

Fig. 11. Melting phase diagram of mixtures of enantiomers $A(+)$ and $A(-)$: calculated curve and experimental melting points.

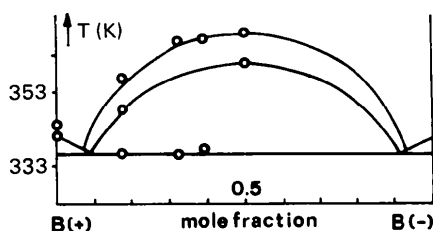


Fig. 12. Melting phase diagram of mixtures of enantiomers $B(+)$ and $B(-)$: calculated curve and experimental points.

between diastereoisomers which have the same chirality at the C atom α to the acid function [e.g. $(-)$ A and $(-)$ B , Fig. 9]. For the same reasons the pair of diastereoisomers having opposite chirality at this same C atom [e.g. $(-)$ A and $(+)$ B] are very similar enantiomers and display a quasi-racemate phase diagram (Fig. 10) similar to the racemate diagrams formed by the true enantiomers (Figs. 11 and 12).

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The Crystal Structure of the 5-Oxotricyclo[2.2.1.0^{2,6}]heptane-3-carboxylic Acid Stereoisomer: An Exercise in the Application of a New Automatic Phasing Procedure

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(Received 8 January 1979; accepted 9 May 1979)

Abstract

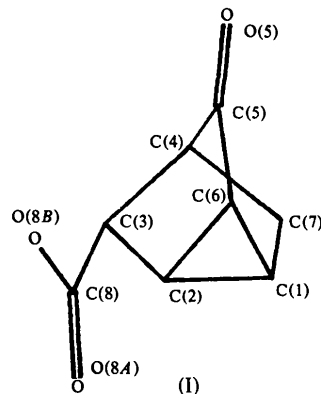
5-Oxotricyclo[2.2.1.0^{2,6}]heptane-3-carboxylic acid, $C_8H_8O_3$, crystallizes in the triclinic space group $P1$ with $a = 7.800$ (1), $b = 7.949$ (1), $c = 6.089$ (1) Å, $\alpha = 88.32$ (1), $\beta = 108.50$ (1), $\gamma = 94.00$ (1)° and $Z = 2$. The structure was determined by the use of quartet and quintet invariants and a new automated phasing procedure and refined by full-matrix least squares to a final R of 0.089.

Introduction

5-Oxotricyclo[2.2.1.0^{2,6}]heptane-3-carboxylic acid (I) is an important prostaglandin synthetic intermediate (Bindra, Grodski, Schaaf & Corey, 1973; Grieco,

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Pogonowski & Niyashita, 1975; Peel & Sutherland, 1974). It can be readily obtained from the reaction of norbornadiene with paraformaldehyde in formic acid containing a trace of H_2SO_4 followed by Jones oxidation (Bindra, Grodski, Schaaf & Corey, 1973).



The simplicity of this structure (11 non-hydrogen atoms in space group $P\bar{1}$) obviously does not present a challenge to current direct method procedures. This work is a preliminary exercise in a program of extensive testing of high-order invariants (quartets and quintets), and of a new automated phasing procedure which differs from the standard approach primarily in its full use of the space-group-dependent relationships, the identities, among the invariants. One of the features of the reduction procedure is the ease with which different invariant types can be incorporated into a single algorithm for phase determination.

Experimental

The crystals were supplied by Professor Paul A. Grieco (Department of Chemistry, University of Pittsburgh). A specimen of dimensions $0.12 \times 0.36 \times 0.95$ mm was used for data collection on an Enraf-Nonius CAD-4 diffractometer. Cell dimensions were determined by a least-squares fit to the settings of 25 reflections. Using Cu $K\alpha$ radiation, a total of 1488 reflections were measured out to a $\sin\theta/\lambda$ limit of 0.63 \AA^{-1} , 1366 of which were considered observable ($I \geq 2\sigma_I$). The intensities were corrected for Lp factors and put on an approximately absolute scale by the κ curve technique. Normalized structure factors were derived from the intensities in the usual manner. Intensity statistics confirmed the $P\bar{1}$ space-group symmetry.

Crystal data

$\text{C}_8\text{H}_8\text{O}_3$, $M_r = 153.16$, $F(000) = 162$, triclinic, $P\bar{1}$, $Z = 2$, $a = 7.800$ (1), $b = 7.949$ (1), $c = 6.089$ (1) Å , $\alpha = 88.32$ (1), $\beta = 108.50$ (1), $\gamma = 94.00$ (1) $^\circ$, $V = 357.1 \text{ Å}^3$, $D_c = 1.424 \text{ Mg m}^{-3}$, $\mu = 0.927 \text{ mm}^{-1}$, $\lambda(\text{Cu } K\alpha) = 1.5418 \text{ Å}$.

Structure determination and refinement

The phasing procedure

Theory. The phasing procedure (Fig. 1) (Hauptman, Smith, Fortier & Fronckowiak, 1977; Fortier, Fronckowiak, Smith, Hauptman & DeTitta, 1978) is essentially the reduction of a redundant set of special linear equations. The linear equations have the general form

$$\sum_{j=1}^N \varphi_j = \Phi_i,$$

where the φ_j are the phases which constitute the structure invariant or seminvariant (Hauptman, 1972) and the Φ_i are the values of the phase sums. As a centrosymmetric, one-dimensional example, let us say the phases being sought are φ_{100} , φ_{200} , φ_{300} , φ_{400} and

φ_{500} , and that the structure invariants which we choose to employ in the phasing are the following quartets and triples (given in the order of their introduction into the reduction procedure):

$$\varphi_{100} + \varphi_{200} + \varphi_{300} = \Phi_1,$$

$$\varphi_{100} + \varphi_{300} + \varphi_{400} = \Phi_2,$$

$$\varphi_{100} + \varphi_{400} + \varphi_{500} = \Phi_3,$$

$$\varphi_{200} + \varphi_{300} + \varphi_{500} = \Phi_4,$$

$$\varphi_{100} + \varphi_{200} + \varphi_{300} + \varphi_{400} = \Phi_5,$$

$$\varphi_{100} + \varphi_{200} + \varphi_{400} + \varphi_{500} = \Phi_6,$$

$$\varphi_{200} + \varphi_{300} + \varphi_{400} + \varphi_{500} = \Phi_7.$$

Sequential substitution as outlined in Fig. 1 reduces these equations to an analogous set of equations with the general form

$$\varphi_j = \sum_{i=1}^N \varphi_i + \sum_{i=1}^M \Phi_i.$$

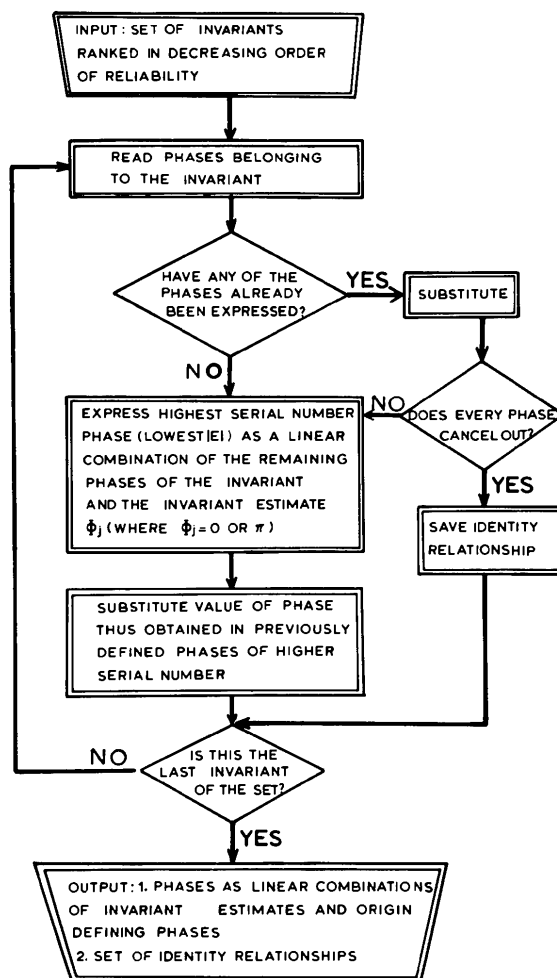


Fig. 1. The reduction algorithm.

In our example the equations resulting from this reduction are:

$$\begin{aligned}\varphi_{200} &= \Phi_2 + \Phi_3 + \Phi_4, \\ \varphi_{300} &= \varphi_1 + \Phi_1 + \Phi_2 + \Phi_3 + \Phi_4, \\ \varphi_{400} &= \Phi_1 + \Phi_3 + \Phi_4, \\ \varphi_{500} &= \varphi_1 + \Phi_1 + \Phi_4; \\ \Phi_3 + \Phi_4 + \Phi_5 &= 0, \\ \Phi_2 + \Phi_4 + \Phi_6 &= 0, \\ \Phi_1 + \Phi_3 + \Phi_7 &= 0.\end{aligned}$$

These equations are of two distinct types: phase equations and identity relationships among the Φ_j . In the former the phases are expressed as linear combinations of the invariant values, Φ_j 's and, where necessary, the phases suitable for origin definition. (In our example φ_{200} and φ_{400} are themselves structure seminvariants; their definitions, suitably enough, involve only the Φ_j 's and do not involve φ_{100} , the phase singled out for origin definition.) The identities express relationships among the Φ_j 's which, due to their nature, must hold. Take for example the first identity $\Phi_3 + \Phi_4 + \Phi_5 = 0$. Substitution of the phase sums for the Φ 's gives $(\varphi_{100} + \varphi_{400} + \varphi_{500}) + (\varphi_{200} + \varphi_{300} + \varphi_{500}) + (\varphi_{100} + \varphi_{200} + \varphi_{300} + \varphi_{400}) = 0$. Note that each phase or its Friedel equivalent appears twice in the identity. Since $2\varphi_h = 0$ in the centrosymmetric case, the identity must hold regardless of the values of φ_h .

The reduction procedure does not depend on prior knowledge of the values of the invariants, the Φ_j 's. The identities and phase equations are strictly correct but are not useful for phasing unless the invariant values can be determined or estimated. Phase estimates are obtained by the substitution of estimated values for the Φ_j 's, obtained from probability formulae, into the phase equations. The validity of the Φ_j estimates used in the phasing may be checked by substitution of these estimates into the identity relationships. In our example, if the initial Φ_j estimates are $\Phi_3 = 0$, $\Phi_4 = 0$ and $\Phi_5 = \pi$ then we know from the first identity relationship that one (or three) of our initial estimates is incorrect. Note that, if only positive estimates are employed (*i.e.* all $\Phi = 0$), then identities can never be violated in this fashion. Invariants thought to be negative (*i.e.* $\Phi = \pi$) are usually introduced at the beginning of the reduction procedure in order to maximize their interaction in identity relationships.

At the end of the reduction procedure a checklist can be compiled for each invariant showing (a) the number of phases, P , defined in terms of its value and dependent upon its estimate, (b) the number of identities, S , satisfied by its estimate, and (c) the number of identities, U , unsatisfied by its estimate. P is a measure of how crucial an invariant is to the phasing procedure. For a given invariant, if S is much greater than

U then one can feel secure about its initially estimated value. On the other hand, if S is much less than U the initial estimate should probably be reversed. Those invariants which are crucial to the phasing process (P large), and for which $S \simeq U$ are termed weak links; their estimated values have not been corroborated by the redundancy of the system and these values should be taken as ambiguities in the phasing.

In the reduction procedure the invariant equations are successively solved for the phase with lowest associated $|E|$ values; this automatically results in each phase being expressed in terms of the largest $|E|$ value phases suitable for origin definition. In some cases the bulk of the phases may be expressed in terms of a few additional phases whose values cannot be arbitrarily defined. This can be due either to the nature of the invariants, for example even-numbered invariants (quartets, sextets) alone cannot define the seminvariant phases, or to the incompleteness of the system of invariant equations. These additional phases can also be introduced as ambiguities.

Application. A total of 117 reflections with $|E| \geq 1.75$ were employed in the various phasing procedures, *i.e.* these were the reflections whose phase values were sought. All of the data, on the other hand, were employed in the estimation of values for the quartet and quintet invariants. A fraction of the total possible set of quintets was generated. Using the discriminant as a screen, probabilities were calculated with the P_{115} distribution (Fortier & Hauptman, 1977) for those quintets whose discriminants, Δ_{15} , had values ≥ 100 or ≤ -15 . A set containing 329 quintet invariants, of which 320 had $P_{115} \geq 0.95$ and nine had $P_{115} \leq 0.01$, were used in the reduction process. They were ranked in decreasing order of reliability with the nine 'negative' invariants arbitrarily at the top of the list. At the end of the reduction, the bulk of the phases were defined in terms of three phases suitable for origin definition, and two additional phases, φ_{604} and φ_{755} . None of the more than 200 identities were violated. Good mingling of the negative and positive invariants in the identities secured most of the crucial invariants. Two weak links (invariants defining 20 phases and appearing in only one identity) showed up in the checklist analysis. For the initial set of phases, the estimates for these two invariants were assumed to be correct. The four ambiguities arising from φ_{604} and φ_{755} were resolved by the use of negative quartets. All of the non-hydrogen atoms appeared in the first E map.

As an exercise, the reduction was carried out again, this time using quartet invariants. Quartets, for which the three cross-term magnitudes $|E_{h+k}|$, $|E_{k+l}|$, and $|E_{l+h}|$ were either all greater than 1.0 or all less than 0.5, were generated. Their probabilities were calculated using the P_{117} distribution (Hauptman & Green, 1976). The set contained 605 'positive' quartets with $P_{117} \geq 0.90$ and 38 'negative' quartets with $P_{117} \leq 0.10$. The

reduction was carried out and all the phases were expressed in terms of three origin-defining phases, one additional phase ϕ_{604} , and a sum of invariants. For theoretical reasons, phase ϕ_{604} , which, as the highest $|E|$ -valued seminvariant phase, served to define all other seminvariant phases, cannot be determined with quartets only. Resolution of the twofold ambiguity arising from ϕ_{604} was accomplished by looking at the most reliably estimated quintet in which it appeared.

Refinement. The structure was refined by full-matrix least squares. All but one of the eight hydrogen atom positions were determined by difference Fourier techniques. The calculated position of H(5) was used. The hydrogen atomic coordinates and isotropic thermal parameters were included, but not refined, in the final cycles of least-squares refinement. The final conventional R was 0.089, the weighted R_w was 0.15. Table 1 gives the atomic coordinates.* The function minimized was $\sum_i w_i |F_o| - |F_c|^2$, where $w = 1/\sigma^2$ and σ is given by equation (H.14) of Stout & Jensen (1968) except that the value 0.01 Npk was replaced by 0.06 Npk. The final e.s.d. of a unit-weight observation is 4.7.

* Lists of structure factors and anisotropic thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 34372 (9 pp.). Copies may be obtained from the authors or through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester, CH1 2HU, England. A more complete description of the reduction of the 11-atom structure using quartets, including lists of invariants, their calculated probabilities and the reduction equations and identities is available from the authors.

Table 1. Atomic positional parameters and e.s.d.'s for 5-oxotricyclo[2.2.1.0^{2,6}]heptane-3-carboxylic acid

	<i>x</i>	<i>y</i>	<i>z</i>
C(1)	0.3087 (3)	0.6268 (3)	0.5098 (4)
C(2)	0.2783 (3)	0.8067 (3)	0.5179 (3)
C(3)	0.1350 (2)	0.8520 (3)	0.2929 (3)
C(4)	0.1812 (3)	0.7246 (3)	0.1373 (3)
C(5)	0.3847 (3)	0.7634 (3)	0.2018 (4)
C(6)	0.4432 (3)	0.7600 (3)	0.4549 (4)
C(7)	0.1850 (3)	0.5586 (3)	0.2804 (5)
C(8)	-0.0549 (2)	0.8258 (3)	0.3049 (3)
O(5)	0.4732 (2)	0.7917 (4)	0.0714 (3)
O(8A)	-0.0908 (2)	0.7964 (3)	0.4818 (3)
O(8B)	-0.1793 (2)	0.8409 (3)	0.1008 (3)

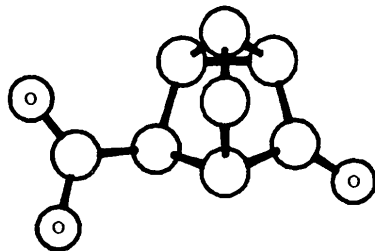


Fig. 2. The conformation of 5-oxotricyclo[2.2.1.0^{2,6}]heptane-3-carboxylic acid. The C(2)–C(1) bond defines the horizontal direction.

Results and discussion

(a) Structure

The relative configuration was determined to be C(1)(*R*), C(2)(*S*), C(3)(*S*), C(4)(*S*), C(6)(*R*); Fig. 2. The bond lengths and angles are shown in Fig. 3. As expected, due to the strain in the tricycloheptane system, many of the bond angles differ considerably from the tetrahedral value, in particular the one-carbon bridge angle [C(1)–C(7)–C(4)] is 97.3° and

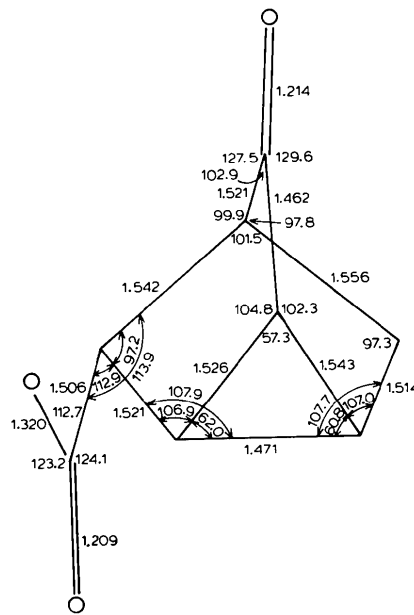


Fig. 3. Bond distances (Å) and angles (°) for 5-oxotricyclo[2.2.1.0^{2,6}]heptane-3-carboxylic acid. The average e.s.d.'s for distances and angles are 0.003 Å and 0.2° respectively.

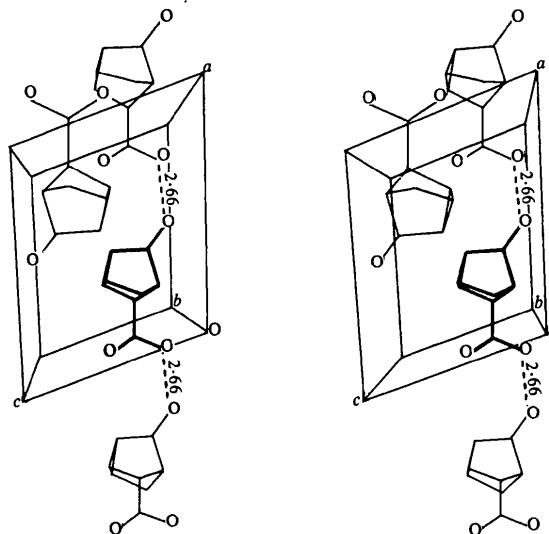


Fig. 4. Stereogram of the hydrogen bonding and crystal packing of 5-oxotricyclo[2.2.1.0^{2,6}]heptane-3-carboxylic acid.

Table 2. Average torsion angles and asymmetry parameters of the five- and six-membered rings

E.s.d.'s are 0.8° for all angles.

Ring	Average torsion angle	ΔC_s^* at C(4)
C(1)–C(2)–C(3)–C(4)–C(5)–C(6)	60.3°	1.0°
C(1)–C(7)–C(4)–C(5)–C(6)–C(2)	59.9	3.1
C(1)–C(7)–C(4)–C(3)–C(2)–C(6)	61.8	0.7
C(1)–C(7)–C(4)–C(5)–C(6)	34.6	1.7
C(2)–C(6)–C(5)–C(4)–C(3)	33.3	5.3
C(1)–C(7)–C(4)–C(3)–C(2)	32.3	0.2

$$*\Delta C_s = \left(\sum_{i=1}^m (\varphi_i + \phi_i)^2 / m \right)^{1/2},$$

where m is the number of individual comparisons and φ_i and ϕ_i are symmetry-related torsion angles.

the two-carbon bridge angle [C(2)–C(3)–C(4)] is 97.2°. The system contains seven rings: 3 six-membered rings, 3 five-membered rings and 1 three-membered ring. The six-membered rings all have sofa conformations and the five-membered rings envelope conformations. A summary of the average torsion angles and asymmetry parameters (Duax, Weeks & Rohrer, 1976) of the five- and six-membered rings is given in Table 2. The carboxylic acid oxygen O(8B) is antiperiplanar to C(2) with torsion angle O(8B)–C(8)–C(3)–C(2) of $-170.5(2)^\circ$. The molecules are linked together in the crystal by hydrogen bonds between the hydroxyl O(8B) of the carboxyl group and O(5). The donor–acceptor distance is 2.660 Å. The packing of the molecules in the crystals is shown in Fig. 4.

(b) Methods

After refinement, the calculated phases were substituted in the invariant equations. It is interesting to note that in this simple example the quintet invariants were more accurately estimated than the quartet invariants. The first error in the quintets occurs at a probability of 0.25 as opposed to a probability of 0.04 in the quartets. The quintet estimates based on the discriminant ($\Delta_{15} \geq 100$ taken to be positive and $\Delta_{15} \leq -15$ negative) were error-free. The reduction process has some clear advantages over its nearest relative, traditional hand phasing. It leaves a pedigree of the

phasing, which in its counterpart is nearly impossible to keep, and provides a mechanism for the identification and correction of poorly estimated invariants. Finally, it identifies those invariants which are crucial to the phasing process.

The phase-reduction procedure has also been applied successfully (using quintets only) in the structure determination of prostaglandin. PGE₁-9-sulfone (C₁₉H₃₄O₆S), space group *P*1 with $Z = 4$ and $N = 104$ (Fronckowiak, Fortier, DeTitta & Hauptman, 1977).

The work was supported in part by NIH Grants HL-15378 and AM-19856 and by NSF Grant No. CHE 76-17582. We thank Douglas Rohrer for supervising the collection of intensity data.

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