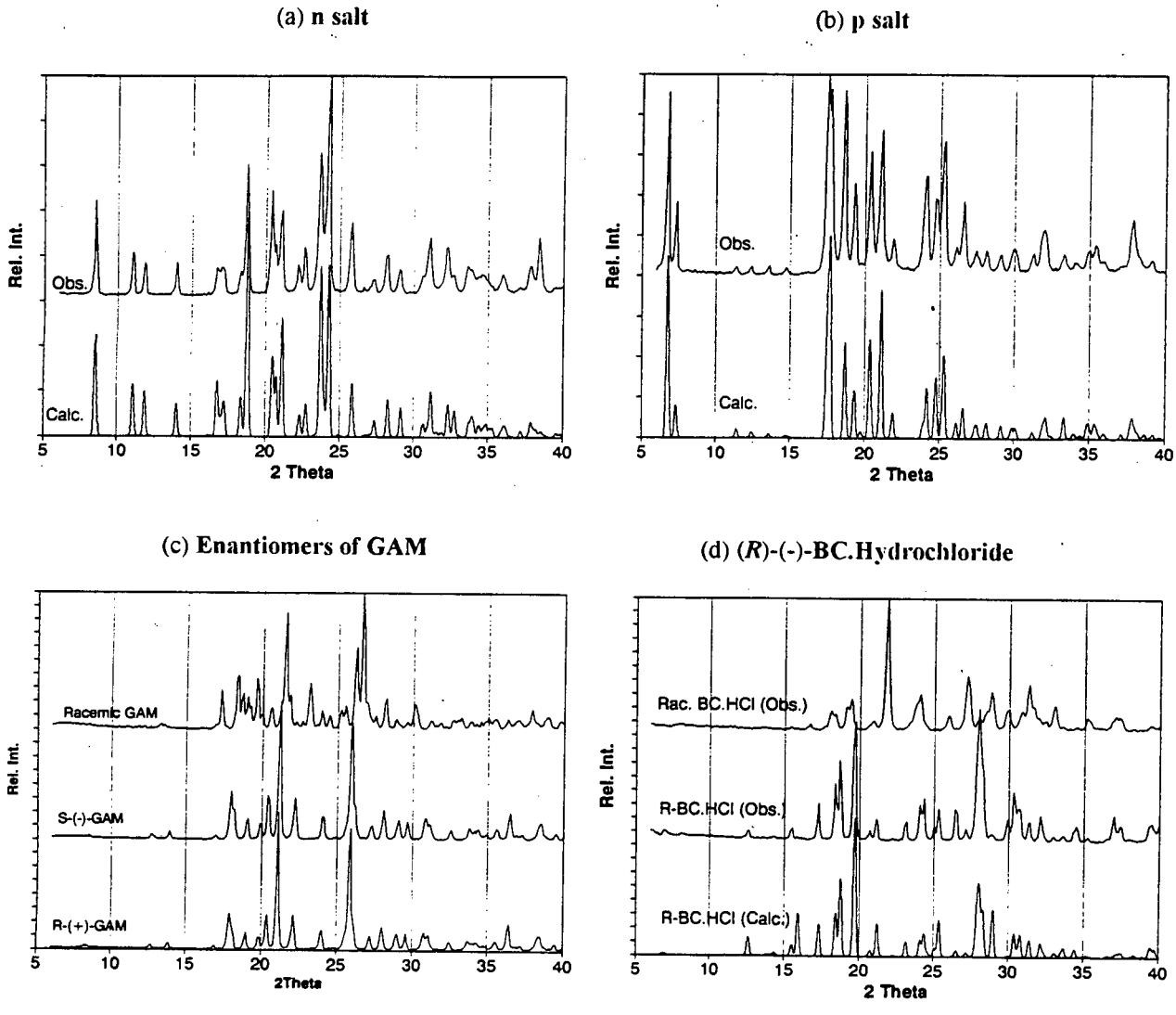
Figure 4. 9 : Stereo diagrams showing A) an inclined view down the unique axis of the p salt with the helical N..O interaction pattern. B) The distinct layers found in the n salt. Nitrogen atoms are represented by filled circles

4.2.6 X-Ray powder Diffractometry

Figures 4.10(a) and (b) show calculated and observed XRD powder patterns of the two diastereomers from large scale (typically 10g salt) separations. The calculated patterns are based on the data from the single crystal X-ray analyses. This was additional proof that the n salt was not contaminated (within a 5% detection limit) with its diastereomeric counterpart due to the intense peaks in the p salt's powder pattern not having counterparts in that of the n salt. Figure 4.10(c) indicates that (±) GAM crystallises as racemic crystals, since its crystal structure differs from those of its R and S enantiomers. It must be emphasised here that this R enantiomer was isolated from the p salt that remained in the mother liquor after removal of the n salt precipitate. The p salt was purified by using a different solvent system (ethanol and ethyl acetate, as described in 4.1.1).

The crystal structure of (*R*)-Baclofen Hydrochloride (R-BC.HCl) has been published[4]. Figure 4.10(d) shows the good agreement between the powder pattern computed from the published data and the powder pattern measured from our sample of R-BC.HCl. The intense peaks in the powder pattern of racemic BC.HCl do not have counterparts in the R-BC.HCl powder pattern. It may be necessary to point out that the "ideal" powder pattern as calculated by LAZY PULVERIX relies on complete random distribution in particle orientation. This condition is not met when particles take on a preferred orientation due to their non spherical morphologies. Throughout the powdered sample, certain crystal planes will be less exposed to the X-ray radiation than others. Intensity discrepancies in Figures 4.10 (a) - (d) can generally be attributed to this effect.

Figure 4.10: XRD Spectra of :



4.2.7 HPLC

A sample of (*R*)-Baclofen as converted from our separated (*R*)-GAM was submitted to Fine Chemicals Coorporation for Chiral High Performance Liquid Chromatography analysis on a (D)-Penicillamine column (2 mmol aq $CuSO_4$ mobile phase). The result indicated an enantiomeric excess of 99.7%.

4.3 Solubility Diagram.

The possibility of scaling up this separation process for industrial purposes prompted the need to optimise the crystallisation conditions such that yield and purity were maximal. In the absence of either salt being solvated, dissolution - crystallisation equilibria were demarcated by concentration vs. diastereomeric salt composition plots as described in section 1.2.1.2 . Concentrations at 24°C of the saturated solutions of p and n salts were determined by UV spectroscopy, using a Philips PU8700 series UV/visible spectrophotometer. Standard solutions were made in the concentration range 0.25-1.5 mg/(ml solution). The linear relationship A = 1.050C (A = absorbance and C = concentration in mg/(ml solution)) was established by measuring absorbances at $\lambda_{max.}$ = 260.6nm (correlation coefficient r = 0.9998). From the measured absorbances of solutions saturated at 24°C and diluted 1:100 the solubilities (in Methanol) were calculated to be:

p salt 136 ± 5 mg/(ml solvent)

n salt 32 ± 1 mg/(ml solvent)

A preliminary eutectic composition was established by measuring the optical rotation of a solution saturated with both salts.

$$[\alpha]_D = -9.4 \pm 0.5^0, \qquad C = 152 \pm 5 \text{ mg/(ml solvent)}$$

Using the optical rotation values listed in Table 4.1 and assuming salt composition directly proportional to rotatory power† this constituted a 84:16 p:n ratio. Four extrapolated points with salt ratios $0 < P < 84 : 100 > N > 16$ and corresponding concentrations $32 < C < 152$ mg/(ml solvent) were calculated. Four 5 ml methanol solutions were made up in accordance with the latter calculated

† This assumption is valid if the p and n salts (dissolved in MeOH) are completely unassociated with one another. This was confirmed within the large error of low optical rotational values (typically ±2° for $-3^0 < [\alpha]_D < +3^0$).

values, adding to these a marginal excess of n salt to ensure saturation of this less soluble component after equilibration. Complete dissolution of the p salt was assumed in the specified composition vs. concentration range.

Mass of salt in 5ml (MeOH)/mg		*C / mg.ml^{-1}*	*Composition*	
N	P		N	P
250	75	44	0.34	0.66
271	179	65	0.55	0.45
250	300	87	0.69	0.31
176	499	117	0.85	0.14

By measuring the densities of the above solutions, concentrations could be expressed in terms of %mass. ($\rho = 3.43x10^{-4}C + 0.786$ mg/ml., correlation coefficient r = 0.997).

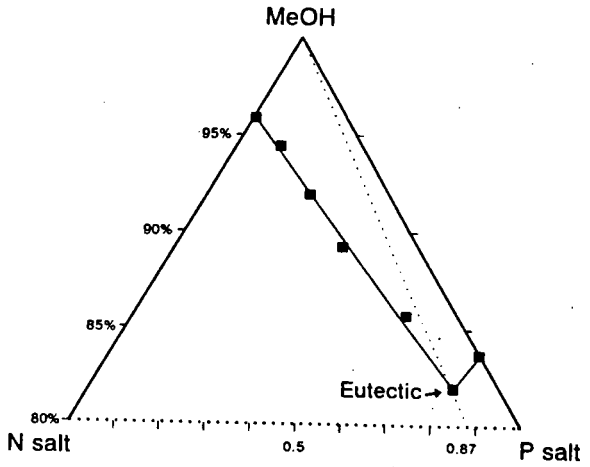


Figure 4. 11 : Solubility diagram showing phase equilibria for the n and p salts dissolved in methanol

Intersection of the "best fit" line through the tabulated data points (as transferred to a triangular phase diagram) with the 152mg/ml (81.8% by mass) horizontal, gave a 87:13 p:n eutectic composition. In theory it would therefore be possible to obtain a 87% recovery of (*R*)-(+)-GAM from the racemic starting material. This is extremely high by many separation standards and is therefore suited to an industrial scale process.

4.4 Possible structural evidence for the selectivity.

The most intriguing studies are those that have probed the crystal structures of diastereomeric salts by X-ray crystallography, such as the studies conducted by Larsen *et al.*[8,9], and Yoshioka *et al.*[10] Various attempts to answer this daunting question have appeared in the literature from time to time.

Zingg *et al.* conducted a careful study of the relations between structure and energetics of association of stereoisomeric salts of mandelic acid with MBA, ephedrine, and pseudoephedrine in the crystalline state and in solution[11]. Physical properties such as heats of fusion, heats of solution, heats of protonation, dissociation constants, and equivalent conductances of the stereoisomeric salts were carefully measured, giving rise to some interesting correlations between these properties and observed selectivities. The concluding remarks of the authors, however, were that they "....were unable to provide a complete structural interpretation of the ion-pairing behaviour, even for this carefully chosen system" (Zingg *et al.*[11]).

Crystalline phase interactions of small molecules.

In terms of large molecular structures exhibiting chiral discrimination when reacted together with racemic mixtures of small chiral molecules, the problem is simplified by rigidity of a "host" with a chiral "receptor" site in which only one enantiomer of the "guest" will fit preferentially. The preferential formation of one diastereomeric salt between the large acid lasalocid and various MBA derivatives was successfully rationalised by this lock and key analogy[12]. Three oxygen atoms of this large cardiotonic agent hydrogen bond to the ammonium cation of MBA and the steric bulk surrounding the acid's "cavity" predetermines the preferred enantiomer of MBA, itself modified with steric "attachments" such as bromine. Similar arguments are used in discussing structural differences in the brucine and strychnine salts with N-benzoyl-D-alanine and N-benzoyl-L-alanine respectively. Brucine, for example, forms monolayered corrugated sheets creating almost rigid channels between the sheets, and "..the preference for complexation with the D or L isomer must depend on the shape and size of the cavity" (Gold *et al.*[13]). When we study small drug molecules interacting with small resolving agent molecules such as those in our present study, we find highly intricate interaction networks that are extremely sensitive to the physical conditions under which interaction occurs. The loss in "bulky rigidity" has increased the variables controlling chiral recognition to such an extent that it becomes increasingly challenging to isolate those variables that play the primary role in stereospecificity.

Phenyl ring interactions.

One set of results from a series of co-crystallisation experiments between MBA and C_6H_6-CH(R)-CO_2^- with R = CH_3, C_2H_5 and OH, conducted by Brianso[14], concluded that anion and cation phenyl ring (φ) interactions determined whether or not the diastereomeric salts would separate by

crystallisation. Where R = CH_3 for example, the dihedral angle between φ-acid and φ-base was 81^0 and 9^0 for the p and n salts respectively. The p salt was the unstable compound and resolution was easier than in the other salts where these angular differences were less pronounced. Judging from Table 4.5 this interpretation clearly fails for our system.

Table 4. 5 : Dihedral angles between planes containing phenyl rings

	n Salt	*p Salt (ring A)*	*p Salt (ring B)*
φ-GAM∠φ-MBA	48^0	44^0	66^0
φ-GAM∠φ-GAM^i	80^0	62	62^0
φ-MBA∠φ-MBA^i	71^0	48	11^0
φ-GAM∠φ-MBA^i	54^0	78	59^0

(i) -x, y+½, -z

As mentioned previously, the phenyl rings B in the p salt have "edge on" interactions with C...C distances less than 3Å.

Density and disorder.

Czugler, Ács *et al.*[15] find similar disorder in the more soluble salt of MBA co-crystallised with *cis*-2-hydroxy-4-cyclopentenylacetic acid. The structure forms a distinctly more globular aggregate whereas the less soluble salt forms "..a well ordered crystal by assuming a rodlike (linear) orientation via two-dimensional hydrogen bonding between anion and cation". What is implied by the term "well ordered"? Clearly X-ray analytical results finding a diffuse electron density in the more soluble salt indicate a not so "well ordered" crystal. The disorder and lower density of the p salt suggest poor recognition between these specific enantiomers of the drug and resolving agent.

Hydrogen bonding between ionic species (like vs. unlike).

This was an interesting observation put forward in discussing the differential solubilities of the Cinchona (*R*)- or (*S*)- Mandelate salts[9]. In our study similar *like* vs. *unlike* hydrogen bonded ions occur in the p and n salts respectively. Assuming the species to be partially or completely ionised Figure 4.12 schematically compares the distribution of cationic and anionic centres between the two modes of stacking.

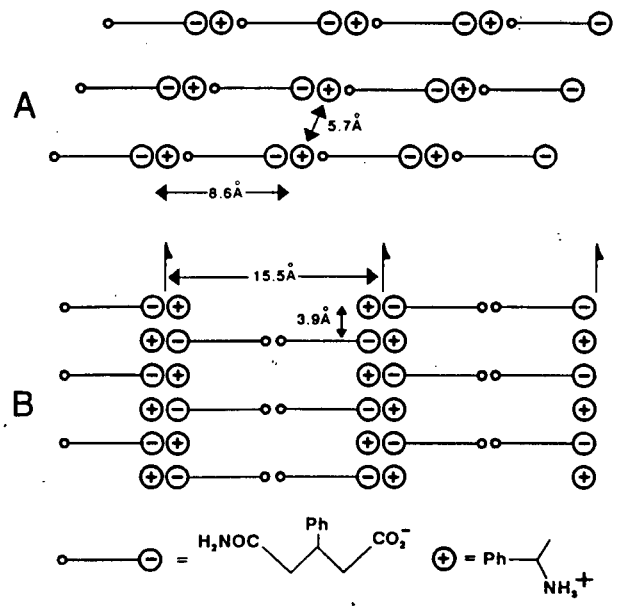


Figure 4. 12: Schematic representation of the charge distribution . A) in the (020) planes (d = 10.3Å) of the n salt. B) in the (10$\bar{1}$) planes (d = 12.0Å) of the p salt. The view directions are perpendicular to these planes.

The p salt has the total charge condensed around 2_1 axes with the ammonium cations spaced at 3.91Å intervals. The n salt distributes this charge more evenly throughout layers stacked vertically with 5.72Å being the shortest interval between cationic centres. This more diffuse vs. aggregated charge distribution in the n and p salts respectively once again suggests a favoured vs. disfavoured packing mode.

Potential Function for Hydrogen Bonds

Table 4.6 shows the geometry of the hydrogen bonded acceptor oxygen atoms around the ammonium cation. In the p salt the acceptor oxygens are slightly more puckered around the nitrogen donor and are not as "tetrahedrally arrayed" as in the n salt.

Table 4.6: Angles about MBA nitrogen

N Salt		P Salt	
C-N...O(13)	$109.5(2)^0$	C-N...O(13)	$117(1)^0$
C-N...O(14)	$111.9(1)^0$	C-N...O(13)*	$113(1)^0$
C-N...O(15)	$117.1(2)^0$	C-N...O(14)	$124(1)^0$
O(13)..N..O(14)	$108.3(1)^0$	O(13)..N..O(13)*	$98(1)^0$
O(13)..N..O(15)	$103.9(1)^0$	O(13)..N..O(14)	$98(1)^0$
O(14)..N..O(15)	$105.5(1)^0$	O(13)*..N..O(14)	$103(1)^0$

* With reference to symmetry operator (iv) in Table 4.4 above

An extensive survey scanning the Crystallographic Structural Database (CSD) investigating N-H···O=C hydrogen bonding patterns found the distribution of N-H···O angles consistent with an overall energetic preference for a linear or nearly linear N-H···O arrangement[16]. Murray-Rust and Glusker have also found that hydrogen bonds involving a ketone oxygen atom as the acceptor (X-H···O=C<, X = O,N) prefer an H···O=C< angle of about 135° [17]. Unfortunately the present structures lack hydrogen co-ordinates for the p salt, restricting us to analysing N···O-C geometries only.

Table 4.7 : Geometry of acceptor oxygens surrounding ammonium cation

N Salt			P Salt		
Acceptor	N···O-C	N···O-C-O†	Acceptor	N···O-C	N···O-C-O†
O(13)	106.1°	2.2°	O(13)	127.8°	3.8°
O(14)	122.0°	7.6°	O(13)•	118.9°	48.3°
O(15)	127.0°	13.5°‡	O(14)	104.7°	24.4°

† i.e. angle between the N···O vector and the O-C-O (carboxylate) plane
‡ In this case we refer to the O-C-N (amide) plane
• With reference to symmetry operator (iv) in Table 4.4

A quantitative measure of comparative hydrogen bond stabilities is the computation of their potential functions as demonstrated by Vedani *et al.*[18].The authors used a modified Lennard-Jones potential function accounting for directionality factors:

$$E_{HB} = (A'/r^{j}_{H\cdots A} - C'/r^{j}_{H\cdots A})\cos^{k}(\theta_{D\text{-}H\cdots A})\cos^{m}(\chi_{H\cdots A\text{-}AA} - \chi_{0})\cos^{n}(\omega_{H\cdots A\text{-}AA\text{-}AB} - \omega_{0}) \quad (1)$$

where coefficients A' and C' depend on various factors such as the donor and acceptor atom type. The various symbols are explained in Figure 4.13

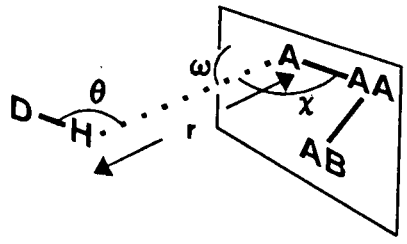


Figure 4.13 : Diagram showing the parameters in equation (1)

If we now consider directional factors only (i.e. the last three terms of the equation) we could use the values in Table 4.7 to make a rough comparison of E_{HB} values in the n and p salts for the three oxygen atoms listed above. In the absence of hydrogen atom positions the following model was put

forward: N-H···O = 180^0 and $r_{H...O}$ is constant for all hydrogen bonds involving the ammonium cation. These assumptions are merely made to demonstrate the influence of directionality. Equation (1) therefore reduces to:

$$/E_{HB}/ = K_1\cos^m(\chi_{N...O-C} - \chi_0)\cos^n(\omega_{N...O-C-O} - \omega_0)$$

Where K_1 is a constant, $\chi_0 = 135^0$ and $\omega_0 = 0^0$ for sp^2 hybridised carboxyl oxygen atoms. The authors derived values m, n = 2 for carboxyl oxygens. Table 4.8 compares the E_{HB} values.

Table 4.8 : Relative E_{HB} values

	$/E_{HB}/$(N salt)		$/E_{HB}/$(P salt)
N...O(13)	$0.77K_1$	N...O(13)	$0.97K_1$
N...O(14)	$0.93K_1$	N...O(13)'	$0.41K_1$
N...O(15)	$0.93K_1$	N...O(14)	$0.62K_1$
$\Sigma/E_{HB}/$	$2.63K_1$		$2.00K_1$

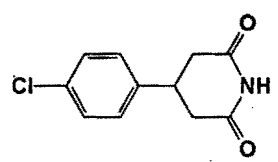
Calculating E_{HB} values is in actual fact complicated by oxygen atoms accepting hydrogen bonds from two donors, as well as some acceptors being carboxylate anions and others embedded in an amide moiety. Table 4.8 nevertheless partially succeeds in quantifying energetics of isolated regions in the crystal structures to explain the relative salt stabilities.

4.5 References

1. D. Kozma, M. Ács, E. Fogassy, *Tetrahedron*, **50**, (1994), 6907.
2. H.D. Flack, D. Schwarzenbach, *Acta Cryst.*, **A44**, (1988), 499.
3. H.D. Flack, *Acta Cryst.*, **A39**, (1983), 876.
4. C.H. Chang, D.S.C. Yang, C.Y. Chung, W. Bi-Cheng, J.Pletcher, M. Sax, C.F. Terrence, *Acta Cryst. Sect. B.*, **B38**, (1982), 2065.
5. M.C. Brianso, *Acta Cryst.*, **B32**, (1976), 3040.
6. M.C. Brianso, M. Leclercq, J. Jaques, *Acta Cryst.*, **B35**, (1979), 2751.
7. M.C. Brianso, *Acta Cryst.*, **B34**, (1978), 679.
8. S. Larsen, H. L. de Diego, *Acta Cryst.*, **B49**, (1993), 303.
9. S. Larsen, H. L. de Diego, D. Kozma, *Acta Cryst.*, **B49**, (1993), 310.
10. R. Yoshioka, O. Ohtsuki, T. Da-Te, K. Okamura, M. Senuma, *Bull. Chem. Soc. Jpn.*, **67**, (1994), 3012.
11. S.P Zingg, E.M. Arnett, A.T. McPhail, A.A. Bothmer-By, W.R. Gilkerson, *J. Am. Chem. Soc.*, **110**, (1988), 1565.
12. J.W. Westley, R.H. Evens, Jr. and J.F. Blount, *J. Am. Chem. Soc.*, **99**, (1977), 6057.
13. R.O. Gold, M.D. Walkinshaw, *J. Am. Chem. Soc.*, **106**, (1984), 7840.
14. M.C. Brianso, *Acta Cryst.*, **B37**, (1981), 618.
15. M. Czugler, I. Csöregh, A. Kálmán, F. Faigl, M. Ács, *J. Mol. Struct.*, **196**, (1989), 157.
16. R. Taylor, O. Kennard, W. Versichel, *Acta Cryst.*, **B40**, (1984), 280.
17. P. Murray-Rust, T. Glusker, *J. Am. Chem. Soc.*, **106**, (1984), 1018.
18. A. Vedani, J.D. Dunitz, *J. Am. Chem. Soc.*, **107**, (1985), 7653.

5. CONCLUSION

As summarised in Section 1.3.1, several methods by which enantiopure (*R*)-(-)-Baclofen are produced have been reported in the literature. No resolution has been reported that makes use of simple *diastereomeric salt formation*. Mostly the reported methods involve multistep syntheses, expensive reagents, or small scale chromatographic resolutions only suitable for analysis. Resolving the drug via its synthetic precursor GAM has involved no introduction and cleavage of protecting groups. The resolving agent used for this resolution is readily available at relatively low cost. Using 2-amino-1-(p-nitrophenyl)-1,3-propanediol as resolving agent in place of MBA is a possibility worthy of investigation. However, the efficiency and purity (99.7% ee) of this resolution make it an attractive option for a large scale process and it is indeed presently being tested on kilogram scale production at Fine Chemicals Corporation in Cape Town. The inherent problem of resolutions allowing for only 50% maximal yield could be surpassed by investigating a suitable method by which the unwanted enantiomer is racemized. Cyclodehydrating (*S*)-(-)-GAM by treatment with an acid yields a symmetric 3-((*p*-chlorophenyl)glutarimide (**21**).



21

Treating this prochiral imide with a suitable base such as NaOH would produce racemic GAM[1] from which the desired R enantiomer could be retrieved by repeating the resolution.

Counting diastereomeric, kinetic, and chromatographic resolutions, 1527 patents dealing with such resolutions were granted between 1967 and 1991. This is only 25% of all publications entered into the *Chemical Abstracts* data base (CA File) over this 25 year period. Yet, few crystal structures of salts employed in the resolution of enantiomers have been determined by X-ray crystallography. Even fewer reports account for the determination of *both* diastereomeric salt structures. This study therefore contributes to the slowly increasing number of literature reports aimed at quantitative explanations for relative diastereomer discrimination. Over the years it has been ascertained that aromatic resolving agents are preferred over aliphatic ones and that polyfunctional resolving agents are preferred over monofunctional ones since it appears that multiple sites of (nonbonding) interactions between the counterions of diastereomeric salts enhance solubility differences[2]. These

kinds of features may only be explained by probing the crystal structures of all possible diastereomeric assemblies and analysing the nature of these various interaction sites.

---

1. F. Morlacchi, V. Losacco, V. Tortorella, *Gazz. Chim. Ital.*, **105**, (1975), 349.
2. S.H. Wilen, "Resolving Agents and Resolutions in Organic Chemistry, *Top. Stereochem.*, **6**, (1971), 107.

Appendix A

(Crystal structure data for *p* and *n* salts of GAM.MBA co-crystals)

Table A.1 : Atomic coordinates ($x10^4$) and equivalent isotropic displacement parameters ($Å^2x10^3$). U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

(A) P SALT

	x/a	y/b	z/c	U(eq)
CL(12)	7649(3)	4671(0)	1790(4)	124(2)
C(6)	4395(5)	5435(23)	1430(8)	65(2)
C(7)	4984(5)	3434(23)	1952(8)	65(2)
C(8)	5993(5)	3195(23)	2062(8)	65(2)
C(9)	6414(5)	4958(23)	1652(8)	65(2)
C(10)	5826(5)	6960(23)	1132(8)	65(2)
C(11)	4817(5)	7198(23)	1021(8)	65(2)
O(15)	1111(11)	6011(69)	131(12)	168(9)
O(13)	4000(7)	6281(25)	3992(7)	78(3)
O(14)	3862(10)	9169(28)	2909(10)	94(4)
N(16)	971(14)	1953(79)	50(15)	161(14)
C(1)	3713(9)	7034(36)	3057(11)	60(4)
C(2)	3100(10)	5173(38)	2232(10)	72(5)
C(3)	3263(9)	5716(42)	1239(10)	74(6)
C(4)	2638(10)	3845(62)	438(12)	114(10)
C(5)	1506(13)	4035(99)	200(15)	127(18)
N(25)	3934(7)	1673(28)	4642(9)	64(3)
C(17)	3353(15)	3162(57)	5916(13)	89(7)
C(18)	3202(13)	1217(36)	5145(17)	79(5)
C(19)a	2084(20)	763(84)	4457(25)	127(4)
C(20)a	1703(20)	1527(84)	3443(25)	127(4)
C(21)a	655(20)	1348(84)	2818(25)	127(4)
C(22)a	-11(20)	403(84)	3208(25)	127(4)
C(23)a	370(20)	-361(84)	4222(25)	127(4)
C(24)a	1418(20)	-179(84)	4846(25)	127(4)
C(19)b	2028(21)	1330(78)	4070(20)	127(4)
C(20)b	1606(21)	3631(78)	3727(20)	127(4)
C(21)b	731(21)	3855(78)	2813(20)	127(4)
C(22)b	276(21)	1779(78)	2243(20)	127(4)
C(23)b	697(21)	-521(78)	2585(20)	127(4)
C(24)b	1573(21)	-746(78)	3499(20)	127(4)

The letters a and b denote the carbon atoms of φA and φB respectively (see Fig. 4.4 page 41). The s.o.f.'s of the carbon atoms were refined to 0.52 and 0.48 for φA and φB respectively.

(B) N SALT

	x/a	y/b	z/c	U(eq)
Cl(12)	5395(2)	9434(1)	8428(1)	83(1)
O(13)	3604(3)	7149(1)	13560(3)	49(1)
O(14)	5539(3)	6882(1)	11722(2)	47(1)
O(15)	9679(4)	7590(1)	18356(3)	59(1)
N(25)	-140(4)	6709(1)	10945(3)	41(1)
N(16)	13660(6)	7577(2)	18488(4)	64(1)
C(1)	5506(4)	7069(1)	13147(3)	35(1)
C(2)	7931(4)	7216(1)	14461(3)	36(1)
C(3)	8203(5)	7938(1)	14918(3)	38(1)
C(4)	10776(5)	8075(2)	16082(3)	47(1)
C(5)	11335(6)	7721(2)	17737(3)	45(1)
C(6)	7620(5)	8353(1)	13352(3)	39(1)
C(7)	9029(5)	8318(2)	12255(4)	45(1)
C(8)	8365(6)	8659(2)	10763(4)	49(1)
C(9)	6299(6)	9036(2)	10371(4)	52(1)
C(10)	4941(6)	9106(2)	11457(5)	60(1)
C(11)	5599(6)	8764(2)	12941(5)	52(1)
C(17)	-310(8)	5610(2)	11957(4)	63(1)
C(18)	288(5)	6014(2)	10624(4)	45(1)
C(19)	-1162(5)	5818(2)	8853(4)	45(1)
C(20)	-3564(6)	6014(2)	8130(4)	55(1)
C(21)	-4842(7)	5832(2)	6514(4)	68(1)
C(22)	-3736(9)	5447(2)	5613(5)	75(1)
C(23)	-1393(10)	5241(2)	6320(5)	79(1)
C(24)	-88(7)	5432(2)	7924(5)	60(1)

Table A.2 : Bond Lengths for GAM.MBA [Å]

	N SALT	*P SALT*
Cl(12)-C(9)	1.755(3)	1.71(1)
O(13)-C(1)	1.248(3)	1.30(2)
O(14)-C(1)	1.257(3)	1.22(3)
O(15)-C(5)	1.239(4)	1.21(6)
N(25)-C(18)	1.494(4)	1.53(3)
N(16)-C(5)	1.326(5)	1.34(6)
C(6)-C(11)	1.392(4)	1.40(2)
C(9)-C(10)	1.367(5)	1.40(2)
C(8)-C(9)	1.372(5)	1.40(2)
C(7)-C(8)	1.384(4)	1.40(2)
C(6)-C(7)	1.393(4)	1.40(2)
C(4)-C(5)	1.511(4)	1.52(2)
C(3)-C(4)	1.530(4)	1.52(3)
C(2)-C(3)	1.537(4)	1.57(2)
C(6)-C(3)	1.517(4)	1.54(2)
C(17)-C(18)	1.511(5)	1.49(3)
C(10)-C(11)	1.379(5)	1.39(1)
C(1)-C(2)	1.522(3)	1.53(2)
C(19)a-C(20)a	1.387(5)	1.40(5)
C(20)a-C(21)a	1.381(5)	1.40(5)
C(21)a-C(22)a	1.374(7)	1.40(5)
C(19)a-C(24)a	1.380(5)	1.40(5)
C(22)a-C(23)a	1.363(7)	1.40(5)
C(23)a-C(24)a	1.383(6)	1.40(5)
C(18)-C(19)a	1.519(4)	1.51(3)
C(18)-C(19)b		1.75(3)
C(19)b-C(20)b		1.40(0)
C(19)b-C(24)b		1.40(0)
C(20)b-C(21)b		1.40(0)
C(21)b-C(22)b		1.40(0)
C(22)b-C(23)b		1.40(0)
C(23)b-C(34)b		1.40(0)

Table A.3: Bond angles for GAM.MBA [deg]

	N SALT	*P SALT*
O(13)-C(1)-C(2)	117.3(2)	115(1)
O(13)-C(1)-O(14)	124.3(2)	119(1)
O(14)-C(1)-C(2)	118.4(2)	126(2)
C(1)-C(2)-C(3)	112.1(2)	109(1)
C(4)-C(3)-C(2)	110.2(2)	107(1)
C(6)-C(3)-C(2)	110.8(2)	111(1)
C(6)-C(3)-C(4)	111.4(2)	108(1)
C(5)-C(4)-C(3)	113.1(2)	111(2)
O(15)-C(5)-C(4)	120.6(3)	120(4)
O(15)-C(5)-N(16)	122.7(3)	122(2)
N(16)-C(5)-C(4)	116.8(3)	118(4)
C(7)-C(6)-C(3)	121.1(2)	122(1)
C(7)-C(6)-C(11)	118.2(3)	120(1)
C(11)-C(6)-C(3)	120.7(2)	118(1)
C(8)-C(7)-C(6)	120.5(3)	120(1)
C(9)-C(8)-C(7)	119.3(3)	120(1)
C(8)-C(9)-Cl(12)	118.8(3)	120(1)
C(10)-C(9)-C(8)	121.6(3)	120(1)
C(10)-C(9)-Cl(12)	119.7(3)	120(1)
C(9)-C(10)-C(11)	119.0(3)	120(1)
C(10)-C(11)-C(6)	121.2(3)	120(1)
C(17)-C(18)-C(19)a	113.1(3)	115(2)
C(17)-C(18)-C(19)b		113(2)
N(25)-C(18)-C(19)a	111.1(2)	118(2)
N(25)-C(18)-C(19)b		100(2)
N(25)-C(18)-C(17)	108.2(2)	109(2)
C(20)a-C(19)a-C(18)	121.9(3)	119(3)
C(20)b-C(19)b-C(18)		117(2)
C(24)a-C(19)a-C(18)	119.7(3)	121(3)
C(24)b-C(19)b-C(18)		122(3)
C(24)a-C(19)a-C(20)a	118.4(3)	120(0)
C(21)a-C(20)a-C(19)a	120.9(3)	120(0)
C(22)a-C(21)a-C(20)a	119.8(4)	120(0)
C(23)a-C(22)a-C(21)a	120.0(3)	120(0)
C(22)a-C(23)a-C(24)a	120.5(4)	120(0)
C(19)a-C(24)a-C(23)a	120.5(4)	120(0)
C(20)b-C(19)b-C(24)b		120(0)
C(19)b-C(20)b-C(21)b		120(0)
C(20)b-C(21)b-C(22)b		120(0)
C(21)b-C(22)b-C(23)b		120(0)
C(22)b-C(23)b-C(24)b		120(0)
C(19)b-C(24)b-C(23)b		120(0)

Table A.4: Anisotropic displacement parameters ($Å^2x10^3$) for GAM.MBA. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11} +...+ 2hka^*b^*U_{12}]$

	N SALT						*P SALT*					
	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
Cl(12)	89(1)	79(1)	64(1)	35(1)	-3(1)	-6(1)	53(2)	185(6)	141(4)	9(5)	49(2)	18(4)
O(15)	59(1)	79(2)	39(1)	5(1)	16(1)	0(1)	45(8)	350(30)	99(10)	-39(15)	19(8)	35(13)
O(13)	30(1)	72(1)	44(1)	-8(1)	11(1)	-4(1)	56(5)	124(9)	43(5)	-3(7)	12(4)	-11(6)
O(14)	32(1)	74(2)	34(1)	-5(1)	7(1)	-3(1)	113(10)	80(8)	88(9)	-18(8)	42(8)	4(9)
N(16)	54(2)	88(2)	46(2)	14(2)	7(1)	2(2)	57(10)	319(43)	105(13)	-77(19)	30(10)	-69(18)
C(1)	27(1)	42(1)	35(1)	4(1)	5(1)	-3(1)	46(7)	57(12)	89(11)	-24(11)	39(7)	-2(9)
C(2)	29(1)	46(1)	31(1)	4(1)	4(1)	-1(1)	60(8)	116(15)	50(8)	-39(11)	31(7)	-19(10)
C(3)	34(1)	47(1)	33(1)	2(1)	9(1)	-1(1)	30(6)	156(17)	42(7)	2(11)	21(6)	9(9)
C(4)	50(2)	51(2)	34(1)	1(1)	4(1)	-14(1)	29(7)	238(30)	78(9)	-82(16)	26(7)	-43(14)
C(5)	50(2)	47(1)	32(1)	-6(1)	5(1)	-5(1)	41(10)	281(54)	61(12)	-41(23)	21(9)	-5(23)
C(6)	34(1)	38(1)	42(1)	0(1)	6(1)	-4(1)						
C(7)	44(1)	46(2)	45(2)	5(1)	11(1)	6(1)						
C(8)	54(2)	48(2)	46(2)	5(1)	16(1)	-2(1)						
C(9)	52(2)	44(2)	49(2)	13(1)	0(1)	-6(1)						
C(10)	46(2)	52(2)	81(2)	20(2)	16(2)	12(1)						
C(11)	43(2)	55(2)	60(2)	9(2)	17(1)	6(1)						
C(17)	71(2)	66(2)	47(2)	6(2)	11(2)	-1(2)	97(12)	112(20)	71(10)	-20(14)	49(9)	9(16)
C(18)	34(1)	55(2)	44(1)	-3(1)	7(1)	1(1)	69(11)	65(13)	87(14)	-2(13)	16(11)	8(10)
N(25)	32(1)	54(1)	35(1)	-3(1)	8(1)	-5(1)	42(6)	82(8)	66(7)	-13(8)	22(6)	-4(7)
C(19)	45(2)	48(2)	44(1)	-2(1)	15(1)	-6(1)						
C(20)	42(2)	70(2)	47(2)	-13(2)	8(1)	-2(2)						
C(21)	57(2)	85(3)	51(2)	-10(2)	-1(2)	-12(2)						
C(22)	93(3)	85(3)	45(2)	-17(2)	18(2)	-26(3)						
C(23)	109(4)	76(3)	64(2)	-18(2)	46(2)	-5(3)						
C(24)	64(2)	63(2)	59(2)	-3(2)	27(2)	4(2)						

Table A.7 Observed and calculated structure factors for p salt

h	k	l	10Fo	10Fc	10s	h	k	l	10Fo	10Fc	10s	h	k	l	10Fo	10Fc	10s	h	k	l	10Fo	10Fc	10s	h	k	l	10Fo	10Fc	10s
1	0	0	398	438	3	-12	0	1	72	74	2	-12	3	1	41	30	4	-8	0	2	123	123	2	-7	3	2	17	30	16
2	0	0	90	118	1	-11	0	1	76	88	2	-11	3	1	0	14	1	-7	0	2	637	560	2	-6	3	2	103	87	2
3	0	0	259	155	2	-10	0	1	166	180	4	-10	3	1	70	58	2	-6	0	2	591	484	2	-5	3	2	43	58	3
4	0	0	381	378	1	-9	0	1	69	68	2	-9	3	1	110	102	2	-5	0	2	345	327	2	-4	3	2	30	32	4
5	0	0	161	133	2	-8	0	1	246	223	3	-8	3	1	62	56	2	-4	0	2	153	92	2	-3	3	2	65	69	1
6	0	0	170	167	2	-7	0	1	277	183	2	-7	3	1	40	34	3	-3	0	2	428	440	1	-2	3	2	93	75	2
7	0	0	119	102	2	-6	0	1	265	230	2	-6	3	1	24	18	24	-2	0	2	56	82	1	-1	3	2	128	130	2
8	0	0	172	197	3	-5	0	1	572	553	2	-5	3	1	0	15	1	-1	0	2	111	188	1	0	3	2	48	66	2
9	0	0	23	33	5	-4	0	1	297	314	2	-4	3	1	127	134	2	0	0	2	103	39	1	1	3	2	81	82	2
10	0	0	48	50	5	-3	0	1	80	127	1	-3	3	1	105	90	2	1	0	2	697	686	6	2	3	2	78	80	2
11	0	0	123	126	2	-2	0	1	12	29	4	-2	3	1	120	132	2	2	0	2	119	123	2	3	3	2	97	91	2
12	0	0	81	82	1	-1	0	1	300	287	1	-1	3	1	140	128	3	3	0	2	47	53	2	4	3	2	33	25	3
13	0	0	59	47	2	0	0	1	125	208	1	0	3	1	37	8	2	4	0	2	563	534	2	5	3	2	49	41	2
14	0	0	48	57	14	1	0	1	248	149	1	1	3	1	41	56	2	5	0	2	165	147	3	6	3	2	42	56	3
15	0	0	35	18	6	2	0	1	24	61	2	2	3	1	160	125	3	6	0	2	392	323	3	7	3	2	42	53	3
1	1	0	272	287	5	3	0	1	792	764	8	3	3	1	110	99	2	7	0	2	83	103	1	8	3	2	50	53	3
2	1	0	199	248	5	4	0	1	49	45	1	4	3	1	76	55	1	8	0	2	86	77	2	9	3	2	58	51	2
3	1	0	148	141	7	5	0	1	296	212	2	5	3	1	30	27	4	9	0	2	34	31	4	10	3	2	43	31	3
4	1	0	197	172	7	6	0	1	129	84	2	6	3	1	21	19	21	10	0	2	0	35	1	11	3	2	0	28	1
5	1	0	103	113	3	7	0	1	157	125	3	7	3	1	58	54	2	11	0	2	40	40	4	12	3	2	9	21	8
6	1	0	349	318	7	8	0	1	33	5	4	8	3	1	82	75	2	12	0	2	59	37	3	-12	4	2	24	10	9
7	1	0	156	158	5	9	0	1	189	170	3	9	3	1	55	57	2	13	0	2	35	39	6	-11	4	2	27	19	7
8	1	0	60	62	1	10	0	1	10	34	10	10	3	1	45	52	3	14	0	2	0	2	1	-10	4	2	27	13	26
9	1	0	101	102	1	11	0	1	22	32	21	11	3	1	27	18	27	-16	1	2	38	30	6	-9	4	2	51	44	3
10	1	0	23	31	23	12	0	1	34	21	5	12	3	1	0	6	1	-15	1	2	52	38	4	-8	4	2	49	32	3
11	1	0	35	46	4	13	0	1	38	28	4	13	3	1	0	16	1	-14	1	2	40	37	5	-7	4	2	41	39	4
12	1	0	55	54	2	14	0	1	0	23	1	-12	4	1	0	10	1	-13	1	2	0	18	1	-6	4	2	0	25	1
13	1	0	14	10	13	15	0	1	21	11	21	-11	4	1	25	20	25	-12	1	2	48	67	3	-5	4	2	0	8	1
14	1	0	40	36	3	-15	1	1	41	32	5	-10	4	1	44	41	4	-11	1	2	0	16	1	-4	4	2	0	24	1
15	1	0	37	23	9	-14	1	1	27	19	26	-9	4	1	29	32	28	-10	1	2	60	74	2	-3	4	2	47	63	3
0	2	0	206	232	2	-13	1	1	36	31	4	-8	4	1	25	10	25	-9	1	2	37	23	3	-2	4	2	114	115	3
1	2	0	175	176	2	-12	1	1	25	31	7	-7	4	1	0	24	1	-8	1	2	91	103	2	-1	4	2	89	96	2
2	2	0	289	256	1	-11	1	1	93	86	2	-6	4	1	69	69	2	-7	1	2	162	143	3	0	4	2	52	29	2
3	2	0	108	112	2	-10	1	1	71	63	2	-5	4	1	70	71	2	-6	1	2	213	171	2	1	4	2	49	54	2
4	2	0	176	185	5	-9	1	1	126	112	2	-4	4	1	50	49	2	-5	1	2	85	105	1	2	4	2	69	58	2
5	2	0	57	55	2	-8	1	1	68	59	2	-3	4	1	30	42	4	-4	1	2	253	252	2	3	4	2	69	74	2
6	2	0	30	19	2	-7	1	1	199	191	3	-2	4	1	56	52	2	-3	1	2	163	130	2	4	4	2	39	47	3
7	2	0	25	41	7	-6	1	1	66	69	1	-1	4	1	99	100	2	-2	1	2	426	337	1	5	4	2	7	19	7
8	2	0	75	76	3	-5	1	1	94	100	2	0	4	1	95	81	2	-1	1	2	533	526	1	6	4	2	0	10	1
9	2	0	152	129	4	-4	1	1	247	250	2	1	4	1	23	11	23	0	1	2	767	754	7	7	4	2	0	13	1
10	2	0	120	115	5	-3	1	1	297	266	2	2	4	1	31	18	4	1	1	2	309	286	2	8	4	2	0	10	1
11	2	0	27	38	8	-2	1	1	446	451	1	3	4	1	77	75	2	2	1	2	393	375	2	9	4	2	0	15	1
12	2	0	44	32	6	-1	1	1	772	745	7	4	4	1	68	41	2	3	1	2	222	220	2	10	4	2	39	33	5
13	2	0	39	37	11	0	1	1	434	441	1	5	4	1	34	24	4	4	1	2	62	68	1	11	4	2	0	23	1
14	2	0	17	25	16	1	1	1	173	197	2	6	4	1	42	55	3	5	1	2	139	111	3	-10	5	2	0	6	1
1	3	0	106	91	1	2	1	1	198	137	2	7	4	1	37	37	4	6	1	2	62	78	1	-9	5	2	0	9	1
2	3	0	108	94	2	3	1	1	102	103	2	8	4	1	23	17	22	7	1	2	242	221	3	-8	5	2	20	8	12
3	3	0	116	107	1	4	1	1	219	213	2	9	4	1	10	11	10	8	1	2	101	97	2	-7	5	2	0	11	1
4	3	0	26	35	4	5	1	1	87	109	2	10	4	1	0	22	1	9	1	2	165	159	3	-6	5	2	0	12	1
5	3	0	38	42	2	6	1	1	180	200	3	11	4	1	32	29	6	10	1	2	55	61	2	-5	5	2	0	2	1
6	3	0	63	54	1	7	1	1	104	88	2	-10	5	1	0	16	1	11	1	2	51	67	3	-4	5	2	0	10	1
7	3	0	51	58	1	8	1	1	111	110	3	-9	5	1	0	22	1	12	1	2	27	27	26	-3	5	2	0	17	1
8	3	0	59	70	3	9	1	1	74	74	2	-8	5	1	20	12	19	13	1	2	41	33	4	-2	5	2	0	39	1
9	3	0	102	94	4	10	1	1	51	51	3	-7	5	1	9	14	8	14	1	2	0	9	1	-1	5	2	29	44	5
10	3	0	46	44	2	11	1	1	79	79	2	-6	5	1	17	15	16	-15	2	2	33	19	32	0	5	2	46	44	3
11	3	0	33	17	4	12	1	1	62	66	2	-5	5	1	22	27	8	-14	2	2	20	22	15	1	5	2	39	46	4
12	3	0	0	7	1	13	1	1	0	44	1	-4	5	1	14	20	13	-13	2	2	45	41	4	2	5	2	32	24	5
13	3	0	13	27	12	14	1	1	0	23	1	-3	5	1	21	18	20	-12	2	2	16	18	16	3	5	2	31	16	5
0	4	0	65	65	2	-15	2	1	45	40	5	-2	5	1	0	34	1	-11	2	2	96	85	2	4	5	2	0	7	1
1	4	0	40	8	4	-14	2	1	16	45	15	-1	5	1	36	25	4	-10	2	2	113	124	2	5	5	2	8	22	8
2	4	0	15	6	15	-13	2	1	49	43	4	0	5	1	64	73	2	-9	2	2	167	145	4	6	5	2	24	15	8
3	4	0	12	9	12	-12	2	1	25	42	24	1	5	1	70	75	2	-8	2	2	91	93	2	7	5	2	23	15	23
4	4	0	50	49	2	-11	2	1	39	26	4	2	5	1	8	40	7	-7	2	2	62	53	2	8	5	2	0	9	1
5	4	0	62	54	1	-10	2	1	26	35	25	3	5	1	0	20	1	-6	2	2	168	157	3	-6	6	2	13	23	12
6	4	0	30	38	3	-9	2	1	116	130	2	4	5	1	35	39	4	-5	2	2	83	75	1	-5	6	2	0	20	1
7	4	0	27	26	5	-8	2	1	136	127	2	5	5	1	27	35	6	-4	2	2	76	93	1	-4	6	2	26	4	25
8	4	0	49	51	2	-7	2	1	52	44	2	6	5	1	8	10	8	-3	2	2	108	108	2	-3	6	2	0	13	1
9	4	0	50	39	4	-6	2	1	155	147	3	7	5	1	15	17	14	-2	2	2	136	116	3	-2	6	2	28	13	28
10	4	0	24	25	23	-5	2	1	108	102	2	8	5	1	0	20	1	-1	2	2	179	181	2	-1	6	2	23	7	23
11	4	0	24	14	9	-4	2	1	73	60	1	9	5	1	26	7	25	0	2	2	323	304	2	0	6	2	0	14	1
12	4	0	29	13	17	-3	2	1	232	265	2	-6	6	1	0	7	1	1	2	2	184	202	2	1	6	2	23	16	23
1	5	0	44	38	2	-2	2	1	251	246	2	-5	6	1	27	9	7	2	2	2	137	147	3	2	6	2	18	15	17
2	5	0	25	14	7	-1	2	1	301	277	2	-4	6	1	22	7	22	3	2	2	212	200	2	3	6	2	0	15	1
3	5	0	23	20	23	0	2	1	160	124	2	-3	6	1	0	12	1	4	2	2	156	151	3	4	6	2	13	14	13
4	5	0	25	23	25	1	2	1	36	56	2	-2	6	1	0	16	1	5	2	2	37	30	2	-16	0	3	21	11	20
5	5	0	22	16	21	2	2	1	221	213	2	-1	6	1	0	12	1	6	2	2	88	93	2	-15	0	3	41	23	5
6	5	0	23	14	7	3	2	1	58	67	1	0	6	1	28	21	7	7	2	2	86	90	2	-14	0	3	0	16	1
7	5	0	8	28	8	4	2	1	77	69	2	1	6	1	35	28	5	8	2	2	100	104	2	-13	0	3	24	3	24
8	5	0	23	19	9	5	2	1	187	162	3	2	6	1	20	26	15	9	2	2	34	35	4	-12	0	3	88	103	2
9	5	0	24	10	9	6	2	1	79	81	2	3	6	1	0	14	1	10	2	2	57	48	2	-11	0	3	236	227	4
0	6	0	29	28	6	7	2	1	92	93	2	4	6	1	30	6	30	11	2	2	20	29	11	-10	0	3	61	51	2
1	6	0	21	26	11	8	2	1	68	62	2	5	6	1	20	5	14	12	2	2	0	23	1	-9	0	3	80	68	2
2	6	0	9	20	8	9	2	1	139	150	3	-16	0	2	22	19	13	13	2	2	17	19	17	-8	0	3	69	95	2
3	6	0	13	13	12	10	2	1	83	66	2	-15	0	2	0	49	1	-14	3	2	28	20	27	-7	0	3	17	2	7
4	6	0	0	12	1	11	2	1	0	22	1	-14	0	2	86	96	2	-13	3	2	24	31	23	-6	0	3	16	14	15
5	6	0	0	9	1	12	2	1	18	11	13	-13	0	2	64	61	2	-12	3	2	48	40	3	-5	0	3	54	24	1
6	6	0	16	1	16	13	2	1	40	43	5	-12	0	2	51	79	3	-11	3	2	0	20	1	-4	0	3	926	832	8
15	0	1	61	55	3	14	2	1	0	7	1	-11	0	2	16	30	16	-10	3	2	43	36	3	-3	0	3	279	181	2
14	0	1	9	22	8	-14	3	1	21	21	21	-10	0	2	72	62	2	-9	3	2	65	56	2	-2	0	3	232	302	1
13	0	1	50	43	3	-13	3	1	13	24	12	-9	0	2	0	8	1	-8	3	2	91	86	2	-1	0	3	863	881	7

Table A.7 Observed and calculated structure factors for p salt

h	k	l	10Fo	10Fc	10s	h	k	l	10Fo	10Fc	10s	h	k	l	10Fo	10Fc	10s	h	k	l	10Fo	10Fc	10s	h	k	l	10Fo	10Fc	10s
0	0	3	234	200	1	3	3	3	102	114	2	10	0	4	61	42	3	-11	4	4	29	11	6	-5	1	5	152	187	3
1	0	3	447	402	2	4	3	3	28	26	4	11	0	4	45	52	4	-10	4	4	15	30	14	-4	1	5	183	130	2
2	0	3	54	69	1	5	3	3	38	33	3	12	0	4	13	18	13	-9	4	4	38	47	4	-3	1	5	295	296	2
3	0	3	103	85	2	6	3	3	10	18	10	13	0	4	19	5	18	-8	4	4	45	41	3	-2	1	5	68	49	1
4	0	3	0	51	1	7	3	3	20	22	19	-16	1	4	36	49	6	-7	4	4	19	6	19	-1	1	5	83	89	1
5	0	3	129	158	2	8	3	3	49	41	3	-15	1	4	59	51	4	-6	4	4	32	24	5	0	1	5	271	234	2
6	0	3	21	12	21	9	3	3	23	33	8	-14	1	4	15	23	14	-5	4	4	21	20	20	1	1	5	197	177	2
7	0	3	165	161	4	10	3	3	0	17	1	-13	1	4	70	80	2	-4	4	4	43	48	3	2	1	5	105	115	2
8	0	3	0	3	1	11	3	3	0	21	1	-12	1	4	83	75	2	-3	4	4	10	22	10	3	1	5	108	129	2
9	0	3	100	88	2	12	3	3	0	4	1	-11	1	4	90	103	1	-2	4	4	19	38	9	4	1	5	37	32	3
10	0	3	0	20	1	-13	4	3	0	9	1	-10	1	4	22	33	21	-1	4	4	56	43	2	5	1	5	157	154	2
11	0	3	84	89	2	-12	4	3	0	26	1	-9	1	4	133	136	2	0	4	4	28	33	5	6	1	5	59	52	2
12	0	3	0	8	1	-11	4	3	28	22	27	-8	1	4	136	132	2	1	4	4	45	27	3	7	1	5	89	97	1
13	0	3	24	65	24	-10	4	3	21	18	9	-7	1	4	166	157	3	2	4	4	15	12	15	8	1	5	78	84	2
-16	1	3	39	34	5	-9	4	3	0	10	1	-6	1	4	133	144	2	3	4	4	43	35	3	9	1	5	72	67	2
-15	1	3	0	31	1	-8	4	3	37	42	4	-5	1	4	294	248	2	4	4	4	26	18	6	10	1	5	25	27	7
-14	1	3	48	50	3	-7	4	3	0	32	1	-4	1	4	103	100	2	5	4	4	0	12	1	11	1	5	29	24	28
-13	1	3	30	47	30	-6	4	3	0	15	1	-3	1	4	186	148	2	6	4	4	28	22	27	12	1	5	13	20	13
-12	1	3	115	99	2	-5	4	3	0	14	1	-2	1	4	246	211	2	7	4	4	29	15	5	-16	2	5	40	33	5
-11	1	3	173	159	4	-4	4	3	27	34	5	-1	1	4	287	274	2	8	4	4	23	19	22	-15	2	5	42	44	4
-10	1	3	57	75	2	-3	4	3	12	39	12	0	1	4	416	353	2	9	4	4	19	14	18	-14	2	5	31	40	31
-9	1	3	179	172	3	-2	4	3	56	55	2	1	1	4	317	279	2	10	4	4	0	7	1	-13	2	5	35	35	5
-8	1	3	114	104	2	-1	4	3	67	60	2	2	1	4	306	275	2	-10	5	4	13	11	13	-12	2	5	83	76	2
-7	1	3	345	304	2	0	4	3	45	58	3	3	1	4	214	193	3	-9	5	4	25	12	25	-11	2	5	117	108	2
-6	1	3	204	210	2	1	4	3	25	28	25	4	1	4	84	72	2	-8	5	4	0	11	1	-10	2	5	53	62	2
-5	1	3	37	58	2	2	4	3	0	18	1	5	1	4	75	68	2	-7	5	4	0	5	1	-9	2	5	90	83	1
-4	1	3	117	115	2	3	4	3	50	44	3	6	1	4	22	22	21	-6	5	4	12	19	12	-8	2	5	15	28	14
-3	1	3	243	208	2	4	4	3	21	45	20	7	1	4	76	73	1	-5	5	4	0	20	1	-7	2	5	102	83	2
-2	1	3	546	509	2	5	4	3	37	38	4	8	1	4	91	82	2	-4	5	4	14	35	14	-6	2	5	74	74	1
-1	1	3	515	501	2	6	4	3	45	35	3	9	1	4	38	28	4	-3	5	4	11	4	11	-5	2	5	38	25	3
0	1	3	307	250	2	7	4	3	28	22	6	10	1	4	50	48	3	-2	5	4	50	34	3	-4	2	5	148	200	3
1	1	3	367	317	2	8	4	3	18	11	17	11	1	4	21	32	10	-1	5	4	43	35	4	-3	2	5	100	122	2
2	1	3	202	175	2	9	4	3	0	21	1	12	1	4	0	16	1	0	5	4	16	21	16	-2	2	5	56	48	1
3	1	3	179	135	2	10	4	3	0	18	1	13	1	4	39	39	5	1	5	4	32	18	5	-1	2	5	65	66	1
4	1	3	131	129	2	-10	5	3	9	6	9	-15	2	4	38	15	5	2	5	4	35	30	4	0	2	5	126	134	2
5	1	3	125	121	2	-9	5	3	24	13	23	-14	2	4	41	35	5	3	5	4	0	15	1	1	2	5	188	183	3
6	1	3	81	84	1	-8	5	3	15	15	15	-13	2	4	0	42	1	4	5	4	0	13	1	2	2	5	103	82	2
7	1	3	103	100	2	-7	5	3	24	35	24	-12	2	4	0	39	1	5	5	4	0	13	1	3	2	5	72	72	2
8	1	3	29	19	4	-6	5	3	0	39	1	-11	2	4	65	68	2	6	5	4	19	9	19	4	2	5	54	42	2
9	1	3	63	58	2	-5	5	3	23	11	23	-10	2	4	77	66	2	7	5	4	9	12	9	5	2	5	64	55	2
10	1	3	16	37	16	-4	5	3	51	42	3	-9	2	4	64	65	2	-6	6	4	13	12	13	6	2	5	105	91	2
11	1	3	21	11	9	-3	5	3	66	66	2	-8	2	4	69	85	2	-5	6	4	22	11	10	7	2	5	23	38	7
12	1	3	29	27	28	-2	5	3	50	55	3	-7	2	4	119	137	2	-4	6	4	0	10	1	8	2	5	57	53	2
13	1	3	30	20	7	-1	5	3	29	30	6	-6	2	4	153	136	3	-3	6	4	0	9	1	9	2	5	25	35	25
-15	2	3	67	64	3	0	5	3	0	27	1	-5	2	4	175	159	3	-2	6	4	0	10	1	10	2	5	27	32	26
-14	2	3	0	15	1	1	5	3	0	36	1	-4	2	4	109	119	2	-1	6	4	22	12	22	11	2	5	0	11	1
-13	2	3	67	48	2	2	5	3	34	27	4	-3	2	4	87	118	2	0	6	4	21	17	10	-15	3	5	16	15	16
-12	2	3	43	50	3	3	5	3	18	18	13	-2	2	4	85	90	2	1	6	4	0	17	1	-14	3	5	29	25	7
-11	2	3	67	60	2	4	5	3	28	17	6	-1	2	4	73	70	1	2	6	4	0	13	1	-13	3	5	0	15	1
-10	2	3	139	138	3	5	5	3	30	24	29	0	2	4	67	80	1	3	6	4	9	7	9	-12	3	5	0	22	1
-9	2	3	110	99	2	6	5	3	27	28	8	1	2	4	345	320	2	-16	0	5	56	48	4	-11	3	5	29	46	29
-8	2	3	76	84	1	7	5	3	30	15	6	2	2	4	192	191	3	-15	0	5	43	55	4	-10	3	5	89	97	2
-7	2	3	147	146	2	8	5	3	0	2	1	3	2	4	45	54	2	-14	0	5	0	7	1	-9	3	5	51	44	3
-6	2	3	57	62	1	-6	6	3	0	12	1	4	2	4	91	75	2	-13	0	5	26	47	6	-8	3	5	57	72	2
-5	2	3	78	93	1	-5	6	3	0	13	1	5	2	4	72	65	1	-12	0	5	28	3	27	-7	3	5	21	24	20
-4	2	3	52	44	1	-4	6	3	0	10	1	6	2	4	82	71	2	-11	0	5	80	72	1	-6	3	5	28	39	4
-3	2	3	68	64	1	-3	6	3	30	13	29	7	2	4	104	115	2	-10	0	5	23	31	23	-5	3	5	25	24	24
-2	2	3	230	257	2	-2	6	3	0	14	1	8	2	4	60	61	2	-9	0	5	204	190	3	-4	3	5	53	53	2
-1	2	3	187	173	2	-1	6	3	0	18	1	9	2	4	51	51	3	-8	0	5	157	149	3	-3	3	5	40	52	3
0	2	3	197	167	2	0	6	3	0	18	1	10	2	4	0	16	1	-7	0	5	371	288	2	-2	3	5	9	9	9
1	2	3	38	43	2	1	6	3	0	15	1	11	2	4	27	2	26	-6	0	5	0	16	1	-1	3	5	33	49	3
2	2	3	239	193	2	2	6	3	0	18	1	12	2	4	38	37	5	-5	0	5	83	102	2	0	3	5	22	20	5
3	2	3	199	187	3	3	6	3	20	21	20	-14	3	4	24	13	24	-4	0	5	116	133	2	1	3	5	55	52	2
4	2	3	65	67	1	4	6	3	13	15	13	-13	3	4	63	56	3	-3	0	5	253	206	2	2	3	5	70	63	2
5	2	3	19	21	6	-16	0	4	62	48	3	-12	3	4	48	48	3	-2	0	5	246	159	2	3	3	5	0	15	1
6	2	3	83	75	2	-15	0	4	0	9	1	-11	3	4	65	62	2	-1	0	5	489	439	2	4	3	5	25	28	6
7	2	3	67	64	2	-14	0	4	31	34	5	-10	3	4	72	61	2	0	0	5	285	269	2	5	3	5	0	21	1
8	2	3	106	99	2	-13	0	4	59	32	2	-9	3	4	54	55	2	1	0	5	79	95	1	6	3	5	0	18	1
9	2	3	83	81	2	-12	0	4	79	89	2	-8	3	4	44	51	3	2	0	5	195	173	2	7	3	5	0	12	1
10	2	3	21	13	20	-11	0	4	44	54	3	-7	3	4	57	40	2	3	0	5	126	122	2	8	3	5	0	9	1
11	2	3	27	28	27	-10	0	4	60	78	2	-6	3	4	29	36	4	4	0	5	18	8	7	9	3	5	12	9	12
12	2	3	19	11	19	-9	0	4	196	167	3	-5	3	4	24	23	5	5	0	5	91	78	2	10	3	5	0	9	1
13	2	3	30	24	30	-8	0	4	0	66	1	-4	3	4	33	51	3	6	0	5	134	134	2	-13	4	5	13	22	13
-14	3	3	0	19	1	-7	0	4	157	185	3	-3	3	4	61	86	2	7	0	5	120	112	3	-12	4	5	0	10	1
-13	3	3	0	7	1	-6	0	4	21	2	21	-2	3	4	176	200	3	8	0	5	72	49	2	-11	4	5	0	6	1
-12	3	3	0	4	1	-5	0	4	321	297	2	-1	3	4	98	85	2	9	0	5	0	18	1	-10	4	5	9	16	8
-11	3	3	56	55	2	-4	0	4	76	132	1	0	3	4	95	95	2	10	0	5	30	29	30	-9	4	5	57	48	3
-10	3	3	14	9	13	-3	0	4	22	53	21	1	3	4	88	93	2	11	0	5	56	32	4	-8	4	5	25	40	25
-9	3	3	66	84	2	-2	0	4	48	35	1	2	3	4	22	19	21	12	0	5	35	19	6	-7	4	5	0	5	1
-8	3	3	92	93	2	-1	0	4	976	887	8	3	3	4	0	48	1	-16	1	5	39	40	5	-6	4	5	22	8	21
-7	3	3	22	38	7	0	0	4	153	101	2	4	3	4	43	50	3	-15	1	5	18	30	17	-5	4	5	26	37	5
-6	3	3	12	15	11	1	0	4	22	51	4	5	3	4	52	60	2	-14	1	5	29	47	29	-4	4	5	30	39	5
-5	3	3	39	47	3	2	0	4	8	6	8	6	3	4	19	34	10	-13	1	5	55	37	3	-3	4	5	41	50	3
-4	3	3	61	67	2	3	0	4	130	92	3	7	3	4	34	30	4	-12	1	5	35	34	5	-2	4	5	91	102	2
-3	3	3	116	118	2	4	0	4	178	182	3	8	3	4	0	18	1	-11	1	5	0	8	1	-1	4	5	105	127	2
-2	3	3	120	117	2	5	0	4	184	159	3	9	3	4	26	21	26	-10	1	5	140	139	3	0	4	5	90	77	2
-1	3	3	60	66	2	6	0	4	100	93	2	10	3	4	27	36	27	-9	1	5	131	144	2	1	4	5	42	45	3
0	3	3	33	26	3	7	0	4	80	96	1	11	3	4	24	18	9	-8	1	5	262	236	3	2	4	5	39	20	4
1	3	3	36	42	3	8	0	4	114	130	3	-13	4	4	9	10	8	-7	1	5	171	169	3	3	4	5	52	61	3
2	3	3	137	123	2	9	0	4	109	109	2	-12	4	4	0	8	1	-6	1	5	248	229	3	4	4	5	47	53	3

Table A.7 Observed and calculated structure factors for p salt

h	k	l	10Fo	10Fc	10s	h	k	l	10Fo	10Fc	10s	h	k	l	10Fo	10Fc	10s	h	k	l	10Fo	10Fc	10s	h	k	l	10Fo	10Fc	10s
5	4	5	11	35	11	-13	2	6	42	29	4	-4	6	6	12	6	12	-14	3	7	15	18	15	-14	1	8	24	44	8
6	4	5	0	11	1	-12	2	6	49	46	3	-3	6	6	0	2	1	-13	3	7	33	45	6	-13	1	8	0	26	1
7	4	5	27	22	27	-11	2	6	86	75	2	-2	6	6	20	11	17	-12	3	7	0	13	1	-12	1	8	68	79	2
8	4	5	28	13	7	-10	2	6	135	134	3	-1	6	6	11	9	10	-11	3	7	0	6	1	-11	1	8	73	58	2
9	4	5	33	27	6	-9	2	6	64	67	2	0	6	6	21	8	20	-10	3	7	0	10	1	-10	1	8	164	157	2
10	5	5	9	16	9	-8	2	6	68	78	2	-17	0	7	10	14	9	-9	3	7	13	18	13	-9	1	8	60	48	2
-9	5	5	30	28	29	-7	2	6	61	67	2	-16	0	7	44	46	4	-8	3	7	36	40	4	-8	1	8	147	151	2
-8	5	5	0	30	1	-6	2	6	81	88	2	-15	0	7	0	7	1	-7	3	7	23	17	23	-7	1	8	80	90	2
-7	5	5	0	18	1	-5	2	6	71	76	2	-14	0	7	32	51	5	-6	3	7	23	53	22	-6	1	8	130	126	2
-6	5	5	9	24	8	-4	2	6	141	135	2	-13	0	7	59	57	2	-5	3	7	35	47	4	-5	1	8	128	127	2
-5	5	5	22	25	8	-3	2	6	161	168	3	-12	0	7	76	92	2	-4	3	7	12	15	12	-4	1	8	165	151	3
-4	5	5	34	22	4	-2	2	6	115	102	2	-11	0	7	82	83	2	-3	3	7	50	67	2	-3	1	8	163	155	3
-3	5	5	44	47	4	-1	2	6	70	89	2	-10	0	7	122	128	3	-2	3	7	83	102	1	-2	1	8	14	15	13
-2	5	5	53	37	3	0	2	6	108	126	2	-9	0	7	58	57	2	-1	3	7	30	53	5	-1	1	8	127	118	2
-1	5	5	39	38	4	1	2	6	50	43	2	-8	0	7	195	153	3	0	3	7	42	42	3	0	1	8	94	93	2
0	5	5	16	22	16	2	2	6	21	33	6	-7	0	7	160	143	3	1	3	7	55	58	2	1	1	8	138	141	3
1	5	5	0	10	1	3	2	6	32	38	4	-6	0	7	240	226	3	2	3	7	55	56	2	2	1	8	53	53	2
2	5	5	21	27	9	4	2	6	50	38	3	-5	0	7	89	95	2	3	3	7	23	37	7	3	1	8	30	48	5
3	5	5	26	21	25	5	2	6	76	77	2	-4	0	7	318	270	2	4	3	7	43	50	3	4	1	8	87	70	2
4	5	5	0	9	1	6	2	6	19	6	11	-3	0	7	201	223	3	5	3	7	71	74	2	5	1	8	85	85	2
5	5	5	0	8	1	7	2	6	23	25	23	-2	0	7	132	155	2	6	3	7	67	64	2	6	1	8	41	49	4
6	5	5	29	14	7	8	2	6	27	28	26	-1	0	7	35	23	3	7	3	7	17	10	17	7	1	8	22	10	22
-6	6	5	16	13	16	9	2	6	47	57	4	0	0	7	180	185	3	8	3	7	13	20	12	8	1	8	30	19	30
-5	6	5	17	22	17	10	2	6	9	15	8	1	0	7	80	69	1	9	3	7	0	7	1	9	1	8	20	4	17
-4	6	5	13	13	13	11	2	6	0	20	1	2	0	7	15	2	11	-13	4	7	0	2	1	10	1	8	28	18	9
-3	6	5	28	6	27	-15	3	6	0	22	1	3	0	7	25	43	24	-12	4	7	20	7	20	-16	2	8	41	38	5
-2	6	5	0	9	1	-14	3	6	13	37	13	4	0	7	105	103	2	-11	4	7	27	2	26	-15	2	8	20	23	20
-1	6	5	30	16	30	-13	3	6	20	20	19	5	0	7	52	51	2	-10	4	7	23	21	8	-14	2	8	26	41	26
0	6	5	30	23	30	-12	3	6	0	25	1	6	0	7	7	9	7	-9	4	7	61	63	2	-13	2	8	0	25	1
1	6	5	0	21	1	-11	3	6	28	20	28	7	0	7	0	17	1	-8	4	7	75	70	2	-12	2	8	70	72	2
16	0	6	0	15	1	-10	3	6	21	36	8	8	0	7	42	36	3	-7	4	7	27	38	26	-11	2	8	90	83	2
15	0	6	91	72	2	-9	3	6	72	106	2	9	0	7	41	29	4	-6	4	7	18	5	12	-10	2	8	102	79	2
14	0	6	44	34	4	-8	3	6	49	65	3	10	0	7	0	10	1	-5	4	7	0	3	1	-9	2	8	23	41	7
13	0	6	74	56	2	-7	3	6	37	49	3	11	0	7	15	15	14	-4	4	7	26	38	6	-8	2	8	41	47	3
12	0	6	100	97	2	-6	3	6	48	61	3	-16	1	7	0	19	1	-3	4	7	49	60	3	-7	2	8	63	60	2
11	0	6	0	10	1	-5	3	6	44	50	3	-15	1	7	68	66	3	-2	4	7	32	32	5	-6	2	8	56	63	2
10	0	6	79	77	2	-4	3	6	0	44	1	-14	1	7	0	33	1	-1	4	7	13	32	13	-5	2	8	21	27	6
-9	0	6	81	88	1	-3	3	6	0	15	1	-13	1	7	19	23	11	0	4	7	18	36	17	-4	2	8	80	85	1
-8	0	6	304	312	3	-2	3	6	39	33	3	-12	1	7	97	106	2	1	4	7	0	28	1	-3	2	8	80	67	2
-7	0	6	62	29	1	-1	3	6	49	65	2	-11	1	7	85	73	2	2	4	7	28	27	28	-2	2	8	37	22	3
-6	0	6	303	322	2	0	3	6	24	29	5	-10	1	7	164	177	2	3	4	7	26	13	6	-1	2	8	87	84	2
-5	0	6	91	94	2	1	3	6	14	34	13	-9	1	7	83	65	2	4	4	7	0	3	1	0	2	8	115	116	2
-4	0	6	0	41	1	2	3	6	81	74	2	-8	1	7	157	135	3	5	4	7	35	14	5	1	2	8	60	64	2
-3	0	6	330	323	2	3	3	6	64	49	2	-7	1	7	176	138	3	6	4	7	0	16	1	2	2	8	25	15	25
-2	0	6	135	96	3	4	3	6	20	16	19	-6	1	7	77	57	1	7	4	7	0	12	1	3	2	8	0	8	1
-1	0	6	89	61	1	5	3	6	0	33	1	-5	1	7	20	18	20	-10	5	7	0	11	1	4	2	8	17	7	17
0	0	6	202	224	2	6	3	6	0	11	1	-4	1	7	183	186	3	-9	5	7	0	12	1	5	2	8	24	40	24
1	0	6	176	167	3	7	3	6	0	8	1	-3	1	7	118	106	2	-8	5	7	14	9	13	6	2	8	23	37	23
2	0	6	275	253	3	8	3	6	19	24	19	-2	1	7	149	163	3	-7	5	7	0	15	1	7	2	8	0	16	1
3	0	6	0	18	1	9	3	6	24	20	9	-1	1	7	127	126	2	-6	5	7	12	17	12	8	2	8	0	28	1
4	0	6	50	63	2	10	3	6	0	20	1	0	1	7	234	217	3	-5	5	7	24	15	24	9	2	8	24	27	11
5	0	6	18	18	18	-13	4	6	28	17	28	1	1	7	191	170	3	-4	5	7	26	8	25	-15	3	8	0	14	1
6	0	6	73	78	2	-12	4	6	0	13	1	2	1	7	94	101	2	-3	5	7	21	26	21	-14	3	8	30	14	30
7	0	6	41	32	3	-11	4	6	20	27	19	3	1	7	25	4	25	-2	5	7	23	23	8	-13	3	8	0	10	1
8	0	6	23	8	23	-10	4	6	15	26	14	4	1	7	19	34	18	-1	5	7	15	13	14	-12	3	8	18	29	18
9	0	6	40	60	4	-9	4	6	0	23	1	5	1	7	42	51	3	0	5	7	26	0	26	-11	3	8	27	23	6
10	0	6	36	27	5	-8	4	6	28	34	6	6	1	7	50	48	3	1	5	7	0	6	1	-10	3	8	50	51	3
11	0	6	0	17	1	-7	4	6	0	22	1	7	1	7	0	25	1	2	5	7	25	10	25	-9	3	8	0	27	1
12	0	6	0	19	1	-6	4	6	43	25	3	8	1	7	57	44	3	3	5	7	18	21	18	-8	3	8	23	34	7
16	1	6	51	41	4	-5	4	6	61	40	2	9	1	7	41	48	5	4	5	7	0	24	1	-7	3	8	11	38	10
15	1	6	37	41	5	-4	4	6	0	43	1	10	1	7	28	25	27	-17	0	8	64	47	3	-6	3	8	11	18	11
14	1	6	0	26	1	-3	4	6	18	27	12	11	1	7	37	20	6	-16	0	8	39	12	28	-5	3	8	27	57	5
13	1	6	115	97	2	-2	4	6	17	43	16	-16	2	7	48	34	4	-15	0	8	31	52	31	-4	3	8	0	10	1
12	1	6	108	107	2	-1	4	6	22	6	8	-15	2	7	27	24	27	-14	0	8	59	50	2	-3	3	8	27	56	26
11	1	6	102	91	2	0	4	6	0	2	1	-14	2	7	52	47	3	-13	0	8	76	63	2	-2	3	8	64	82	2
10	1	6	111	105	2	1	4	6	20	27	20	-13	2	7	42	46	4	-12	0	8	75	67	2	-1	3	8	68	85	2
-9	1	6	23	50	22	2	4	6	45	44	3	-12	2	7	0	45	1	-11	0	8	15	2	14	0	3	8	24	34	7
-8	1	6	97	85	2	3	4	6	28	8	27	-11	2	7	48	39	3	-10	0	8	49	28	3	1	3	8	34	39	5
-7	1	6	88	88	2	4	4	6	34	18	5	-10	2	7	97	80	2	-9	0	8	0	12	1	2	3	8	0	47	1
-6	1	6	112	89	2	5	4	6	48	30	3	-9	2	7	37	28	3	-8	0	8	72	70	1	3	3	8	14	26	13
-5	1	6	67	62	1	6	4	6	17	25	17	-8	2	7	53	45	2	-7	0	8	16	12	16	4	3	8	31	21	5
-4	1	6	81	54	1	7	4	6	9	10	8	-7	2	7	87	86	1	-6	0	8	95	77	2	5	3	8	21	20	10
-3	1	6	175	188	2	8	4	6	0	7	1	-6	2	7	107	105	2	-5	0	8	101	98	2	6	3	8	15	9	15
-2	1	6	244	205	2	-10	5	6	26	5	26	-5	2	7	66	73	2	-4	0	8	260	250	3	7	3	8	18	12	18
-1	1	6	191	187	3	-9	5	6	26	15	25	-4	2	7	39	43	3	-3	0	8	206	155	3	8	3	8	16	9	16
0	1	6	289	286	2	-8	5	6	34	26	5	-3	2	7	56	60	2	-2	0	8	71	64	1	-13	4	8	14	27	13
1	1	6	203	208	3	-7	5	6	12	14	12	-2	2	7	144	174	2	-1	0	8	88	93	2	-12	4	8	0	28	1
2	1	6	63	67	1	-6	5	6	9	25	8	-1	2	7	159	161	3	0	0	8	0	25	1	-11	4	8	0	21	1
3	1	6	60	56	2	-5	5	6	17	23	17	0	2	7	56	59	2	1	0	8	33	5	3	-10	4	8	28	28	27
4	1	6	22	20	6	-4	5	6	33	27	5	1	2	7	51	50	2	2	0	8	60	42	2	-9	4	8	23	22	22
5	1	6	62	61	2	-3	5	6	0	8	1	2	2	7	45	43	3	3	0	8	127	125	3	-8	4	8	0	18	1
6	1	6	96	98	2	-2	5	6	0	10	1	3	2	7	63	68	2	4	0	8	40	49	3	-7	4	8	0	22	1
7	1	6	18	21	12	-1	5	6	23	18	8	4	2	7	25	27	25	5	0	8	98	84	2	-6	4	8	7	12	7
8	1	6	85	82	2	0	5	6	24	14	24	5	2	7	22	20	21	6	0	8	28	29	5	-5	4	8	23	32	22
9	1	6	52	49	3	1	5	6	33	13	6	6	2	7	40	50	4	7	0	8	111	92	3	-4	4	8	36	46	4
10	1	6	0	27	1	2	5	6	31	14	6	7	2	7	25	29	8	8	0	8	92	89	2	-3	4	8	36	41	4
11	1	6	29	17	28	3	5	6	28	7	27	8	2	7	15	23	14	9	0	8	40	43	5	-2	4	8	37	41	4
16	2	6	21	24	21	4	5	6	16	2	16	9	2	7	18	15	17	10	0	8	0	6	1	-1	4	8	21	44	21
15	2	6	32	28	7	5	5	6	0	9	1	10	2	7	22	8	12	-16	1	8	0	29	1	0	4	8	0	8	1
14	2	6	21	2	21	-5	6	6	0	12	1	-15	3	7	16	15	16	-15	1	8	0	21	1	1	4	8	25	14	6

Table A.7 Observed and calculated structure factors for p salt

h	k	l	10Fo	10Fc	10s	h	k	l	10Fo	10Fc	10s	h	k	l	10Fo	10Fc	10s	h	k	l	10Fo	10Fc	10s	h	k	l	10Fo	10Fc	10s
2	4	8	20	13	10	3	2	9	37	38	4	-8	1	10	64	81	2	-12	0	11	28	34	5	-6	4	11	22	13	21
3	4	8	9	10	8	4	2	9	0	24	1	-7	1	10	95	85	2	-11	0	11	0	16	1	-5	4	11	0	4	1
4	4	8	13	23	13	5	2	9	57	45	3	-6	1	10	58	60	2	-10	0	11	0	34	1	-4	4	11	0	18	1
5	4	8	29	15	28	6	2	9	34	40	6	-5	1	10	14	21	13	-9	0	11	53	40	2	-3	4	11	9	22	8
6	4	8	16	4	16	7	2	9	27	14	27	-4	1	10	107	109	2	-8	0	11	69	57	2	-2	4	11	17	14	16
-10	5	8	13	18	13	8	2	9	0	21	1	-3	1	10	30	31	4	-7	0	11	141	124	3	-1	4	11	0	7	1
-9	5	8	36	15	5	-14	3	9	16	8	16	-2	1	10	61	68	2	-6	0	11	0	37	1	0	4	11	0	24	1
-8	5	8	0	18	1	-13	3	9	27	18	8	-1	1	10	92	88	2	-5	0	11	75	73	2	1	4	11	0	19	1
-7	5	8	6	23	5	-12	3	9	21	15	21	0	1	10	59	58	2	-4	0	11	61	51	2	2	4	11	30	8	29
-6	5	8	27	13	26	-11	3	9	19	15	11	1	1	10	36	23	4	-3	0	11	74	72	2	-16	0	12	0	3	1
-5	5	8	0	8	1	-10	3	9	16	33	15	2	1	10	47	41	3	-2	0	11	0	9	1	-15	0	12	0	18	1
-4	5	8	0	22	1	-9	3	9	55	73	3	3	1	10	55	41	3	-1	0	11	136	119	3	-14	0	12	15	16	15
-3	5	8	26	26	26	-8	3	9	21	11	20	4	1	10	43	38	4	0	0	11	0	20	1	-13	0	12	15	13	14
-2	5	8	3	13	3	-7	3	9	44	56	3	5	1	10	42	39	4	1	0	11	17	16	16	-12	0	12	0	5	1
-1	5	8	27	5	26	-6	3	9	53	54	3	6	1	10	0	17	1	2	0	11	47	27	3	-11	0	12	0	22	1
0	5	8	0	8	1	-5	3	9	18	36	18	7	1	10	0	35	1	3	0	11	96	86	2	-10	0	12	89	76	2
1	5	8	22	11	22	-4	3	9	25	25	24	8	1	10	0	21	1	4	0	11	21	2	9	-9	0	12	90	99	2
2	5	8	21	6	12	-3	3	9	0	29	1	-15	2	10	24	8	24	5	0	11	37	29	5	-8	0	12	28	24	28
3	5	8	26	9	26	-2	3	9	74	106	2	-14	2	10	21	16	11	6	0	11	10	11	9	-7	0	12	23	38	22
-16	0	9	18	5	18	-1	3	9	88	110	2	-13	2	10	40	43	5	7	0	11	0	12	1	-6	0	12	25	29	24
-15	0	9	15	1	14	0	3	9	42	47	4	-12	2	10	41	32	4	-16	1	11	25	22	24	-5	0	12	84	75	2
-14	0	9	12	4	11	1	3	9	24	16	23	-11	2	10	57	50	3	-15	1	11	18	14	18	-4	0	12	59	55	2
-13	0	9	0	29	1	2	3	9	20	11	10	-10	2	10	57	49	2	-14	1	11	25	20	24	-3	0	12	45	31	3
-12	0	9	13	31	13	3	3	9	12	18	11	-9	2	10	0	18	1	-13	1	11	0	25	1	-2	0	12	84	78	2
-11	0	9	105	96	3	4	3	9	28	33	7	-8	2	10	39	47	4	-12	1	11	0	18	1	-1	0	12	12	30	12
-10	0	9	210	212	4	5	3	9	31	19	6	-7	2	10	60	70	2	-11	1	11	79	74	2	0	0	12	0	37	1
-9	0	9	0	34	1	6	3	9	0	7	1	-6	2	10	38	43	3	-10	1	11	76	60	2	1	0	12	65	65	2
-8	0	9	96	86	2	7	3	9	16	20	16	-5	2	10	45	69	3	-9	1	11	26	15	6	2	0	12	74	62	2
-7	0	9	64	69	2	-12	4	9	14	9	13	-4	2	10	40	58	3	-8	1	11	66	54	2	3	0	12	0	1	1
-6	0	9	0	19	1	-11	4	9	13	15	12	-3	2	10	26	35	26	-7	1	11	44	38	3	4	0	12	0	18	1
-5	0	9	109	99	2	-10	4	9	23	31	23	-2	2	10	84	95	2	-6	1	11	66	76	2	5	0	12	25	13	25
-4	0	9	71	49	2	-9	4	9	33	22	5	-1	2	10	123	133	2	-5	1	11	7	22	7	6	0	12	16	20	15
-3	0	9	80	73	2	-8	4	9	9	20	8	0	2	10	59	58	2	-4	1	11	30	39	4	-15	1	12	0	23	1
-2	0	9	133	146	2	-7	4	9	0	16	1	1	2	10	0	24	1	-3	1	11	88	94	2	-14	1	12	27	19	26
-1	0	9	140	146	2	-6	4	9	0	11	1	2	2	10	22	8	9	-2	1	11	85	96	2	-13	1	12	31	18	31
0	0	9	0	8	1	-5	4	9	8	8	7	3	2	10	0	10	1	-1	1	11	90	95	2	-12	1	12	37	27	4
1	0	9	73	70	2	-4	4	9	0	18	1	4	2	10	0	35	1	0	1	11	47	53	3	-11	1	12	74	57	2
2	0	9	0	8	1	-3	4	9	16	44	16	5	2	10	21	12	12	1	1	11	71	74	2	-10	1	12	27	20	26
3	0	9	32	24	4	-2	4	9	23	48	23	6	2	10	0	5	1	2	1	11	51	49	3	-9	1	12	0	33	1
4	0	9	0	2	1	-1	4	9	27	17	6	7	2	10	11	14	10	3	1	11	21	13	9	-8	1	12	35	45	4
5	0	9	46	47	3	0	4	9	29	13	6	-14	3	10	16	7	16	4	1	11	0	6	1	-7	1	12	42	49	3
6	0	9	75	56	2	1	4	9	20	12	11	-13	3	10	25	13	9	5	1	11	22	20	12	-6	1	12	0	22	1
7	0	9	20	25	11	2	4	9	0	12	1	-12	3	10	0	11	1	6	1	11	13	17	13	-5	1	12	47	45	3
8	0	9	0	18	1	3	4	9	0	7	1	-11	3	10	26	14	25	7	1	11	33	19	32	-4	1	12	90	98	2
9	0	9	0	6	1	4	4	9	0	8	1	-10	3	10	9	24	9	-15	2	11	31	16	31	-3	1	12	90	92	2
-16	1	9	18	35	18	5	4	9	28	10	28	-9	3	10	43	52	3	-14	2	11	35	17	5	-2	1	12	0	12	1
-15	1	9	47	45	4	-9	5	9	27	15	8	-8	3	10	0	63	1	-13	2	11	9	26	8	-1	1	12	74	57	2
-14	1	9	69	66	2	-8	5	9	0	9	1	-7	3	10	9	27	8	-12	2	11	24	16	24	0	1	12	16	25	16
-13	1	9	49	45	3	-7	5	9	26	3	26	-6	3	10	24	38	23	-11	2	11	62	53	2	1	1	12	0	5	1
-12	1	9	62	61	2	-6	5	9	29	5	28	-5	3	10	41	62	4	-10	2	11	23	15	7	2	1	12	0	19	1
-11	1	9	70	61	2	-5	5	9	25	15	25	-4	3	10	0	10	1	-9	2	11	0	21	1	3	1	12	29	7	7
-10	1	9	99	80	2	-4	5	9	0	17	1	-3	3	10	0	20	1	-8	2	11	60	53	2	4	1	12	0	11	1
-9	1	9	16	16	15	-3	5	9	30	11	29	-2	3	10	27	27	6	-7	2	11	64	63	2	5	1	12	16	7	15
-8	1	9	18	22	9	-2	5	9	12	12	11	-1	3	10	0	25	1	-6	2	11	25	12	25	-14	2	12	0	7	1
-7	1	9	87	92	2	-1	5	9	0	17	1	0	3	10	0	8	1	-5	2	11	40	30	4	-13	2	12	12	5	12
-6	1	9	80	84	1	0	5	9	0	17	1	1	3	10	18	16	14	-4	2	11	0	20	1	-12	2	12	31	22	6
-5	1	9	36	45	3	1	5	9	25	9	9	2	3	10	23	9	8	-3	2	11	0	15	1	-11	2	12	19	20	19
-4	1	9	136	123	2	-16	0	10	26	35	26	3	3	10	0	10	1	-2	2	11	62	59	2	-10	2	12	43	43	4
-3	1	9	89	98	2	-15	0	10	33	46	6	4	3	10	36	21	5	-1	2	11	62	56	2	-9	2	12	28	38	28
-2	1	9	18	12	8	-14	0	10	48	51	4	5	3	10	30	28	8	0	2	11	29	28	28	-8	2	12	61	71	2
-1	1	9	103	81	2	-13	0	10	20	36	20	6	3	10	0	10	1	1	2	11	0	20	1	-7	2	12	51	46	3
0	1	9	68	49	2	-12	0	10	0	3	1	-12	4	10	0	13	1	2	2	11	26	9	7	-6	2	12	19	47	19
1	1	9	76	82	2	-11	0	10	129	112	3	-11	4	10	21	17	12	3	2	11	30	22	6	-5	2	12	0	33	1
2	1	9	43	32	3	-10	0	10	205	173	4	-10	4	10	0	27	1	4	2	11	0	10	1	-4	2	12	0	35	1
3	1	9	65	65	2	-9	0	10	44	53	3	-9	4	10	0	31	1	5	2	11	18	25	18	-3	2	12	61	67	2
4	1	9	81	80	2	-8	0	10	7	22	7	-8	4	10	0	6	1	6	2	11	29	13	28	-2	2	12	49	52	3
5	1	9	55	68	3	-7	0	10	33	23	3	-7	4	10	9	5	8	-14	3	11	35	29	6	-1	2	12	12	25	11
6	1	9	39	26	4	-6	0	10	42	61	3	-6	4	10	23	12	7	-13	3	11	0	12	1	0	2	12	27	18	26
7	1	9	20	49	19	-5	0	10	0	26	1	-5	4	10	25	17	6	-12	3	11	0	19	1	1	2	12	0	16	1
8	1	9	58	54	4	-4	0	10	26	9	25	-4	4	10	0	18	1	-11	3	11	18	16	18	2	2	12	0	14	1
9	1	9	43	39	5	-3	0	10	81	82	1	-3	4	10	0	29	1	-10	3	11	0	35	1	3	2	12	0	10	1
-16	2	9	0	20	1	-2	0	10	80	80	1	-2	4	10	36	29	4	-9	3	11	17	4	16	4	2	12	0	17	1
-15	2	9	41	23	5	-1	0	10	29	26	4	-1	4	10	35	28	5	-8	3	11	29	33	28	-13	3	12	13	22	13
-14	2	9	0	32	1	0	0	10	125	146	3	0	4	10	0	16	1	-7	3	11	18	46	18	-12	3	12	28	32	7
-13	2	9	12	18	12	1	0	10	139	143	3	1	4	10	23	6	9	-6	3	11	0	31	1	-11	3	12	25	29	9
-12	2	9	0	35	1	2	0	10	39	28	3	2	4	10	18	6	18	-5	3	11	22	10	21	-10	3	12	20	16	19
-11	2	9	25	38	7	3	0	10	47	44	3	3	4	10	24	11	11	-4	3	11	19	29	12	-9	3	12	9	18	8
-10	2	9	0	20	1	4	0	10	57	83	2	4	4	10	25	10	25	-3	3	11	0	46	1	-8	3	12	0	27	1
-9	2	9	18	45	18	5	0	10	0	15	1	-8	5	10	0	7	1	-2	3	11	16	36	16	-7	3	12	0	25	1
-8	2	9	110	113	2	6	0	10	20	25	11	-7	5	10	0	8	1	-1	3	11	12	44	11	-6	3	12	12	3	12
-7	2	9	48	40	3	7	0	10	32	37	32	-6	5	10	19	16	18	0	3	11	15	41	14	-5	3	12	0	15	1
-6	2	9	49	56	3	8	0	10	42	41	5	-5	5	10	13	15	13	1	3	11	0	34	1	-4	3	12	23	12	22
-5	2	9	23	25	23	-16	1	10	0	12	1	-4	5	10	21	11	13	2	3	11	0	18	1	-3	3	12	32	41	5
-4	2	9	23	2	6	-15	1	10	0	34	1	-3	5	10	0	9	1	3	3	11	0	14	1	-2	3	12	52	64	3
-3	2	9	34	46	3	-14	1	10	0	12	1	-2	5	10	21	15	20	4	3	11	14	7	13	-1	3	12	44	48	4
-2	2	9	31	34	4	-13	1	10	36	22	4	-1	5	10	0	14	1	-11	4	11	0	4	1	0	3	12	25	31	25
-1	2	9	72	93	2	-12	1	10	57	46	2	-16	0	11	26	16	9	-10	4	11	0	25	1	1	3	12	0	12	1
0	2	9	77	82	2	-11	1	10	85	88	2	-15	0	11	59	60	3	-9	4	11	24	31	9	2	3	12	0	15	1
1	2	9	41	43	3	-10	1	10	103	90	2	-14	0	11	39	27	4	-8	4	11	18	10	17	3	3	12	0	14	1
2	2	9	26	55	6	-9	1	10	52	52	2	-13	0	11	38	42	4	-7	4	11	0	12	1	-10	4	12	0	14	1

Table A.7 Observed and calculated structure factors for p salt

h	k	l	10Fo	10Fc	10s	h	k	l	10Fo	10Fc	10s	h	k	l	10Fo	10Fc	10s	h	k	l	10Fo	10Fc	10s	h	k	l	10Fo	10Fc	10s
-9	4	12	25	3	24	1	1	13	30	14	29	-10	0	14	0	15	1	-11	3	14	0	10	1	-6	2	15	18	27	18
-8	4	12	0	15	1	2	1	13	22	6	21	-9	0	14	17	9	16	-10	3	14	0	22	1	-5	2	15	41	32	5
-7	4	12	0	22	1	3	1	13	13	2	12	-8	0	14	46	41	3	-9	3	14	0	22	1	-4	2	15	24	22	24
-6	4	12	9	16	9	4	1	13	19	21	18	-7	0	14	31	20	30	-8	3	14	0	13	1	-3	2	15	11	21	10
-5	4	12	18	3	18	-14	2	13	0	7	1	-6	0	14	0	2	1	-7	3	14	27	7	27	-2	2	15	32	16	32
-4	4	12	30	13	30	-13	2	13	24	18	24	-5	0	14	22	42	21	-6	3	14	0	6	1	-1	2	15	15	16	15
-3	4	12	0	13	1	-12	2	13	33	27	6	-4	0	14	26	17	6	-5	3	14	6	3	6	-8	3	15	27	6	26
-2	4	12	0	5	1	-11	2	13	0	27	1	-3	0	14	8	17	8	-4	3	14	0	4	1	-7	3	15	0	12	1
-1	4	12	21	8	20	-10	2	13	0	14	1	-2	0	14	0	9	1	-3	3	14	29	4	7	-6	3	15	0	6	1
0	4	12	9	12	9	-9	2	13	9	6	8	-1	0	14	0	35	1	-2	3	14	0	12	1	-5	3	15	0	5	1
-15	0	13	0	6	1	-8	2	13	30	33	5	0	0	14	0	17	1	-1	3	14	0	25	1	-4	3	15	7	14	7
-14	0	13	42	24	4	-7	2	13	52	52	3	1	0	14	20	9	19	-13	0	15	16	27	15	-12	0	16	26	11	26
-13	0	13	40	31	4	-6	2	13	0	16	1	2	0	14	0	10	1	-12	0	15	31	15	31	-11	0	16	20	15	19
-12	0	13	79	71	2	-5	2	13	18	23	18	3	0	14	0	6	1	-11	0	15	9	31	8	-10	0	16	26	11	8
-11	0	13	105	93	2	-4	2	13	0	22	1	-14	1	14	31	17	31	-10	0	15	50	48	4	-9	0	16	20	17	20
-10	0	13	0	11	1	-3	2	13	21	22	20	-13	1	14	0	21	1	-9	0	15	0	3	1	-8	0	16	20	0	20
-9	0	13	0	8	1	-2	2	13	31	37	30	-12	1	14	13	24	12	-8	0	15	19	6	19	-7	0	16	9	20	8
-8	0	13	55	60	2	-1	2	13	42	34	4	-11	1	14	53	40	3	-7	0	15	0	7	1	-6	0	16	0	6	1
-7	0	13	22	39	22	0	2	13	30	28	30	-10	1	14	58	52	3	-6	0	15	27	31	26	-5	0	16	0	19	1
-6	0	13	27	32	6	1	2	13	22	13	11	-9	1	14	0	20	1	-5	0	15	21	28	20	-4	0	16	22	4	22
-5	0	13	0	34	1	2	2	13	0	13	1	-8	1	14	0	29	1	-4	0	15	43	43	4	-3	0	16	0	8	1
-4	0	13	90	113	2	3	2	13	0	15	1	-7	1	14	0	10	1	-3	0	15	0	20	1	-2	0	16	0	4	1
-3	0	13	65	74	2	-12	3	13	0	30	1	-6	1	14	26	32	26	-2	0	15	30	35	30	-11	1	16	0	25	1
-2	0	13	55	42	2	-11	3	13	24	10	24	-5	1	14	14	18	14	-1	0	15	0	11	1	-10	1	16	29	22	7
-1	0	13	20	24	19	-10	3	13	24	19	9	-4	1	14	0	33	1	0	0	15	0	16	1	-9	1	16	28	17	27
0	0	13	0	4	1	-9	3	13	0	9	1	-3	1	14	0	30	1	1	0	15	0	18	1	-8	1	16	16	11	15
1	0	13	21	24	20	-8	3	13	18	15	17	-2	1	14	29	28	6	-13	1	15	0	8	1	-7	1	16	21	11	13
2	0	13	0	21	1	-7	3	13	0	29	1	-1	1	14	0	19	1	-12	1	15	0	22	1	-6	1	16	16	21	15
3	0	13	20	17	19	-6	3	13	15	11	15	0	1	14	13	6	12	-11	1	15	39	22	4	-5	1	16	30	30	30
4	0	13	0	4	1	-5	3	13	0	5	1	1	1	14	29	17	28	-10	1	15	30	22	7	-4	1	16	22	16	12
-15	1	13	0	26	1	-4	3	13	0	12	1	2	1	14	0	5	1	-9	1	15	27	25	7	-3	1	16	31	23	30
-14	1	13	33	27	5	-3	3	13	30	15	6	-13	2	14	22	19	11	-8	1	15	34	21	5	-2	1	16	28	21	28
-13	1	13	0	33	1	-2	3	13	0	13	1	-12	2	14	24	26	24	-7	1	15	19	26	19	-9	2	16	25	27	25
-12	1	13	18	11	16	-1	3	13	0	11	1	-11	2	14	13	21	12	-6	1	15	0	15	1	-8	2	16	0	17	1
-11	1	13	0	8	1	0	3	13	24	23	10	-10	2	14	37	44	5	-5	1	15	0	16	1	-7	2	16	0	23	1
-10	1	13	22	37	21	1	3	13	10	14	9	-9	2	14	41	41	5	-4	1	15	23	18	23	-6	2	16	0	17	1
-9	1	13	20	23	20	-8	4	13	0	10	1	-8	2	14	18	24	18	-3	1	15	29	24	7	-5	2	16	0	4	1
-8	1	13	52	39	3	-7	4	13	0	12	1	-7	2	14	0	17	1	-2	1	15	0	22	1	-4	2	16	10	13	10
-7	1	13	23	22	22	-6	4	13	0	8	1	-6	2	14	0	11	1	-1	1	15	18	5	18	-9	0	17	25	29	24
-6	1	13	21	13	20	-5	4	13	0	10	1	-5	2	14	12	21	12	0	1	15	0	0	1	-8	0	17	0	20	1
-5	1	13	26	17	6	-4	4	13	0	8	1	-4	2	14	35	33	5	-12	2	15	19	22	19	-7	0	17	25	3	24
-4	1	13	23	10	22	-3	4	13	6	3	6	-3	2	14	29	28	29	-11	2	15	0	12	1	-6	0	17	30	6	29
-3	1	13	0	21	1	-14	0	14	16	27	15	-2	2	14	44	36	4	-10	2	15	0	11	1						
-2	1	13	36	27	4	-13	0	14	28	10	28	-1	2	14	32	28	32	-9	2	15	0	18	1						
-1	1	13	40	34	4	-12	0	14	42	36	4	0	2	14	32	18	31	-8	2	15	0	3	1						
0	1	13	0	32	1	-11	0	14	43	34	4	1	2	14	0	29	1	-7	2	15	13	12	12						

Table A.8 : Observed and calculated structure factors for n salt

h	k	l	10Fo	10Fc	10s
0-24	0		25	25	1
1-24	0		28	29	1
1-23	0		23	22	1
2-23	0		43	43	1
0-22	0		45	46	1
1-22	0		10	12	3
2-22	0		25	23	1
1-21	0		22	25	1
2-21	0		24	28	1
3-21	0		9	9	9
0-20	0		12	23	11
1-20	0		58	56	1
2-20	0		37	39	1
3-20	0		45	45	1
1-19	0		47	51	1
2-19	0		32	29	1
3-19	0		21	21	1
4-19	0		4	7	4
0-18	0		87	84	1
1-18	0		11	7	2
2-18	0		38	37	2
3-18	0		38	40	1
4-18	0		30	27	1
1-17	0		20	23	1
2-17	0		23	22	1
3-17	0		47	50	2
4-17	0		25	29	1
0-16	0		69	67	1
1-16	0		87	84	1
2-16	0		93	93	1
3-16	0		58	53	1
4-16	0		28	26	1
1-15	0		31	30	2
2-15	0		90	89	1
3-15	0		48	53	2
4-15	0		51	54	1
5-15	0		53	53	1
0-14	0		54	56	1
1-14	0		59	56	1
2-14	0		65	64	1
3-14	0		131	131	3
4-14	0		18	20	3
5-14	0		16	14	4
1-13	0		11	5	3
2-13	0		57	56	1
3-13	0		32	32	1
4-13	0		101	102	4
5-13	0		55	59	2
0-12	0		228	225	1
1-12	0		130	135	1
2-12	0		116	113	1
3-12	0		82	81	1
4-12	0		30	32	1
5-12	0		30	34	1
1-11	0		9	11	2
2-11	0		91	86	3
3-11	0		96	96	2
4-11	0		88	85	3
5-11	0		53	53	2
0-10	0		51	48	1
1-10	0		151	140	1
2-10	0		122	117	1
3-10	0		34	35	1
4-10	0		51	52	1
5-10	0		9	10	4
1 -9	0		85	81	1
2 -9	0		144	135	3
3 -9	0		51	48	1
4 -9	0		104	106	2
5 -9	0		20	23	5
6 -9	0		52	53	1
0 -8	0		413	417	4
1 -8	0		178	170	1
2 -8	0		232	229	5
3 -8	0		102	101	3
4 -8	0		76	74	2
5 -8	0		28	27	2
6 -8	0		32	33	1
1 -7	0		235	236	2
2 -7	0		187	181	3
3 -7	0		76	74	2
4 -7	0		66	69	2
5 -7	0		76	71	2
6 -7	0		42	42	4
0 -6	0		562	572	3
1 -6	0		340	340	2
2 -6	0		174	173	6
3 -6	0		61	55	1
4 -6	0		30	32	1
5 -6	0		54	54	1
6 -6	0		48	49	1
1 -5	0		135	142	2
2 -5	0		33	33	1
3 -5	0		153	153	8
4 -5	0		78	82	3
5 -5	0		117	117	4
6 -5	0		22	20	1
0 -4	0		220	225	1
1 -4	0		852	866	12
2 -4	0		206	207	1
3 -4	0		81	86	2
4 -4	0		82	82	3
5 -4	0		38	39	1
6 -4	0		21	14	2
1 -3	0		490	485	8
2 -3	0		317	315	8
3 -3	0		264	250	6
4 -3	0		53	57	2
5 -3	0		113	115	1
6 -3	0		42	40	1
0 -2	0		361	369	2
1 -2	0		332	343	4
2 -2	0		221	214	3
3 -2	0		234	232	5
4 -2	0		64	64	1
5 -2	0		79	79	1
6 -2	0		36	36	1
1 -1	0		361	380	5
2 -1	0		143	138	1
3 -1	0		78	75	1
4 -1	0		175	179	1
5 -1	0		121	124	1
6 -1	0		25	25	1
1 0	0		49	47	1
2 0	0		670	709	2
3 0	0		56	64	1
4 0	0		16	16	4
5 0	0		65	68	1
6 0	0		44	46	1
-1-24	1		13	21	12
0-24	1		47	43	1
1-24	1		40	39	1
-2-23	1		33	33	1
-1-23	1		42	42	1
0-23	1		64	66	1
1-23	1		0	6	1
-3-22	1		33	35	1
-2-22	1		12	15	12
-1-22	1		6	12	6
0-22	1		49	48	1
1-22	1		35	35	1
2-22	1		8	17	8
-3-21	1		37	37	1
-2-21	1		33	29	1
-1-21	1		33	34	1
0-21	1		30	31	1
1-21	1		67	64	1
2-21	1		9	16	9
3-21	1		20	14	1
-3-20	1		23	28	1
-2-20	1		25	23	1
-1-20	1		19	19	1
0-20	1		32	34	1
1-20	1		59	59	1
2-20	1		5	8	5
3-20	1		19	20	1
-4-19	1		14	12	2
-3-19	1		79	83	1
-2-19	1		68	68	1
-1-19	1		56	53	1
0-19	1		56	56	1
1-19	1		97	98	1
2-19	1		0	9	1
3-19	1		39	37	1
-4-18	1		33	35	1
-3-18	1		37	45	1
-2-18	1		49	53	1
-1-18	1		72	72	1
0-18	1		0	12	1
1-18	1		63	66	1
2-18	1		133	130	1
3-18	1		0	6	1
4-18	1		39	37	1
-4-17	1		34	33	1
-3-17	1		21	21	1
-2-17	1		101	103	1
-1-17	1		0	6	1
0-17	1		105	102	1
1-17	1		78	76	1
2-17	1		82	80	1
3-17	1		28	22	1
4-17	1		5	11	5
-5-16	1		29	32	1
-4-16	1		28	30	1
-3-16	1		80	74	1
-2-16	1		0	1	1
-1-16	1		67	64	1
0-16	1		58	62	1
1-16	1		15	14	1
2-16	1		66	63	1
3-16	1		31	29	1
4-16	1		46	43	1
-5-15	1		38	37	1
-4-15	1		58	58	1
-3-15	1		45	46	1
-2-15	1		34	30	1
-1-15	1		86	90	1
0-15	1		124	121	1
1-15	1		93	88	1
2-15	1		69	70	1
3-15	1		28	29	1
4-15	1		0	10	1
-5-14	1		44	44	1
-4-14	1		20	22	1
-3-14	1		53	56	1
-2-14	1		79	79	1
-1-14	1		91	89	1
0-14	1		124	126	1
1-14	1		100	98	1
2-14	1		22	23	1
3-14	1		65	67	1
4-14	1		36	35	1
5-14	1		36	32	1
-5-13	1		36	37	1
-4-13	1		49	48	1
-3-13	1		111	110	1
-2-13	1		48	54	1
-1-13	1		99	95	1
0-13	1		30	29	1
1-13	1		38	38	1
2-13	1		54	55	1
3-13	1		55	53	1
4-13	1		90	82	1
5-13	1		45	44	1
-5-12	1		70	67	1
-4-12	1		91	94	1
-3-12	1		70	71	1
-2-12	1		94	96	1
-1-12	1		31	32	1
0-12	1		301	287	1
1-12	1		71	70	1
2-12	1		57	59	1
3-12	1		31	31	1
4-12	1		0	3	1
5-12	1		11	9	10
-5-11	1		58	57	1
-4-11	1		45	43	1
-3-11	1		72	75	1
-2-11	1		41	38	1
-1-11	1		313	305	1
0-11	1		219	222	1
1-11	1		204	200	1
2-11	1		229	218	1
3-11	1		59	57	1
4-11	1		85	87	1
5-11	1		39	40	1
-6-10	1		28	26	1
-5-10	1		81	87	2
-4-10	1		64	67	1
-3-10	1		48	47	1
-2-10	1		69	74	1
-1-10	1		95	89	1
0-10	1		275	273	1
1-10	1		234	227	1
2-10	1		148	151	1
3-10	1		153	150	1
4-10	1		87	83	1
5-10	1		60	57	1
-6 -9	1		43	42	1
-5 -9	1		42	45	1
-4 -9	1		92	88	1
-3 -9	1		162	164	1
-2 -9	1		262	269	1
-1 -9	1		206	206	1
0 -9	1		234	241	1
1 -9	1		220	214	1
2 -9	1		188	188	1
3 -9	1		30	32	1
4 -9	1		28	25	1
5 -9	1		52	52	1
-8 -8	1		24	26	1
-5 -8	1		113	113	1
-4 -8	1		17	19	1
-3 -8	1		35	38	1
-2 -8	1		114	120	1
-1 -8	1		162	159	1
0 -8	1		92	89	1
1 -8	1		133	126	1
2 -8	1		228	226	1
3 -8	1		113	114	1
4 -8	1		124	121	1
5 -8	1		45	44	1
-6 -7	1		30	28	1
-5 -7	1		100	95	1
-4 -7	1		36	35	1
-3 -7	1		133	137	1
-2 -7	1		179	180	1
-1 -7	1		19	20	1
0 -7	1		562	564	3
1 -7	1		218	218	1
2 -7	1		26	26	1
3 -7	1		49	50	1
4 -7	1		50	47	1
5 -7	1		99	100	1
-6 -6	1		42	42	1
-5 -6	1		128	125	1
-4 -6	1		113	113	1
-3 -6	1		189	188	1
-2 -6	1		76	71	1
-1 -6	1		264	269	1
0 -6	1		357	360	3
1 -6	1		311	316	1
2 -6	1		170	164	1
3 -6	1		84	86	1
4 -6	1		116	110	1
5 -6	1		117	114	1
6 -6	1		24	21	1
-6 -5	1		47	47	1
-5 -5	1		41	39	1
-4 -5	1		60	60	1
-3 -5	1		77	75	1
-2 -5	1		278	277	1
-1 -5	1		337	338	3
0 -5	1		918	960	3
1 -5	1		414	423	3
2 -5	1		336	326	1
3 -5	1		84	82	1
4 -5	1		47	47	1
5 -5	1		32	33	1
6 -5	1		28	23	1
-6 -4	1		32	31	1
-5 -4	1		20	25	1
-4 -4	1		103	111	1
-3 -4	1		107	104	1
-2 -4	1		250	253	1
-1 -4	1		185	190	1
0 -4	1		533	549	3
1 -4	1		387	371	3
2 -4	1		86	92	1
3 -4	1		76	77	1
4 -4	1		33	31	1
5 -4	1		62	63	1
6 -4	1		39	37	1
-6 -3	1		19	21	1
-5 -3	1		45	44	1
-4 -3	1		89	94	1
-3 -3	1		134	130	1
-2 -3	1		64	63	1
-1 -3	1		668	695	3
0 -3	1		205	206	1
1 -3	1		178	178	1
2 -3	1		265	249	1
3 -3	1		92	91	1
4 -3	1		81	87	1
5 -3	1		50	53	1
6 -3	1		20	20	1
-6 -2	1		54	52	1
-5 -2	1		66	67	1
-4 -2	1		161	167	1
-3 -2	1		146	139	1
-2 -2	1		195	194	1
-1 -2	1		791	854	2
0 -2	1		248	247	2
1 -2	1		389	397	3
2 -2	1		111	106	1
3 -2	1		250	250	1
4 -2	1		111	115	1
5 -2	1		88	86	1
6 -2	1		61	60	1
-6 -1	1		34	34	1
-5 -1	1		26	28	1
-4 -1	1		158	162	1
-3 -1	1		123	127	1
-2 -1	1		157	163	1
-1 -1	1		282	277	2
0 -1	1		235	238	2
1 -1	1		157	148	1
2 -1	1		100	107	1
3 -1	1		213	207	1
4 -1	1		35	36	1
5 -1	1		48	48	1
6 -1	1		0	8	1
-6 0	1		66	69	1
-5 0	1		63	61	1
-4 0	1		132	136	1
-3 0	1		123	118	1
-2 0	1		276	283	1
-1 0	1		53	57	1
0 0	1		338	343	2
1 0	1		224	232	1
2 0	1		520	515	4
3 0	1		114	105	1
4 0	1		32	28	1
5 0	1		47	51	1
6 0	1		0	2	1
0-24	2		0	5	1
-2-23	2		9	1	3
-1-23	2		32	30	1
0-23	2		46	46	1
1-23	2		8	15	7
-2-22	2		25	23	1
-1-22	2		37	34	1
0-22	2		33	33	1
1-22	2		0	7	1
2-22	2		37	32	1
-3-21	2		0	17	1
-2-21	2		38	38	1
-1-21	2		73	71	1
0-21	2		35	36	1
1-21	2		78	77	1
2-21	2		19	17	1
-3-20	2		20	18	1
-2-20	2		18	19	1
-1-20	2		39	43	1
0-20	2		44	41	1
1-20	2		27	30	1
2-20	2		7	6	6
3-20	2		39	36	1
-4-19	2		0	13	1
-3-19	2		43	41	1
-2-19	2		30	32	1
-1-19	2		5	46	4
0-19	2		49	50	1
1-19	2		82	75	1
2-19	2		12	9	11
3-19	2		52	50	1
-4-18	2		33	31	1
-3-18	2		43	45	1
-2-18	2		38	39	1
-1-18	2		30	31	1
0-18	2		83	86	1
1-18	2		60	59	1
2-18	2		42	42	1
3-18	2		31	33	1
-4-17	2		36	39	1
-3-17	2		61	64	1
-2-17	2		76	71	1
-1-17	2		45	46	1
0-17	2		182	181	1
1-17	2		84	85	1
2-17	2		104	103	1
3-17	2		40	40	1
4-17	2		40	37	1
-5-16	2		44	43	1
-4-16	2		16	17	1
-3-16	2		66	67	1
-2-16	2		62	63	1
-1-16	2		36	36	1
0-16	2		129	131	1
1-16	2		69	69	1
2-16	2		7	10	7
3-16	2		44	46	1
4-16	2		43	41	1
-5-15	2		30	29	1
-4-15	2		20	20	1
-3-15	2		10	8	2
-2-15	2		99	94	1
-1-15	2		136	133	1
0-15	2		60	64	1
1-15	2		150	152	1

Table A.8 : Observed and calculated structure factors for n salt

h	k	l	10Fo	10Fc	10s	h	k	l	10Fo	10Fc	10s	h	k	l	10Fo	10Fc	10s	h	k	l	10Fo	10Fc	10s	h	k	l	10Fo	10Fc	10s
2	-15	2	83	80	1	2	-7	2	133	128	1	-2	-22	3	24	22	1	-5	-11	3	59	59	1	3	-4	3	9	169	9
3	-15	2	75	73	1	3	-7	2	134	131	1	-1	-22	3	12	13	2	-4	-11	3	37	36	1	4	-4	3	99	100	1
4	-15	2	53	53	1	4	-7	2	109	102	1	0	-22	3	30	29	1	-3	-11	3	102	106	1	5	-4	3	30	27	1
-5	-14	2	25	24	1	5	-7	2	22	21	1	1	-22	3	21	22	1	-2	-11	3	33	38	1	-6	-3	3	40	42	1
-4	-14	2	52	50	1	-6	-6	2	64	60	1	-3	-21	3	19	20	1	-1	-11	3	148	140	1	-5	-3	3	14	12	1
-3	-14	2	61	62	1	-5	-6	2	30	32	1	-2	-21	3	24	23	1	0	-11	3	40	40	1	-4	-3	3	81	77	1
-2	-14	2	76	78	1	-4	-6	2	72	79	1	-1	-21	3	19	19	1	1	-11	3	156	154	1	-3	-3	3	100	91	1
-1	-14	2	194	192	1	-3	-6	2	178	185	1	0	-21	3	18	19	1	2	-11	3	48	50	1	-2	-3	3	265	258	1
0	-14	2	99	99	1	-2	-6	2	59	50	1	1	-21	3	8	17	8	3	-11	3	82	83	1	-1	-3	3	29	29	1
1	-14	2	91	91	1	-1	-6	2	281	284	1	2	-21	3	8	8	7	4	-11	3	45	44	1	0	-3	3	249	242	1
2	-14	2	64	63	1	0	-6	2	93	92	1	-3	-20	3	32	33	1	-6	-10	3	0	8	1	1	-3	3	298	284	1
3	-14	2	109	110	1	1	-6	2	177	169	1	-2	-20	3	28	27	1	-5	-10	3	21	20	1	2	-3	3	0	76	1
4	-14	2	28	31	1	2	-6	2	223	216	1	-1	-20	3	60	58	1	-4	-10	3	13	13	1	3	-3	3	159	163	1
-5	-13	2	38	39	1	3	-6	2	150	143	1	0	-20	3	44	43	1	-3	-10	3	79	83	1	4	-3	3	60	53	1
-4	-13	2	39	38	1	4	-6	2	40	36	1	1	-20	3	37	38	1	-2	-10	3	213	216	1	5	-3	3	36	34	1
-3	-13	2	51	51	1	5	-6	2	30	28	1	2	-20	3	37	38	1	-1	-10	3	118	118	1	-6	-2	3	61	59	1
-2	-13	2	48	47	1	-6	-5	2	91	88	2	-4	-19	3	54	54	1	0	-10	3	227	227	1	-5	-2	3	86	89	1
-1	-13	2	226	222	1	-5	-5	2	61	60	1	-3	-19	3	27	27	1	1	-10	3	112	106	1	-4	-2	3	44	48	1
0	-13	2	175	174	1	-4	-5	2	99	99	1	-2	-19	3	19	19	1	2	-10	3	146	147	1	-3	-2	3	82	82	1
1	-13	2	72	73	1	-3	-5	2	87	74	1	-1	-19	3	21	25	1	3	-10	3	98	95	1	-2	-2	3	166	169	1
2	-13	2	222	222	1	-2	-5	2	257	259	1	0	-19	3	58	56	1	4	-10	3	57	56	1	-1	-2	3	326	327	3
3	-13	2	83	77	1	-1	-5	2	177	180	1	1	-19	3	26	25	1	-6	-9	3	21	20	1	0	-2	3	53	45	1
4	-13	2	53	53	1	0	-5	2	468	474	3	2	-19	3	31	31	1	-5	-9	3	91	91	1	1	-2	3	234	228	1
-5	-12	2	32	31	1	1	-5	2	166	151	1	3	-19	3	33	34	1	-4	-9	3	41	47	1	2	-2	3	142	139	1
-4	-12	2	77	78	1	2	-5	2	182	184	1	-4	-18	3	21	22	1	-3	-9	3	47	51	1	3	-2	3	117	117	1
-3	-12	2	64	66	1	3	-5	2	0	10	1	-3	-18	3	64	63	1	-2	-9	3	50	53	1	4	-2	3	35	32	1
-2	-12	2	160	160	1	4	-5	2	99	103	1	-2	-18	3	28	27	1	-1	-9	3	309	302	1	5	-2	3	24	23	1
-1	-12	2	103	104	1	5	-5	2	23	21	1	-1	-18	3	17	17	1	0	-9	3	47	43	1	-6	-1	3	46	45	1
0	-12	2	141	142	1	-6	-4	2	54	51	1	0	-18	3	25	28	1	1	-9	3	9	10	8	-5	-1	3	0	88	1
1	-12	2	148	147	1	-5	-4	2	47	46	1	1	-18	3	34	36	1	2	-9	3	173	170	1	-4	-1	3	34	34	1
2	-12	2	91	91	1	-4	-4	2	82	84	1	2	-18	3	56	58	1	3	-9	3	131	129	1	-3	-1	3	124	121	1
3	-12	2	91	89	1	-3	-4	2	184	188	1	3	-18	3	44	47	1	4	-9	3	13	12	2	-2	-1	3	233	229	1
4	-12	2	22	21	1	-2	-4	2	79	82	1	-4	-17	3	31	30	1	5	-9	3	0	5	1	-1	-1	3	33	29	1
5	-12	2	36	35	1	-1	-4	2	479	485	3	-3	-17	3	24	26	1	-6	-8	3	32	31	1	0	-1	3	98	95	1
-6	-11	2	4	7	3	0	-4	2	102	100	1	-2	-17	3	39	40	1	-5	-8	3	59	62	1	1	-1	3	252	246	1
-5	-11	2	50	49	1	1	-4	2	389	386	4	-1	-17	3	54	54	1	-4	-8	3	123	129	1	2	-1	3	43	41	1
-4	-11	2	65	66	1	2	-4	2	210	205	1	0	-17	3	85	85	1	-3	-8	3	157	158	1	3	-1	3	105	103	1
-3	-11	2	64	63	1	3	-4	2	99	100	1	1	-17	3	52	53	1	-2	-8	3	173	173	1	4	-1	3	103	103	1
-2	-11	2	112	109	1	4	-4	2	89	90	1	2	-17	3	36	40	1	-1	-8	3	193	194	1	5	-1	3	54	54	1
-1	-11	2	120	124	1	5	-4	2	41	41	1	3	-17	3	28	32	1	0	-8	3	279	272	1	-6	0	3	97	100	2
0	-11	2	127	119	1	-6	-3	2	34	31	1	-5	-16	3	20	24	1	1	-8	3	71	76	1	-5	0	3	4	4	4
1	-11	2	112	112	1	-5	-3	2	87	89	1	-4	-16	3	34	33	1	2	-8	3	111	108	1	-4	0	3	63	56	1
2	-11	2	201	200	1	-4	-3	2	191	192	1	-3	-16	3	61	61	1	3	-8	3	111	112	1	-3	0	3	194	186	1
3	-11	2	36	33	1	-3	-3	2	123	126	1	-2	-16	3	98	97	1	4	-8	3	19	19	1	-2	0	3	284	280	1
4	-11	2	9	14	3	-2	-3	2	151	156	1	-1	-16	3	61	60	1	5	-8	3	27	25	1	-1	0	3	19	19	1
5	-11	2	64	58	1	-1	-3	2	115	115	1	0	-16	3	110	109	1	-6	-7	3	46	46	1	0	0	3	489	492	3
-6	-10	2	19	20	1	0	-3	2	381	385	3	1	-16	3	114	114	1	-5	-7	3	105	112	1	1	0	3	41	41	1
-5	-10	2	73	74	1	1	-3	2	244	241	1	2	-16	3	72	72	1	-4	-7	3	133	141	1	2	0	3	175	172	1
-4	-10	2	87	90	1	2	-3	2	79	72	1	3	-16	3	43	43	1	-3	-7	3	57	56	1	3	0	3	43	38	1
-3	-10	2	52	48	1	3	-3	2	143	135	1	-5	-15	3	67	64	1	-2	-7	3	172	174	1	4	0	3	26	24	1
-2	-10	2	107	103	1	4	-3	2	35	35	1	-4	-15	3	71	72	1	-1	-7	3	32	33	1	5	0	3	27	26	1
-1	-10	2	202	200	1	5	-3	2	44	43	1	-3	-15	3	0	33	1	0	-7	3	208	197	1	-2	-22	4	40	40	1
0	-10	2	163	160	1	-6	-2	2	49	46	1	-2	-15	3	84	88	1	1	-7	3	72	75	1	-1	-22	4	21	20	1
1	-10	2	130	129	1	-5	-2	2	131	138	1	-1	-15	3	60	60	1	2	-7	3	118	119	1	0	-22	4	54	54	1
2	-10	2	48	48	1	-4	-2	2	146	152	1	0	-15	3	82	86	1	3	-7	3	133	128	1	-2	-21	4	45	46	1
3	-10	2	7	11	4	-3	-2	2	168	169	1	1	-15	3	145	142	1	4	-7	3	75	77	1	-1	-21	4	24	23	1
4	-10	2	50	48	1	-2	-2	2	346	348	4	2	-15	3	11	12	2	5	-7	3	45	45	1	0	-21	4	35	35	1
5	-10	2	56	58	1	-1	-2	2	99	108	1	3	-15	3	59	60	1	-6	-6	3	0	9	1	1	-21	4	66	65	1
-6	-9	2	25	23	1	0	-2	2	30	30	1	4	-15	3	5	6	5	-5	-6	3	10	20	10	-3	-20	4	32	28	1
-5	-9	2	14	14	2	1	-2	2	176	172	1	-5	-14	3	16	17	2	-4	-6	3	54	53	1	-2	-20	4	22	20	1
-4	-9	2	122	125	1	2	-2	2	284	277	1	-4	-14	3	18	20	1	-3	-6	3	31	35	1	-1	-20	4	4	11	3
-3	-9	2	36	35	1	3	-2	2	55	55	1	-3	-14	3	79	77	1	-2	-6	3	153	143	1	0	-20	4	18	21	1
-2	-9	2	240	233	1	4	-2	2	41	41	1	-2	-14	3	11	20	10	-1	-6	3	253	248	1	1	-20	4	60	58	1
-1	-9	2	134	139	1	5	-2	2	59	58	1	-1	-14	3	67	65	1	0	-6	3	393	388	4	-3	-19	4	38	41	1
0	-9	2	357	357	1	-6	-1	2	54	55	1	0	-14	3	42	42	1	1	-6	3	220	211	1	-2	-19	4	9	7	8
1	-9	2	332	326	1	-5	-1	2	156	158	1	1	-14	3	87	87	1	2	-6	3	157	157	1	-1	-19	4	64	66	1
2	-9	2	125	131	1	-4	-1	2	100	100	1	2	-14	3	125	126	1	3	-6	3	84	87	1	0	-19	4	54	55	1
3	-9	2	110	107	1	-3	-1	2	209	205	1	3	-14	3	39	36	1	4	-6	3	66	67	1	1	-19	4	30	29	1
4	-9	2	65	64	1	-2	-1	2	322	315	1	4	-14	3	41	38	1	5	-6	3	19	17	1	2	-19	4	51	52	1
5	-9	2	36	37	1	-1	-1	2	406	431	3	-5	-13	3	46	49	1	-6	-5	3	45	47	1	-4	-18	4	62	60	1
-6	-8	2	10	14	10	0	-1	2	362	372	3	-4	-13	3	21	23	1	-5	-5	3	78	79	1	-3	-18	4	61	62	1
-5	-8	2	41	38	1	1	-1	2	153	156	1	-3	-13	3	67	70	1	-4	-5	3	16	19	1	-2	-18	4	67	68	1
-4	-8	2	69	70	1	2	-1	2	202	199	1	-2	-13	3	142	140	1	-3	-5	3	86	85	1	-1	-18	4	60	59	1
-3	-8	2	47	47	1	3	-1	2	56	63	1	-1	-13	3	91	95	1	-2	-5	3	158	153	1	0	-18	4	30	30	1
-2	-8	2	97	98	1	4	-1	2	133	135	1	0	-13	3	78	81	1	-1	-5	3	155	150	1	1	-18	4	36	38	1
-1	-8	2	368	361	1	5	-1	2	56	61	1	1	-13	3	119	118	1	0	-5	3	220	208	1	2	-18	4	37	35	1
0	-8	2	115	108	1	-6	0	2	17	16	1	2	-13	3	108	113	1	1	-5	3	95	93	1	-4	-17	4	56	52	1
1	-8	2	38	38	1	-5	0	2	190	189	1	3	-13	3	58	58	1	2	-5	3	81	83	1	-3	-17	4	64	65	1
2	-8	2	113	107	1	-4	0	2	37	42	1	4	-13	3	67	66	1	3	-5	3	35	36	1	-2	-17	4	30	30	1
3	-8	2	43	41	1	-3	0	2	14	15	1	-5	-12	3	23	20	1	4	-5	3	57	53	1	-1	-17	4	87	87	1
4	-8	2	61	62	1	-2	0	2	207	225	1	-4	-12	3	71	71	1	5	-5	3	27	29	1	0	-17	4	97	95	1
5	-8	2	36	33	1	-1	0	2	139	144	1	-3	-12	3	69	69	1	-6	-4	3	0	19	1	1	-17	4	26	27	1
-6	-7	2	35	34	1	0	0	2	386	393	3	-2	-12	3	86	85	1	-5	-4	3	121	124	1	2	-17	4	71	69	1
-5	-7	2	28	26	1	1	0	2	201	203	1	-1	-12	3	203	199	1	-4	-4	3	176	176	1	3	-17	4	34	33	1
-4	-7	2	89	87	1	2	0	2	403	396	1	0	-12	3	160	162	1	-3	-4	3	189	189	1	-4	-16	4	0	34	1
-3	-7	2	159	151	1	3	0	2	23	22	1	1	-12	3	116	118	1	-2	-4	3	275	274	1	-3	-16	4	42	43	1
-2	-7	2	99	103	1	4	0	2	5	5	5	2	-12	3	204	206	1	-1	-4	3	194	189	1	-2	-16	4	45	44	1
-1	-7	2	179	184	1	5	0	2	41	44	1	3	-12	3	24	26	1	0	-4	3	279	266	1	-1	-16	4	65	68	1
0	-7	2	231	227	1	-1	-23	3	18	15	1	4	-12	3	39	39	1	1	-4	3	347	341	1	0	-16	4	70	68	1
1	-7	2	235	234	1	0	-23	3	32	34	1	-6	-11	3	46	44	1	2	-4	3	46	53	1	1	-16	4	35	36	1

Table A.8 : Observed and calculated structure factors for n salt

h	k	l	10Fo	10Fc	10s
2	-16	4	22	23	1
3	-16	4	9	11	4
-5	-15	4	8	13	8
-4	-15	4	50	47	1
-3	-15	4	0	4	1
-2	-15	4	136	136	1
-1	-15	4	25	25	1
0	-15	4	107	105	1
1	-15	4	10	8	9
2	-15	4	40	38	1
3	-15	4	30	30	1
-5	-14	4	30	31	1
-4	-14	4	80	82	1
-3	-14	4	58	56	1
-2	-14	4	44	44	1
-1	-14	4	62	61	1
0	-14	4	91	96	1
1	-14	4	38	36	1
2	-14	4	59	62	1
3	-14	4	44	45	1
-5	-13	4	63	59	1
-4	-13	4	29	32	1
-3	-13	4	139	137	1
-2	-13	4	95	94	1
-1	-13	4	103	101	1
0	-13	4	91	86	1
1	-13	4	157	154	1
2	-13	4	24	25	1
3	-13	4	65	63	1
4	-13	4	9	16	9
-5	-12	4	31	32	1
-4	-12	4	79	78	1
-3	-12	4	62	61	1
-2	-12	4	52	49	1
-1	-12	4	66	66	1
0	-12	4	90	91	1
1	-12	4	102	101	1
2	-12	4	24	22	1
3	-12	4	40	43	1
4	-12	4	23	21	1
-6	-11	4	29	31	1
-5	-11	4	0	13	1
-4	-11	4	58	58	1
-3	-11	4	123	127	1
-2	-11	4	0	13	1
-1	-11	4	64	64	1
0	-11	4	69	74	1
1	-11	4	150	151	1
2	-11	4	38	37	1
3	-11	4	45	47	1
4	-11	4	22	20	1
-6	-10	4	32	33	1
-5	-10	4	81	78	1
-4	-10	4	40	41	1
-3	-10	4	15	12	1
-2	-10	4	125	122	1
-1	-10	4	51	50	1
0	-10	4	46	45	1
1	-10	4	74	82	1
2	-10	4	54	52	1
3	-10	4	44	41	1
4	-10	4	30	29	1
-6	-9	4	0	9	1
-5	-9	4	51	48	1
-4	-9	4	91	90	1
-3	-9	4	45	40	1
-2	-9	4	100	100	1
-1	-9	4	130	132	1
0	-9	4	93	95	1
1	-9	4	128	132	1
2	-9	4	59	56	1
3	-9	4	40	38	1
4	-9	4	22	20	1
-6	-8	4	34	34	1
-5	-8	4	33	33	1
-4	-8	4	89	85	1
-3	-8	4	110	108	1
-2	-8	4	36	35	1
-1	-8	4	163	163	1
0	-8	4	145	142	1
1	-8	4	107	105	1
2	-8	4	126	128	1
3	-8	4	22	21	1
4	-8	4	30	31	1
-6	-7	4	5	16	5
-5	-7	4	24	22	1
-4	-7	4	122	124	1
-3	-7	4	73	74	1
-2	-7	4	168	164	1
-1	-7	4	52	47	1
0	-7	4	135	135	1
1	-7	4	25	25	1
2	-7	4	144	147	1
3	-7	4	38	38	1
4	-7	4	28	29	1
-6	-6	4	23	23	1
-5	-6	4	42	43	1
-4	-6	4	83	86	1
-3	-6	4	70	73	1
-2	-6	4	86	84	1
-1	-6	4	166	158	1
0	-6	4	70	69	1
1	-6	4	74	75	1
2	-6	4	186	188	1
3	-6	4	103	103	1
4	-6	4	43	44	1
-6	-5	4	49	46	1
-5	-5	4	51	50	1
-4	-5	4	40	41	1
-3	-5	4	40	40	1
-2	-5	4	69	62	1
-1	-5	4	147	147	1
0	-5	4	108	116	1
1	-5	4	133	134	1
2	-5	4	183	186	1
3	-5	4	94	91	1
4	-5	4	47	52	1
-6	-4	4	30	29	1
-5	-4	4	88	91	1
-4	-4	4	47	51	1
-3	-4	4	163	160	1
-2	-4	4	243	236	1
-1	-4	4	261	253	1
0	-4	4	180	182	1
1	-4	4	112	111	1
2	-4	4	42	42	1
3	-4	4	121	121	1
4	-4	4	71	71	1
5	-4	4	35	34	1
-6	-3	4	38	35	1
-5	-3	4	116	117	1
-4	-3	4	22	24	1
-3	-3	4	65	66	1
-2	-3	4	74	70	1
-1	-3	4	254	254	1
0	-3	4	142	139	1
1	-3	4	41	41	1
2	-3	4	89	91	1
3	-3	4	111	108	1
4	-3	4	21	21	1
5	-3	4	31	31	1
-6	-2	4	15	16	1
-5	-2	4	108	112	1
-4	-2	4	60	62	1
-3	-2	4	202	201	1
-2	-2	4	170	165	1
-1	-2	4	137	129	1
0	-2	4	113	102	1
1	-2	4	206	204	1
2	-2	4	91	86	1
3	-2	4	203	201	1
4	-2	4	109	109	1
5	-2	4	45	46	1
-6	-1	4	74	77	1
-5	-1	4	43	37	1
-4	-1	4	35	36	1
-3	-1	4	202	192	1
-2	-1	4	124	131	1
-1	-1	4	146	139	1
0	-1	4	352	346	1
1	-1	4	179	175	1
2	-1	4	123	124	1
3	-1	4	151	147	1
4	-1	4	31	33	1
5	-1	4	53	53	1
-6	0	4	0	2	1
-5	0	4	6	1	5
-4	0	4	13	14	1
-3	0	4	28	28	1
-2	0	4	21	22	1
-1	0	4	144	142	1
0	0	4	408	390	4
1	0	4	178	172	1
2	0	4	279	274	1
3	0	4	21	19	1
4	0	4	65	67	1
5	0	4	36	33	1
-1	-21	5	0	13	1
-2	-20	5	49	47	1
-1	-20	5	32	37	1
0	-20	5	12	13	2
-3	-19	5	8	12	8
-2	-19	5	31	30	1
-1	-19	5	46	44	1
0	-19	5	28	30	1
1	-19	5	45	44	1
-3	-18	5	46	44	1
-2	-18	5	4	10	3
-1	-18	5	25	25	1
0	-18	5	40	40	1
1	-18	5	20	17	1
-4	-17	5	48	46	1
-3	-17	5	34	37	1
-2	-17	5	91	86	2
-1	-17	5	24	24	1
0	-17	5	55	52	1
1	-17	5	46	46	1
2	-17	5	34	33	1
-4	-16	5	38	41	1
-3	-16	5	52	50	1
-2	-16	5	45	48	1
-1	-16	5	63	62	1
0	-16	5	33	35	1
1	-16	5	67	68	1
2	-16	5	44	43	1
-4	-15	5	0	19	1
-3	-15	5	68	69	1
-2	-15	5	68	67	1
-1	-15	5	24	24	1
0	-15	5	77	79	1
1	-15	5	54	55	1
2	-15	5	57	58	1
-5	-14	5	38	36	1
-4	-14	5	83	84	1
-3	-14	5	0	6	1
-2	-14	5	31	32	1
-1	-14	5	126	127	1
0	-14	5	83	79	1
1	-14	5	39	41	1
2	-14	5	61	59	1
3	-14	5	9	11	4
-5	-13	5	23	22	1
-4	-13	5	93	93	2
-3	-13	5	185	185	1
-2	-13	5	8	10	8
-1	-13	5	135	135	1
0	-13	5	74	72	1
1	-13	5	14	15	1
2	-13	5	0	12	1
3	-13	5	62	55	1
-5	-12	5	10	14	9
-4	-12	5	54	51	1
-3	-12	5	126	130	1
-2	-12	5	41	38	1
-1	-12	5	83	87	1
0	-12	5	31	33	1
1	-12	5	127	132	1
2	-12	5	34	35	1
3	-12	5	22	21	1
-5	-11	5	21	19	1
-4	-11	5	70	65	1
-3	-11	5	65	63	1
-2	-11	5	93	95	1
-1	-11	5	121	116	1
0	-11	5	146	141	1
1	-11	5	96	93	1
2	-11	5	125	125	1
3	-11	5	42	40	1
-5	-10	5	54	53	1
-4	-10	5	48	49	1
-3	-10	5	74	76	1
-2	-10	5	97	102	1
-1	-10	5	88	88	1
0	-10	5	120	118	1
1	-10	5	39	38	1
2	-10	5	66	62	1
3	-10	5	23	21	1
-6	-9	5	0	13	1
-5	-9	5	37	38	1
-4	-9	5	41	41	1
-3	-9	5	70	68	1
-2	-9	5	164	161	1
-1	-9	5	26	20	1
0	-9	5	111	115	1
1	-9	5	62	64	1
2	-9	5	49	49	1
3	-9	5	81	81	2
4	-9	5	26	26	1
-6	-8	5	13	23	2
-5	-8	5	53	57	1
-4	-8	5	5	8	5
-3	-8	5	36	38	1
-2	-8	5	114	117	1
-1	-8	5	33	36	1
0	-8	5	88	87	1
1	-8	5	57	55	1
2	-8	5	67	67	1
3	-8	5	41	38	1
4	-8	5	0	9	1
-6	-7	5	60	57	1
-5	-7	5	77	76	1
-4	-7	5	74	74	1
-3	-7	5	116	119	1
-2	-7	5	37	32	1
-1	-7	5	116	115	1
0	-7	5	144	139	1
1	-7	5	110	111	1
2	-7	5	98	104	1
3	-7	5	80	80	1
4	-7	5	33	31	1
-6	-6	5	41	42	1
-5	-6	5	86	88	1
-4	-6	5	90	91	1
-3	-6	5	100	101	1
-2	-6	5	73	75	1
-1	-6	5	85	88	1
0	-6	5	66	66	1
1	-6	5	86	88	1
2	-6	5	24	20	1
3	-6	5	50	49	1
4	-6	5	49	47	1
-6	-5	5	33	31	1
-5	-5	5	47	50	1
-4	-5	5	78	77	1
-3	-5	5	49	52	1
-2	-5	5	88	86	1
-1	-5	5	127	123	1
0	-5	5	184	180	1
1	-5	5	113	113	1
2	-5	5	155	159	1
3	-5	5	47	43	1
4	-5	5	44	45	1
-6	-4	5	67	69	1
-5	-4	5	9	11	9
-4	-4	5	45	44	1
-3	-4	5	95	92	1
-2	-4	5	42	41	1
-1	-4	5	222	224	1
0	-4	5	129	125	1
1	-4	5	119	120	1
2	-4	5	178	176	1
3	-4	5	71	73	1
4	-4	5	13	16	12
-6	-3	5	0	30	1
-5	-3	5	43	43	1
-4	-3	5	47	47	1
-3	-3	5	42	42	1
-2	-3	5	46	48	1
-1	-3	5	82	80	1
0	-3	5	156	154	1
1	-3	5	191	195	1
2	-3	5	96	101	1
3	-3	5	68	73	1
4	-3	5	76	75	1
-6	-2	5	92	90	2
-5	-2	5	69	73	1
-4	-2	5	119	122	1
-3	-2	5	83	85	1
-2	-2	5	134	129	1
-1	-2	5	66	62	1
0	-2	5	38	36	1
1	-2	5	99	100	1
2	-2	5	90	86	1
3	-2	5	96	98	1
4	-2	5	25	25	1
-6	-1	5	43	41	1
-5	-1	5	36	36	1
-4	-1	5	70	69	1
-3	-1	5	30	25	1
-2	-1	5	54	50	1
-1	-1	5	199	195	1
0	-1	5	136	137	1
1	-1	5	176	168	1
2	-1	5	112	115	1
3	-1	5	12	15	11
4	-1	5	31	30	1
-6	0	5	13	19	13
-5	0	5	29	31	1
-4	0	5	11	19	10
-3	0	5	20	18	1
-2	-9	6	6	14	6
-1	-9	6	97	93	1
0	-9	6	112	111	1
1	-9	6	120	115	1
2	-9	6	85	84	1
3	-9	6	109	107	1
4	-9	6	61	62	1
-2	-19	6	9	9	8
-1	-19	6	22	23	1
0	-19	6	34	33	1
-3	-18	6	58	56	1
-2	-18	6	18	22	1
-1	-18	6	13	18	2
0	-18	6	0	11	1
-3	-17	6	31	30	1
-2	-17	6	44	44	1
-1	-17	6	28	27	1
0	-17	6	22	22	1
1	-17	6	42	42	1
-4	-16	6	24	21	1
-3	-16	6	0	7	1
-2	-16	6	27	29	1
-1	-16	6	41	41	1
0	-16	6	69	70	1
1	-16	6	7	5	7
-4	-15	6	28	31	1
-3	-15	6	23	24	1
-2	-15	6	24	24	1
-1	-15	6	36	36	1
0	-15	6	71	72	1
1	-15	6	42	38	1
2	-15	6	23	21	1
-4	-14	6	43	44	1
-3	-14	6	22	23	1
-2	-14	6	7	6	6
-1	-14	6	20	21	1
0	-14	6	31	29	1
1	-14	6	77	75	1
2	-14	6	61	60	1
-5	-13	6	35	37	1
-4	-13	6	17	17	1
-3	-13	6	46	47	1
-2	-13	6	18	22	1
-1	-13	6	36	37	1
0	-13	6	18	18	1
1	-13	6	10	12	3
2	-13	6	29	26	1
-5	-12	6	5	4	5
-4	-12	6	57	53	1
-3	-12	6	30	32	1
-2	-12	6	65	63	1
-1	-12	6	70	75	1
0	-12	6	68	60	1
1	-12	6	81	77	1
2	-12	6	56	55	1
-5	-11	6	6	11	6
-4	-11	6	33	37	1
-3	-11	6	72	72	1
-2	-11	6	14	15	1
-1	-11	6	48	51	1
0	-11	6	60	66	1
1	-11	6	25	27	1
2	-11	6	60	62	1
-5	-10	6	20	22	1
-4	-10	6	61	61	1
-3	-10	6	21	22	1
-2	-10	6	66	66	1
-1	-10	6	41	40	1
0	-10	6	40	44	1
1	-10	6	72	69	1
2	-10	6	20	20	1
3	-10	6	32	32	1
-5	-9	6	26	25	1
-4	-9	6	85	84	1
-3	-9	6	55	57	1
-2	-9	6	58	57	1
-1	-9	6	122	123	1
0	-9	6	29	31	1
1	-9	6	15	15	1
2	-9	6	81	83	1
3	-9	6	25	24	1
-5	-8	6	23	20	1
-4	-8	6	17	17	1
-3	-8	6	175	179	1
-2	-8	6	71	71	1
-1	-8	6	170	173	1
0	-8	6	75	79	1
1	-8	6	121	122	1
2	-8	6	53	56	1

Table A.8 : Observed and calculated structure factors for n salt

h	k	l	10Fo	10Fc	10s
3	-8	6	50	50	1
-6	-7	6	45	39	1
-5	-7	6	21	24	1
-4	-7	6	85	84	1
-3	-7	6	70	72	1
-2	-7	6	71	66	1
-1	-7	6	76	77	1
0	-7	6	48	47	1
1	-7	6	166	171	1
2	-7	6	51	50	1
3	-7	6	54	57	1
-6	-6	6	67	65	1
-5	-6	6	19	14	1
-4	-6	6	46	44	1
-3	-6	6	96	95	1
-2	-6	6	100	100	1
-1	-6	6	54	54	1
0	-6	6	118	117	1
1	-6	6	30	34	1
2	-6	6	98	98	1
3	-6	6	31	31	1
-6	-5	6	56	57	1
-5	-5	6	44	44	1
-4	-5	6	94	98	1
-3	-5	6	140	141	1
-2	-5	6	165	163	1
-1	-5	6	135	137	1
0	-5	6	45	45	1
1	-5	6	55	58	1
2	-5	6	22	20	1
3	-5	6	11	12	11
-6	-4	6	48	45	1
-5	-4	6	46	48	1
-4	-4	6	0	15	1
-3	-4	6	27	35	1
-2	-4	6	186	185	1
-1	-4	6	156	157	1
0	-4	6	140	139	1
1	-4	6	172	172	1
2	-4	6	54	56	1
3	-4	6	56	73	1
-6	-3	6	47	43	1
-5	-3	6	14	12	2
-4	-3	6	55	50	1
-3	-3	6	67	64	1
-2	-3	6	128	127	1
-1	-3	6	95	96	1
0	-3	6	73	72	1
1	-3	6	50	49	1
2	-3	6	118	119	1
3	-3	6	68	70	1
-6	-2	6	33	32	1
-5	-2	6	51	49	1
-4	-2	6	62	60	1
-3	-2	6	63	62	1
-2	-2	6	126	125	1
-1	-2	6	38	44	1
0	-2	6	44	46	1
1	-2	6	76	78	1
2	-2	6	36	36	1
3	-2	6	47	46	1
-6	-1	6	31	32	1
-5	-1	6	69	72	1
-4	-1	6	97	98	1
-3	-1	6	118	122	1
-2	-1	6	30	31	1
-1	-1	6	17	14	1
0	-1	6	30	26	1
1	-1	6	75	77	1
2	-1	6	25	23	1
3	-1	6	23	21	1
-6	0	6	39	39	1
-5	0	6	9	14	3
-4	0	6	9	5	3
-3	0	6	75	78	1
-2	0	6	25	24	1
-1	0	6	242	237	1
0	0	6	203	198	1
1	0	6	214	217	1
2	0	6	126	127	1
3	0	6	6	2	6
-2	-17	7	24	25	1
-1	-17	7	40	39	1
-3	-16	7	0	15	1
-2	-16	7	59	59	1
-1	-16	7	24	24	1
0	-16	7	55	56	1
-3	-15	7	24	23	1
-2	-15	7	43	45	1
-1	-15	7	42	42	1
0	-15	7	60	62	1
-4	-14	7	9	6	9
-3	-14	7	11	9	2
-2	-14	7	34	35	1
-1	-14	7	32	33	1
0	-14	7	23	24	1
1	-14	7	36	39	1
-4	-13	7	20	15	1
-3	-13	7	52	53	1
-2	-13	7	37	35	1
-1	-13	7	76	79	1
0	-13	7	31	28	1
1	-13	7	16	16	2
-4	-12	7	42	42	1
-3	-12	7	53	46	1
-2	-12	7	45	45	1
-1	-12	7	41	41	1
0	-12	7	27	29	1
1	-12	7	76	77	1
-5	-11	7	34	33	1
-4	-11	7	30	30	1
-3	-11	7	11	10	11
-2	-11	7	41	42	1
-1	-11	7	25	25	1
0	-11	7	94	95	1
1	-11	7	44	45	1
2	-11	7	82	79	1
-5	-10	7	30	31	1
-4	-10	7	66	68	1
-3	-10	7	48	48	1
-2	-10	7	29	28	1
-1	-10	7	45	44	1
0	-10	7	57	55	1
1	-10	7	63	62	1
2	-10	7	49	46	1
-5	-9	7	36	34	1
-4	-9	7	36	37	1
-3	-9	7	23	22	1
-2	-9	7	56	57	1
-1	-9	7	69	71	1
0	-9	7	57	61	1
1	-9	7	31	30	1
2	-9	7	26	23	1
-5	-8	7	33	35	1
-4	-8	7	32	32	1
-3	-8	7	75	78	1
-2	-8	7	37	38	1
-1	-8	7	55	59	1
0	-8	7	10	5	9
1	-8	7	57	56	1
2	-8	7	29	29	1
-5	-7	7	24	25	1
-4	-7	7	31	29	1
-3	-7	7	22	21	1
-2	-7	7	94	89	1
-1	-7	7	30	32	1
0	-7	7	77	73	1
1	-7	7	53	52	1
2	-7	7	94	92	2
-5	-6	7	39	39	1
-4	-6	7	38	38	1
-3	-6	7	99	101	1
-2	-6	7	51	51	1
-1	-6	7	47	49	1
0	-6	7	56	56	1
1	-6	7	63	63	1
2	-6	7	55	54	1
-5	-5	7	0	12	1
-4	-5	7	51	49	1
-3	-5	7	6	4	5
-2	-5	7	57	62	1
-1	-5	7	135	136	1
0	-5	7	28	25	1
1	-5	7	127	129	1
2	-5	7	50	48	1
-5	-4	7	32	32	1
-4	-4	7	78	78	1
-3	-4	7	152	152	1
-2	-4	7	105	108	1
-1	-4	7	5	14	5
0	-4	7	131	137	1
1	-4	7	14	15	2
2	-4	7	23	19	1
3	-4	7	39	35	1
-5	-3	7	19	21	1
-4	-3	7	42	41	1
-3	-3	7	72	72	1
-2	-3	7	67	64	1
-1	-3	7	77	76	1
0	-3	7	41	41	1
1	-3	7	142	144	1
2	-3	7	26	25	1
3	-3	7	53	49	1
-6	-2	7	0	19	1
-5	-2	7	28	30	1
-4	-2	7	129	128	1
-3	-2	7	126	126	1
-2	-2	7	192	190	1
-1	-2	7	59	62	1
0	-2	7	59	57	1
1	-2	7	70	74	1
2	-2	7	77	74	1
3	-2	7	19	20	1
-6	-1	7	30	31	1
-5	-1	7	40	41	1
-4	-1	7	18	17	1
-3	-1	7	91	87	1
-2	-1	7	86	83	1
-1	-1	7	7	37	6
0	-1	7	59	59	1
1	-1	7	35	34	1
2	-1	7	11	12	2
3	-1	7	75	69	1
-6	0	7	0	9	1
-5	0	7	32	32	1
-4	0	7	111	119	1
-3	0	7	5	4	5
-2	0	7	71	71	1
-1	0	7	187	192	1
0	0	7	37	36	1
1	0	7	104	106	1
2	0	7	0	5	1
3	0	7	45	43	1
-4	-7	7	31	29	1
-3	-7	7	22	21	1
-2	-7	7	94	89	1
-1	-7	7	30	32	1
0	-7	7	77	73	1
1	-7	7	53	52	1
2	-7	7	94	92	2
-5	-6	7	39	39	1
-4	-6	7	38	38	1
-3	-6	7	99	101	1
-2	-6	7	51	51	1
-1	-6	7	47	49	1
0	-6	7	56	56	1
1	-6	7	63	63	1
2	-6	7	55	54	1
-5	-5	7	0	12	1
-4	-5	7	51	49	1
-3	-5	7	6	4	5
-2	-5	7	57	62	1
-1	-5	7	135	136	1
0	-5	7	28	25	1
1	-5	7	127	129	1
2	-5	7	50	48	1
-5	-4	7	32	32	1
-4	-4	7	78	78	1
-3	-4	7	152	152	1
-2	-4	7	105	108	1
-1	-4	7	5	14	5
0	-4	7	131	137	1
1	-4	7	14	15	2
2	-4	7	23	19	1
3	-4	7	39	35	1
-5	-3	7	19	21	1
-4	-3	7	42	41	1
-3	-3	7	72	72	1
-2	-3	7	67	64	1
-1	-3	7	77	76	1
0	-3	7	41	41	1
1	-3	7	142	144	1
2	-3	7	26	25	1
3	-3	7	53	49	1
-6	-2	7	0	19	1
-5	-2	7	28	30	1
-4	-2	7	129	128	1
-3	-2	7	126	126	1
-2	-2	7	192	190	1
-1	-2	7	59	62	1
0	-2	7	59	57	1
1	-2	7	70	74	1
2	-2	7	77	74	1
3	-2	7	19	20	1
-6	-1	7	30	31	1
-5	-1	7	40	41	1
-4	-1	7	18	17	1
-3	-1	7	91	87	1
-2	-1	7	86	83	1
-1	-1	7	7	37	6
0	-1	7	59	59	1
1	-1	7	35	34	1
2	-1	7	11	12	2
3	-1	7	75	69	1
-6	0	7	0	9	1
-5	0	7	32	32	1
-4	0	7	111	119	1
-3	0	7	5	4	5
-2	0	7	71	71	1
-1	0	7	187	192	1
0	0	7	37	36	1
1	0	7	104	106	1
2	0	7	0	5	1
3	0	7	45	43	1
-2	-14	8	36	31	1
-1	-14	8	27	27	1
-3	-13	8	31	32	1
-2	-13	8	46	40	1
-1	-13	8	42	39	1
0	-13	8	24	28	1
1	-13	8	15	17	2
-2	-12	8	31	30	1
-1	-12	8	40	39	1
0	-12	8	22	23	1
-4	-11	8	31	30	1
-3	-11	8	28	28	1
-2	-10	8	64	66	1
-1	-10	8	20	20	1
0	-10	8	30	30	1
1	-10	8	63	62	1
-4	-9	8	42	35	1
-3	-9	8	74	72	1
-2	-9	8	56	52	1
-1	-9	8	52	53	1
0	-9	8	82	79	1
1	-9	8	76	74	1
-4	-8	8	31	32	1
-3	-8	8	25	23	1
-2	-8	8	58	60	1
-1	-8	8	52	55	1
0	-8	8	27	27	1
1	-8	8	47	47	1
-5	-7	8	7	11	6
-4	-7	8	77	77	1
-3	-7	8	20	17	1
-2	-7	8	70	72	1
-1	-7	8	65	67	1
0	-7	8	54	54	1
1	-7	8	0	4	1
-5	-6	8	26	26	1
-4	-6	8	27	25	1
-3	-6	8	22	21	1
-2	-6	8	24	20	1
-1	-6	8	46	47	1
0	-6	8	90	87	1
1	-6	8	32	31	1
-5	-5	8	33	31	1
-4	-5	8	63	63	1
-3	-5	8	39	38	1
-2	-5	8	26	23	1
-1	-5	8	82	86	2
0	-5	8	25	24	1
1	-5	8	82	84	1
-5	-4	8	39	40	1
-4	-4	8	47	46	1
-3	-4	8	95	95	1
-2	-4	8	0	0	1
-1	-4	8	17	18	1
0	-4	8	46	45	1
1	-4	8	28	28	1
-5	-3	8	38	39	1
-4	-3	8	24	23	1
-3	-3	8	79	80	1
-2	-3	8	55	52	1
-1	-3	8	26	28	1
0	-3	8	46	44	1
1	-3	8	26	27	1
-5	-2	8	21	21	1
-4	-2	8	18	19	1
-3	-2	8	53	54	1
-2	-2	8	99	100	1
-1	-2	8	57	56	1
0	-2	8	44	46	1
1	-2	8	23	26	1
-3	-12	8	15	17	2
-2	-2	8	66	64	1
-5	-1	8	55	54	1
-1	-2	8	31	30	1
-1	-12	8	40	39	1
-4	-1	8	19	16	1
-3	-1	8	104	99	1
-2	-1	8	90	90	1
-1	-1	8	108	106	1
0	-1	8	93	99	2
1	-1	8	22	21	1
2	-1	8	37	32	1
-5	0	8	26	25	1
-4	0	8	67	66	1
-3	0	8	63	66	1
-2	0	8	42	44	1
-1	0	8	52	50	1
0	0	8	68	65	1
1	0	8	14	16	2
2	0	8	82	81	1
-2	-10	9	33	31	1
-3	-9	9	25	26	1
-2	-9	9	59	55	1
-1	-9	9	57	56	1
-3	-8	9	70	63	1
-2	-8	9	58	57	1
-1	-8	9	53	47	1
-3	-7	9	43	40	1
-2	-7	9	0	12	1
-1	-7	9	37	56	1
0	-7	9	27	28	1
-4	-6	9	29	25	1
-3	-6	9	0	66	1
-2	-6	9	16	17	2
-1	-6	9	42	45	1
0	-6	9	61	60	1
-4	-5	9	27	23	1
-3	-5	9	13	17	12
-2	-5	9	38	40	1
-1	-5	9	18	15	1
0	-5	9	14	10	2
-4	-4	9	14	11	2
-3	-4	9	41	41	1
-2	-4	9	67	64	1
-1	-4	9	78	80	1
0	-4	9	35	34	1
-4	-3	9	59	58	1
-3	-3	9	49	49	1
-2	-3	9	41	38	1
-1	-3	9	14	15	2
0	-3	9	23	24	1
-4	-2	9	15	12	2
-3	-2	9	21	21	1
-2	-2	9	57	61	1
-1	-2	9	11	18	10
0	-2	9	37	39	1
-4	-1	9	21	19	1
-3	-1	9	31	30	1
-2	-1	9	31	32	1
-1	-1	9	8	8	4
0	-1	9	26	28	1
-4	0	9	30	31	1
-3	0	9	32	31	1
-2	0	9	45	45	1
-1	0	9	41	41	1
0	0	9	17	18	1

Table A.5: Hydrogen atom coordinates ($x10^4$) and isotropic displacement parameters ($Å^2x10^3$) for GAM.MBA (n salt)

	x/a	y/b	z/c	U_{iso}
H(251)	-1636(53)	6803(18)	11201(45)	53(9)
H(252)	-266(60)	6990(14)	10023(35)	37(7)
H(253)	1063(70)	6871(25)	11884(44)	80(13)
H(3)	7028(5)	8044(1)	15523(3)	35(7)
H(10)	3594(6)	9381(2)	11198(5)	71(4)
H(20)	-4324(6)	6270(2)	8742(4)	71(4)
H(161)	14007(78)	7463(23)	19495(59)	64(8)
H(162)	14782(69)	7700(20)	17899(49)	64(8)
H(8)	9310(6)	8634(2)	10033(4)	71(4)
H(7)	10429(5)	8062(2)	12528(4)	71(4)
H(2A)	9262(4)	7085(1)	14037(3)	57(5)
H(2B)	8049(4)	6965(1)	15463(3)	57(5)
H(11)	4676(6)	8807(2)	13680(5)	71(4)
H(4A)	11964(5)	7949(2)	15521(3)	57(5)
H(4B)	10948(5)	8536(2)	16296(3)	57(5)
H(171)	655(8)	5755(2)	13046(4)	63(7)
H(172)	51(8)	5164(2)	11813(4)	63(7)
H(173)	-2015(8)	5655(2)	11860(4)	63(7)
H(18)	2030(5)	5959(2)	10741(4)	44(8)
H(24)	1527(7)	5299(2)	8381(5)	71(4)
H(21)	-6445(7)	5971(2)	6038(4)	71(4)
H(23)	-667(10)	4969(2)	5719(5)	71(4)
H(22)	-4586(9)	5327(2)	4521(5)	71(4)

Table A. 6 Torsion angles (degrees) with e.s.d.'s in parentheses

(Right-Hand Rule,Klyne & Prelog.(1960).*Experientia*,16,521)

(e.s.d.'s, following Stanford & Waser, *Acta Cryst.*(1972).A28,213)

N Salt					P Salt				
(253)	- N(25)	- C(18)	- H(18)	-44(3)	C(11)	- C(6)	- C(3)	- C(4)	105(2)
(252)	- N(25)	- C(18)	- H(18)	80(2)	C(7)	- C(6)	- C(3)	- C(4)	-72(2)
(251)	- N(25)	- C(18)	- H(18)	-162(2)	C(11)	- C(6)	- C(3)	- C(2)	-137(1)
(253)	- N(25)	- C(18)	- C(19)	-163(3)	C(7)	- C(6)	- C(3)	- C(2)	46(2)
(252)	- N(25)	- C(18)	- C(19)	-39(2)	C(3)	- C(6)	- C(11)	- C(10)	-177(1)
(251)	- N(25)	- C(18)	- C(19)	80(2)	C(7)	- C(6)	- C(11)	- C(10)	0(2)
(253)	- N(25)	- C(18)	- C(17)	73(3)	C(11)	- C(6)	- C(7)	- C(8)	0(2)
(252)	- N(25)	- C(18)	- C(17)	-163(2)	C(3)	- C(6)	- C(7)	- C(8)	177(1)
(251)	- N(25)	- C(18)	- C(17)	-45(2)	C(6)	- C(7)	- C(8)	- C(9)	0(2)
(2)	- C(3)	- C(4)	- H(4A)	58.9(4)	C(7)	- C(8)	- C(9)	- CL(12)	180(1)
(6)	- C(3)	- C(4)	- H(4A)	-64.5(4)	C(7)	- C(8)	- C(9)	- C(10)	0(2)
(3)	- C(3)	- C(4)	- H(4A)	176.8(4)	C(8)	- C(9)	- C(10)	- C(11)	0(2)
(2)	- C(3)	- C(4)	- H(4B)	176.2(3)	CL(12)	- C(9)	- C(10)	- C(11)	-180(1)
(6)	- C(3)	- C(4)	- H(4B)	52.8(4)	C(9)	- C(10)	- C(11)	- C(6)	0(2)
(3)	- C(3)	- C(4)	- H(4B)	-65.9(5)	O(14)	- C(1)	- C(2)	- C(3)	34(2)
(2)	- C(3)	- C(4)	- C(5)	-62.4(3)	O(13)	- C(1)	- C(2)	- C(3)	-153(1)
(6)	- C(3)	- C(4)	- C(5)	174.1(3)	C(1)	- C(2)	- C(3)	- C(6)	62(2)
(3)	- C(3)	- C(4)	- C(5)	55.5(4)	C(1)	- C(2)	- C(3)	- C(4)	-180(1)
(6)	- C(3)	- C(2)	- H(2A)	71.5(4)	C(2)	- C(3)	- C(4)	- C(5)	60(2)
(3)	- C(3)	- C(2)	- H(2A)	-170.2(4)	C(6)	- C(3)	- C(4)	- C(5)	-179(2)
(6)	- C(3)	- C(2)	- H(2B)	-170.7(3)	C(3)	- C(4)	- C(5)	- N(16)	-141(3)
(3)	- C(3)	- C(2)	- H(2B)	-52.4(4)	C(3)	- C(4)	- C(5)	- O(15)	40(4)
(4)	- C(3)	- C(2)	- C(1)	-173.4(2)	C(17)	- C(18)	- C(19)b	- C(20)b	34(4)
(6)	- C(3)	- C(2)	- C(1)	-49.6(3)	N(25)	- C(18)	- C(19)b	- C(20)b	-83(3)
(3)	- C(3)	- C(2)	- C(1)	68.7(4)	C(17)	- C(18)	- C(19)b	- C(24)b	-153(3)
(3)	- C(3)	- C(6)	- C(7)	178.7(3)	N(25)	- C(18)	- C(19)b	- C(24)b	90(3)
(3)	- C(3)	- C(6)	- C(11)	-3.8(5)	C(17)	- C(18)	- C(19)a	- C(20)a	108(3)
(2)	- C(3)	- C(6)	- C(11)	114.5(3)	N(25)	- C(18)	- C(19)a	- C(20)a	-20(4)
(2)	- C(3)	- C(6)	- C(7)	-63.0(4)	C(17)	- C(18)	- C(19)a	- C(24)a	-66(4)
(4)	- C(3)	- C(6)	- C(11)	-122.4(3)	N(25)	- C(18)	- C(19)a	- C(24)a	166(3)
(4)	- C(3)	- C(6)	- C(7)	60.0(4)	C(18)	- C(19)a	- C(24)a	- C(23)a	174(3)
(4)	- C(3)	- C(2)	- H(2B)	65.5(4)	C(18)	- C(19)a	- C(20)a	- C(21)a	-174(3)
(4)	- C(3)	- C(2)	- H(2A)	-52.3(4)	C(20)a	- C(19)a	- C(24)a	- C(23)a	0(6)
(13)	- C(1)	- C(2)	- C(3)	-65.8(3)	C(24)a	- C(19)a	- C(20)a	- C(21)a	0(6)
(14)	- C(1)	- C(2)	- C(3)	113.6(3)	C(20)a	- C(21)a	- C(22)a	- C(23)a	0(6)
(14)	- C(1)	- C(2)	- H(2A)	-7.6(4)	C(22)a	- C(23)a	- C(24)a	- C(19)a	0(6)
(13)	- C(1)	- C(2)	- H(2A)	173.0(3)	C(18)	- C(19)b	- C(24)b	- C(23)b	-173(3)
(14)	- C(1)	- C(2)	- H(2B)	-125.3(3)	C(18)	- C(19)b	- C(20)b	- C(21)b	173(3)
(13)	- C(1)	- C(2)	- H(2B)	55.3(4)	C(20)b	- C(19)b	- C(24)b	- C(23)b	0(5)
(3)	- C(6)	- C(11)	- H(11)	5.0(6)	C(24)b	- C(19)b	- C(20)b	- C(21)b	0(5)
(3)	- C(6)	- C(11)	- C(10)	-175.0(3)	C(19)b	- C(20)b	- C(21)b	- C(22)b	0(5)
(3)	- C(6)	- C(7)	- H(7)	-5.3(5)	C(20)b	- C(21)b	- C(22)b	- C(23)b	0(5)
(3)	- C(6)	- C(7)	- C(8)	174.7(3)	C(21)b	- C(22)b	- C(23)b	- C(24)b	0(5)
(7)	- C(6)	- C(11)	- H(11)	-177.4(4)	C(22)b	- C(23)b	- C(24)b	- C(19)b	0(5)
(7)	- C(6)	- C(11)	- C(10)	2.6(5)					
(11)	- C(6)	- C(7)	- C(8)	-2.9(5)					
(11)	- C(6)	- C(7)	- H(7)	177.1(4)					

n salt continued....

N(16)	- C(5)	- C(4)	- C(3)	151.7(3)
O(15)	- C(5)	- C(4)	- H(4A)	-151.2(4)
O(15)	- C(5)	- C(4)	- H(4B)	91.5(4)
O(15)	- C(5)	- N(16)	- H(161)	-12(4)
O(15)	- C(5)	- N(16)	- H(162)	180(3)
N(16)	- C(5)	- C(4)	- H(4A)	30.4(5)
N(16)	- C(5)	- C(4)	- H(4B)	-87.0(4)
C(4)	- C(5)	- N(16)	- H(162)	-2(3)
C(4)	- C(5)	- N(16)	- H(161)	167(4)
C(11)	- C(10)	- C(9)	- CL(12)	176.6(3)
H(10)	- C(10)	- C(9)	- CL(12)	-3.4(7)
H(10)	- C(10)	- C(11)	- C(6)	-179.6(5)
C(9)	- C(10)	- C(11)	- C(6)	0.4(6)
C(11)	- C(10)	- C(9)	- C(8)	-3.3(6)
H(10)	- C(10)	- C(9)	- C(8)	176.7(5)
H(10)	- C(10)	- C(11)	- H(11)	0.4(8)
C(9)	- C(10)	- C(11)	- H(11)	-179.6(5)
C(19)	- C(20)	- C(21)	- H(21)	-179.3(5)
H(20)	- C(20)	- C(21)	- H(21)	0.8(8)
C(19)	- C(20)	- C(21)	- C(22)	0.7(6)
H(20)	- C(20)	- C(21)	- C(22)	-179.2(5)
H(20)	- C(20)	- C(19)	- C(18)	-0.4(6)
H(20)	- C(20)	- C(19)	- C(24)	179.3(5)
C(21)	- C(20)	- C(19)	- C(24)	-0.6(6)
C(21)	- C(20)	- C(19)	- C(18)	179.6(4)
C(20)	- C(19)	- C(18)	- N(25)	-42.2(4)
C(20)	- C(19)	- C(24)	- H(24)	179.3(5)
C(20)	- C(19)	- C(24)	- C(23)	-0.7(6)
C(20)	- C(19)	- C(18)	- H(18)	-160.6(4)
C(20)	- C(19)	- C(18)	- C(17)	79.8(4)
C(24)	- C(19)	- C(18)	- N(25)	138.1(3)
C(18)	- C(19)	- C(24)	- H(24)	-1.0(7)
C(18)	- C(19)	- C(24)	- C(23)	179.0(4)
C(24)	- C(19)	- C(18)	- C(17)	-99.9(4)
C(24)	- C(19)	- C(18)	- H(18)	19.7(5)
C(7)	- C(8)	- C(9)	- CL(12)	-176.8(3)
C(8)	- C(8)	- C(9)	- CL(12)	3.2(6)
C(7)	- C(8)	- C(9)	- C(10)	3.1(6)
C(8)	- C(8)	- C(9)	- C(10)	-176.9(4)
C(8)	- C(8)	- C(7)	- C(6)	-179.9(4)
C(9)	- C(8)	- C(7)	- C(6)	0.1(5)
C(8)	- C(8)	- C(7)	- H(7)	0.1(7)
C(9)	- C(8)	- C(7)	- H(7)	-179.9(4)
C(173)	- C(17)	- C(18)	- N(25)	63.6(5)
C(172)	- C(17)	- C(18)	- N(25)	-176.4(4)
C(171)	- C(17)	- C(18)	- N(25)	-56.4(5)
C(173)	- C(17)	- C(18)	- C(19)	-60.0(5)
C(172)	- C(17)	- C(18)	- C(19)	60.0(5)
C(171)	- C(17)	- C(18)	- C(19)	-180.0(4)
C(173)	- C(17)	- C(18)	- H(18)	-179.6(5)
C(172)	- C(17)	- C(18)	- H(18)	-59.6(6)
C(171)	- C(17)	- C(18)	- H(18)	60.4(6)
C(19)	- C(24)	- C(23)	- H(23)	-178.0(6)
C(19)	- C(24)	- C(23)	- C(22)	2.0(7)
C(24)	- C(24)	- C(23)	- H(23)	2.0(9)
C(24)	- C(24)	- C(23)	- C(22)	-178.0(5)
C(20)	- C(21)	- C(22)	- H(22)	-179.5(6)
C(20)	- C(21)	- C(22)	- C(23)	0.5(7)
C(21)	- C(21)	- C(22)	- H(22)	0.5(9)
C(21)	- C(21)	- C(22)	- C(23)	-179.5(6)
C(24)	- C(23)	- C(22)	- C(21)	-1.9(8)
C(23)	- C(23)	- C(22)	- C(21)	178.1(6)
C(24)	- C(23)	- C(22)	- H(22)	178.1(6)
C(23)	- C(23)	- C(22)	- H(22)	-2(1)