Structural Studies of Compounds with Aliphatic Chains.
7. The Structure of Piperazinium Glutarate and the Geometry of the Piperazinium Cation

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Abstract

$C_5H_6O_4^{2-} \cdot C_4H_{12}N_2^{2+}$, $M_r = 218 \cdot 25$, crystallizes in the triclinic space group $P\bar{1}$, with $Z = 2$, $a = 5 \cdot 841$ (4), $b = 7 \cdot 503$ (2), $c = 12 \cdot 698$ (3) Å, $\alpha = 97 \cdot 81$ (2), $\beta = 99 \cdot 92$ (2), $\gamma = 94 \cdot 89$ (4)°, $V = 539 \cdot 7$ Å^3, $D_o = 1 \cdot 35$, $D_c = 1 \cdot 343$ Mg m^{-3}, $F(000) = 118$. The structure was solved by direct methods. The anisotropic block-diagonal least-squares refinement was concluded with the final $R = 0 \cdot 044$ for 1522 observed reflections. The piperazinium cations lie on centers of symmetry and are bonded through hydrogen bonds to the glutarate anions. The torsion angles within the anion correspond to a *gauche–trans* conformation. The carboxylate groups are tilted by 15 and 60° from their respective methylenic planes. The piperazinium cations are in the chair conformation. A standard geometry is proposed for this cation. Each piperazinium cation is hydrogen-bonded to four different anions and *vice versa*. The N···O distances range from 2·636 (2) to 2·734 (3) Å. These hydrogen-bonded structural units form planes parallel to (102).

Introduction

Recently, it has been shown that both the melting points and the densities in the series of piperazinium alkanedioates were strongly correlated to the parity of the number of C atoms in the alkanedioate (Brisse & Vanier, 1982, unpublished). In a previous study of the piperazinium salts of linear monoacids it was found that the conformation of the alkanoate anion was dependent upon the parity of the number of the C atoms in the acid chain (Brisse & Sangin, 1982). The present study has been undertaken to determine whether the parity of the number of C atoms also plays a role in the conformation of the alkanedioate anions and to try to explain the effect of parity on the melting points and the densities in the series of piperazinium alkanedioates. After having solved a number of structures containing the piperazinium cation, a standard geometry for this cation can be arrived at and is presented here.

Experimental

Piperazinium glutarate was synthesized following a procedure similar to that described by Pollard, Adelson & Bain (1934). Single crystals in the shape of elongated platelets were grown by slow evaporation from a methanolic solution of the salt. The crystals, m.p. 432 K, are triclinic, space group $P\bar{1}$. The unit-cell dimensions (see *Abstract*) were obtained by a least-squares fit to the settings of 25 reflections centered on an automatic diffractometer.

Integrated intensities were collected on a Nonius CAD-4 diffractometer using Cu $K\bar{\alpha}$ ($\lambda = 1 \cdot 54178$ Å) graphite-monochromatized radiation for all the reflections within the hkl, $hk\bar{l}$, $h\bar{k}l$ and $h\bar{k}\bar{l}$ octants of the reflection sphere limited by $2\theta \le 140°$. The $\omega/2\theta$ scan technique was used with scan range of $\omega = (1 \cdot 00 + 0 \cdot 14 \tan \theta)°$. The orientation of the crystal and the intensities of three reference reflections were checked every 100 reflections and every hour respectively. The fluctuations of the intensities were less than 1·8% over the duration of the data collection. The data reduction was performed in the usual way.* No absorption correction was applied since the absorption coefficient was low, μ(Cu $K\bar{\alpha}$) = 0·84 mm^{-1}. Among the 2406 measured reflections there were 1522 for which $I/\sigma(I) \ge 2 \cdot 50$. The X-ray scattering factors for O, N and C were obtained from Cromer & Mann (1968) and from Stewart, Davidson & Simpson (1965) for H atoms.

The normalized structure-factor distribution indicated a centrosymmetric space group. The structure was solved by direct methods in the $P\bar{1}$ space group using the *MULTAN* program with all E's $\ge 1 \cdot 46$. The E map revealed all non-H atoms. The atomic coordinates and individual isotropic temperature factors were refined with unit weights by the least-squares block-diagonal approximation. Once the refinement

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* The programs used in this work are modified versions of *NRC*-2, data reduction, *NRC*-10, bond distances and angles, and *NRC*-22, mean planes (Ahmed, Hall, Pippy & Huber, 1973); *FORDAP*, Fourier and Patterson maps (A. Zalkin); *NUCLS*, least-squares refinement (R. J. Doedens & J. A. Ibers); *MULTAN*, multisolution program (Main, Woolfson, Lessinger, Germain & Declercq, 1978); *ORTEP*, stereoviews (Johnson, 1965).

had converged, the H atoms were located on a difference Fourier map. The refinement was continued with anisotropic temperature factors for O, N and C, and isotropic temperature factors for H atoms. When the refinement was concluded, the average shift to σ ratio was 0·8 while $R = \sum \Delta F / \sum F_o = 0\cdot044^*$ for the observed reflections only and 0·066 for all measured reflections.† The extreme fluctuations of the electron density on the final difference Fourier map were in the range $-0\cdot23$ to 0·26 e Å^{-3}. The final fractional coordinates of the structure are given in Table 1. The atomic numbering is given in Fig. 1 and Fig. 2 shows the organization of the structural units in the unit cell.

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* Five strong reflections, for which $|F_c| > F_o$, have been removed from the last least-squares cycle.

† Lists of structure factors, anisotropic thermal parameters, bond distances, angles and torsion angles from various structures containing the piperazinium cation and C—H distances in the anion have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 38075 (12 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.
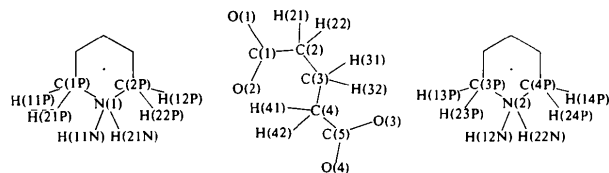

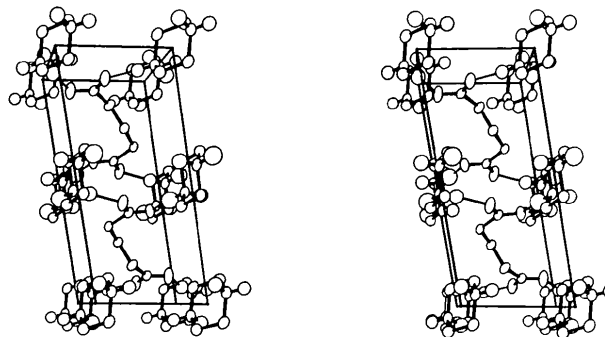Fig. 1. Schematic representation of the structural units and atomic numbering.

Fig. 2. Stereopair showing the organization of the structural units in the unit cell. The origin is at the front, lower, right corner with a into the page, b horizontal and c vertical.

Results and discussion

The piperazinium cations

The piperazinium cations, both in the chair conformation, are located on the centers of symmetry of the unit cell at (000) and at (00½). The bond distances and angles as well as the torsion angles are presented in Table 2 where they are compared to mean values from other piperazinium cations. This table allows for some clear characteristics of the cation to emerge. Both

Table 1. *Fractional atomic coordinates* ($\times 10^4$ *for* O, N *and* C; $\times 10^3$ *for* H *atoms*), U_{eq} ($\times 10^4$ *for* O, N *and* C) *and* U_{iso} ($\times 10^3$ *for* H *atoms*)

	x	y	z	U_{eq}/U_{iso} (Å^2)
O(1)	7121 (3)	4088 (2)	3916 (1)	391 (6)
O(2)	4252 (3)	2113 (2)	4132 (2)	461 (7)
O(3)	8607 (3)	6307 (3)	1240 (2)	551 (8)
O(4)	5697 (3)	7953 (2)	940 (2)	469 (7)
C(1)	4987 (4)	3527 (3)	3809 (2)	287 (7)
C(2)	3186 (4)	4640 (3)	3291 (2)	280 (7)
C(3)	4146 (4)	6058 (3)	2677 (2)	282 (7)
C(4)	4978 (4)	5235 (3)	1663 (2)	331 (8)
C(5)	6540 (4)	6588 (3)	1249 (2)	308 (7)
N(1)	9840 (3)	1674 (2)	4577 (2)	308 (6)
C(1P)	9840 (4)	1598 (3)	5739 (2)	344 (8)
C(2P)	8822 (4)	−75 (3)	3902 (2)	351 (8)
N(2)	11329 (3)	8698 (2)	482 (2)	314 (6)
C(3P)	10681 (4)	8546 (3)	−716 (2)	347 (8)
C(4P)	11548 (4)	10609 (3)	1020 (2)	356 (8)
H(21)	193 (4)	375 (3)	280 (2)	45 (7)
H(22)	248 (4)	528 (3)	390 (2)	43 (7)
H(31)	283 (4)	688 (3)	247 (2)	49 (7)
H(32)	553 (4)	681 (3)	316 (2)	41 (7)
H(41)	584 (4)	428 (3)	179 (2)	47 (7)
H(42)	361 (4)	475 (3)	105 (2)	52 (8)
H(11P)	1067 (5)	281 (4)	623 (2)	58 (8)
H(21P)	817 (4)	141 (3)	583 (2)	44 (7)
H(12P)	713 (4)	−25 (3)	399 (2)	42 (7)
H(22P)	897 (5)	−5 (4)	314 (2)	68 (9)
H(13P)	1200 (4)	918 (3)	−102 (2)	41 (7)
H(23P)	1041 (4)	722 (3)	−108 (2)	48 (7)
H(14P)	1191 (5)	1070 (4)	184 (2)	72 (9)
H(24P)	1287 (4)	1128 (3)	79 (2)	38 (7)
H(11N)	866 (6)	258 (4)	430 (3)	83 (10)
H(21N)	1135 (5)	191 (4)	448 (2)	58 (8)
H(12N)	1022 (5)	798 (4)	78 (2)	57 (8)
H(22N)	1282 (4)	831 (3)	66 (2)	45 (7)

Table 2. *Bond distances* (Å), *angles and torsion angles* (°) *for the piperazinium cation*

	Cation at (000)	Cation at (00½)	$\bar{x}$ (s)*
N(1)—C(1P)	1·484 (3)	1·489 (3)	1·484 (2)
N(1)—C(2P)	1·482 (2)	1·487 (3)	1·484 (4)
C(1P)—C(2P)	1·515 (3)	1·510 (3)	1·509 (3)
C(1P)—N(1)—C(2P)	110·9 (2)	111·6 (2)	111·2 (2)
N(1)—C(1P)—C(2P′)	110·2 (2)	111·1 (2)	110·9 (3)
N(1)—C(2P)—C(1P′)	110·4 (2)	110·1 (2)	110·3 (2)
N(1′)—C(2P′)—C(1P)—N(1)	−57·1 (3)	−55·8 (3)	−56·5 (2)
C(2P′)—C(1P)—N(1)—C(2P)	57·5 (6)	56·0 (3)	56·9 (1)
C(1P)—N(1)—C(2P)—C(1P′)	−57·6 (3)	−56·6 (3)	−56·5 (2)

* $\bar{x} = \text{mean} = (1/n)\sum_{i=1}^{n} x_i$; $s = $ standard deviation of mean value $[\sum_{i=1}^{n} |x_i - \bar{x}|^2 / n(n-1)]^{1/2}$.

The averages and standard deviations given in the last column have been obtained from ten different structures containing the piperazinium cation. The full table has been deposited. Those ten compounds are: piperazine hydrochloride monohydrate (Rérat, 1960); piperazine terephthalate (Kashino, Sasaki & Haisa, 1973); piperazinium bis(n-heptanoate) and bis(n-decanoate) (Sangin, 1981); piperazinium bis(n-dodecanoate) (Brisse & Sangin, 1982); piperazinium succinate, adipate and suberate (Vanier & Brisse, 1983); piperazinium glutarate (this work).

N(1)–C(1P) and N(1)–C(2P) distances are equal but are significantly shorter than the C(1P)–C(2P) distance. The three bond angles C(1P)–N(1)–C(2P), N(1)–C(1P)–C(2P') and N(1)–C(2P)–C(1P') have practically the same values. Similarly, the three torsion angles in the piperazinium cation are indistinguishable. The C(sp^3)–H distances average 1·02 (4) Å while the N$^+$(sp^3)–H average 0·98 (6) Å.

The glutarate anion

The bond distances and angles of the glutarate anion are given in Table 3 together with their e.s.d.'s. The four C$\leftrightharpoons$O distances average 1·254 Å and have values halfway between those for C=O and C–O bonds thus indicating the complete delocalization of the π electrons of the carboxylate group especially since the C–C$\leftrightharpoons$O bond angles are also very similar and average 118·3°. The C(sp^3)–C(sp^3) distances are very close to their average of 1·525 Å, while the two C(sp^2)–C(sp^3) distances average 1·515 Å. The bond angles ranging in value from 112·4 (2) to 114·9 (2)° are all larger than the tetrahedral angle. The conformation of the anion, described by the torsion angles given in Table 3, is *gauche–trans*. This situation is to be contrasted to that observed for the piperazinium succinate, adipate and suberate where the anions are all in the fully extended (*trans*) conformation (Vanier & Brisse, 1983). Thus it seems that in this series of compounds the parity of the number of C atoms determines the conformation of the alkanedioate anion. The two carboxylate groups are tilted by 15 and 60° with respect to the C(1)–C(2)–C(3) or C(3) to C(5) planes respectively. In the case of the β-form of glutaric acid (MacGillavry, Hoogschagen & Sixma, 1948) the conformation of the chain is nearly *trans–trans* and both carboxylate planes are inclined by 32° to the plane of the three central C atoms of the acid.

Packing of the molecules

The piperazinium cations are centered at (000) and (00½) while the anions are within the unit cell between cations of the two different types (Fig. 3). The shortest contacts take place between cations and anions. The
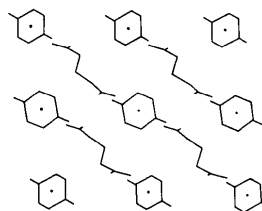

Fig. 3. Projection on the *ac* plane of the unit-cell content. In order to visualize the hydrogen bonding, the N–H bonds have been added to the piperazinium cations.

Table 4. *Hydrogen-bonding characteristics*

| | Distances (Å) | | | Angles (°) |
	N···O	N–H	H···O	N–H···O
Cation at (000)				
N(1)–H(11N)···O(1)	2·636 (2)	1·06 (3)	1·58 (3)	174 (3)
N(1)–H(21N)···O(2)	2·734 (3)	0·92 (3)	1·83 (3)	172 (2)
Cation at (00½)				
N(2)–H(12N)···O(3)	2·680 (3)	0·94 (3)	1·73 (3)	167 (3)
N(2)–H(22N)···O(4)	2·642 (3)	0·94 (3)	1·71 (3)	171 (2)

hydrogen-bond parameters are listed in Table 4. The three distinct structural units are all involved in the hydrogen-bonding scheme. There are four hydrogen bonds linking each piperazinium cation to different glutarate groups while each anion in turn forms two hydrogen bonds with each of the two different piperazinium cations. These hydrogen-bonded structural units are organized in pseudo-planes parallel to (102).

Table 3. *Bond distances* (Å), *angles and torsion angles* (°) *for the glutarate ion*

C(1)–O(1)	1·259 (3)	C(5)–O(3)	1·245 (3)
C(1)–O(2)	1·257 (3)	C(5)–O(4)	1·255 (3)
C(1)–C(2)	1·515 (3)	C(5)–C(4)	1·514 (3)
C(2)–C(3)	1·526 (3)	C(4)–C(3)	1·524 (3)
O(1)–C(1)–O(2)	123·8 (2)	O(3)–C(5)–O(4)	123·0 (2)
C(2)–C(1)–O(1)	118·6 (2)	C(4)–C(5)–O(3)	118·6 (2)
C(2)–C(1)–O(2)	117·7 (2)	C(4)–C(5)–O(4)	118·4 (2)
C(1)–C(2)–C(3)	114·9 (2)	C(3)–C(4)–C(5)	112·4 (2)
C(2)–C(3)–C(4)	113·2 (2)		
O(1)–C(1)–C(2)–C(3)	16·0 (3)	O(3)–C(5)–C(4)–C(3)	116·5 (3)
O(2)–C(1)–C(2)–C(3)	−165·8 (3)	O(4)–C(5)–C(4)–C(3)	62·8 (3)
C(1)–C(2)–C(3)–C(4)	67·5 (3)	C(2)–C(3)–C(4)–C(5)	163·3 (3)

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Structure of a Complex of Cycloheptaamylose with 1-Adamantanecarboxylic Acid*

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Abstract

The structure of cycloheptaamylose complexed with 1-adamantanecarboxylic acid (an inhibitor of phenyl ester hydrolysis by cycloheptaamylose), determined by single-crystal X-ray diffraction at 108 K, is triclinic, space group $P1$, $a = 17\cdot747$ (5), $b = 15\cdot255$ (5), $c = 15\cdot491$ (5) Å, $\alpha = 102\cdot54$ (1), $\beta = 113\cdot54$ (1) and $\gamma = 98\cdot87$ (1)°, $V = 3615$ Å^3, $Z = 1$, $D_x = 1\cdot455$ g cm^{-3}. Two molecules of each of cycloheptaamylose and 1-adamantanecarboxylic acid per unit cell form a dimer of composition $2C_{11}H_{16}O_2.2C_{42}H_{70}O_{35}.30H_2O$. The final R was 0·11 for 6433 observed reflections (Mo $K\alpha$ radiation, $\mu = 1\cdot407$ cm^{-1}). Two cycloheptaamylose molecules are in a head-to-head dimer produced by tight hydrogen bonding involving the secondary hydroxyl groups on both molecules. The two 1-adamantanecarboxylic acid guests have different orientations in the cycloheptaamylose cavities and different depths of penetration.

Introduction

The cycloamyloses (cyclodextrins) are cyclic oligosaccharides containing 6 to 12 D-glucopyranose residues linked α-(1 → 4). They have attracted great attention as models for enzymes such as the serine acylase enzymes, in particular chymotrypsin (Van Etten, Sebastian, Clowes & Bender, 1967; Bender & Komiyama, 1978). Cyclohexaamylose (α-cyclodextrin), cycloheptaamylose (β-cyclodextrin) and to a lesser extent cyclooctaamylose (γ-cyclodextrin) have been studied to examine the mode of binding of organic molecules in their cavities. This complexation process is the basis for all of the wide variety of phenomena produced by the cycloamyloses including catalysis of

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* Adamantane is tricyclo[3.3.1.1^{3,7}]decane.

ester hydrolysis. These phenomena and other applications of the cycloamyloses in research and industry have recently been reviewed by Saenger (1980).

Early studies showed that the cycloamyloses caused stereoselective acceleration of the cleavage of phenyl esters (Van Etten, Sebastian, Clowes & Bender, 1967; Van Etten, Clowes, Sebastian & Bender, 1967). Cycloheptaamylose is a better catalyst than cyclohexaamylose. 1-Adamantanecarboxylic acid, which binds well in the cavity of cycloheptaamylose, is a competitive inhibitor of phenyl ester hydrolysis (Van Etten, Sebastian, Clowes & Bender, 1967; Breslow & Overman, 1970). 1-Adamantanecarboxylic acid also binds to cyclohexaamylose but is probably too large to enter the cavity entirely and must sit on top (Bender & Komiyama, 1978).

The best ratio of catalyzed *vs* uncatalyzed reaction found by Bender & Komiyama (1978) for acetyl transfer to cycloheptaamylose was only 250 for the substrate *tert*-butylphenyl acetate. However, as pointed out by Breslow, Czarniecki, Emert & Hamaguchi (1980), true enzymes often achieve ratios of 10^5–10^{10} or greater. They suggested, on the basis of model building, that substrates such as *tert*-butylphenyl acetate can bind fully in the cavity in the complex but they are pulled up partly out of the cavity by formation of the tetrahedral intermediate. They proposed several types of new substrates which were selected to retain as much binding as possible while proceeding from bound substrate to bound transition state to bound tetrahedral intermediate to product. One particular class of these new substrates is based on the adamantane framework. On the basis of binding studies and model building they have proposed that in the complex of 1-adamantanecarboxylic acid with cycloheptaamylose only half of the adamantane moiety would be enclosed by the cycloheptaamylose. Breslow *et al.* (1980) discussed the kinetic results of ester hydrolysis of two adamantane derivatives on the basis of this model. In