

The Crystal and Molecular Structure of *cis-trans-cis*-Cyclodeca-2,4,8-triene-1,6-dione*

BY OLGA KENNARD†, D. L. WAMPLER, J. C. COPPOLA, W. D. S. MOTHERWELL AND D. G. WATSON
University Chemical Laboratory, Cambridge, England

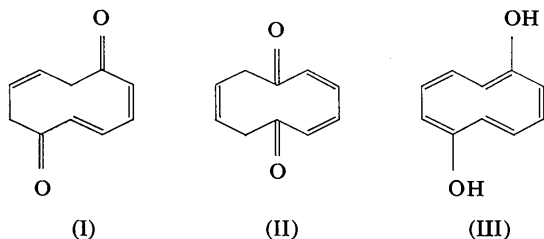
AND ALLEN C. LARSON
University of California, Los Alamos Scientific Laboratory, Los Alamos, New Mexico, U.S.A.

(Received 6 August 1970)

The crystal and molecular structure of *cis-trans-cis*-cyclodeca-2,4,8-triene-1,6-dione was determined by X-ray diffraction. The crystals are triclinic, $P\bar{1}$, $a=5.641$, $b=12.025$, $c=6.326$ Å, $\alpha=80.29^\circ$, $\beta=87.93^\circ$ and $\gamma=80.40^\circ$. There are two molecules in the unit cell. Diffractometer data were used and the structure was refined anisotropically to $R=5.2\%$. The analysis showed considerable distortion about the *trans* double bond.

Introduction

Cyclodeca-2,4,8-triene-1,6-dione [(I) or (II)], recently synthesized by Mulligan & Sondheimer (1967), is a compound of considerable interest, since it is the diketone tautomer of 1,6-dihydroxy[10]annulene [*e.g.* (III)].



Unfortunately, it was not possible to determine by chemical methods whether the substance possesses the *cis*, *trans*, *cis* configuration (I) or the all-*cis* configuration (II). However, a three-dimensional X-ray diffraction analysis has now been carried out, and it has been found that the compound in fact is the *cis*, *trans*, *cis* stereoisomer (I). The analysis also afforded an opportunity of examining the precise geometry of the *trans* double bond in a ten-membered ring system.

Crystal data

cis-trans-cis-Cyclodeca-2,4,8-triene-1,6-dione.

$C_{10}H_{10}O_2$; F.W. 162.2; m.p. 80–81°C. Light brown, very rough plates. Triclinic, $a=5.641$ (10); $b=12.025$ (20); $c=6.326$ (10) Å; $\alpha=80.29$ (5)°; $\beta=87.93$ (5)°, $\gamma=80.40$ (5)°; $V=417.0$ Å³; $Z=2$; $D(\text{calc})=1.27\text{g.cm}^{-3}$. $|F_{000}|=172$. Space group $P\bar{1}$ from statistical distribution of E 's and from the solved structure. The particular choice of the cell constants was experimentally convenient and is not the conventional reduced cell.

Experimental

Crystals of *cis-trans-cis*-cyclodeca-2,4,8-triene-1,6-dione are moderately stable in air but decay rapidly in the X-ray beam to a dark brown powder. The rate of decay in the beam was reduced by mounting the crystals in capillaries which were sealed after being flushed with helium. Even with this precaution, however, it was necessary to use five crystals (typical size $0.6 \times 0.4 \times 0.2$ mm) to collect a full set of intensity measurements. The data from the various crystals were scaled to give a consistency of $R=3.8\%$ for $|F_o|$ for the 366 equivalent reflexions measured more than once.

The intensity data and unit-cell parameters were measured with a Picker 4-circle diffractometer using Ni-filtered Cu $K\alpha$ radiation. The cell-parameters were obtained from the diffractometer settings for a number of reflections. Intensity data were collected for 1508 independent reflections in the range $0 < 2\theta < 136.5^\circ$ using the θ - 2θ scan mode. The 2θ scan range was $\pm 1.6^\circ$; the scan rate $1^\circ/\text{min}$. There were 1386 reflexions with $I > 2\sigma(I)$. The data were corrected for polarization and geometrical factors.

Solution and refinement of the structure

The structure was solved by the use of direct, mathematical methods. The phases of a small group of reflexions were derived independently, both by the symbolic-addition procedure (Karle & Karle, 1966), and by the use of the tangent formula (Karle & Karle, 1968, 1969). The structure was solved from Karle maps (E maps) based on these phases.

The calculations were carried out on an IBM 360/44 computer in Cambridge and a CDC 6600 at Los Alamos. The two approaches were tried in parallel. For each, several false starts were made, leading to Karle maps which could not be interpreted.

The symbolic-addition program assigns symbolic signs to the phases of the first terms in a list of E 's ar-

* Work was partially performed under the auspices of the U.S. Atomic Energy Commission.

† External Staff, Medical Research Council.

ranged in descending order of magnitude. The program then proceeds to examine the \sum_2 relationships involving these reflexions and assigns the appropriate combination of symbolic signs to additional reflexions if the triple-products are equal to or greater than a preset value. The next member of the list of E 's is assigned and the \sum_2 relationships involving this reflexions are examined. The procedure is repeated until, in the list, a minimum E of about 2.0 is reached. At this stage all E 's above this minimum have been given symbolic signs. Reflexions with symbolic sign-combinations are next examined and some of the symbols may be eliminated when the triple-products involved meet a certain, predetermined criterion.

When the above procedure was applied to *cis-trans-cis-cyclodeca-2,4,8-triene-1,6-dione*, combinations of 26 symbols were assigned to the 137 reflexions with $|E| > 2.0$. Symbols were eliminated on the criterion that the sign relationships involved had a probability > 0.98 , and various Karle maps were prepared by using permutations of the remaining phase. None of the maps could be interpreted. When the probability criterion was raised to > 0.999 , 18 symbols were eliminated by being found to be equivalent to combinations of the eight remaining symbols or to (+). Of the remaining eight symbols three were used to determine the origin and two could be disregarded since they were involved with two reflexions only. The three undetermined symbols gave eight permutations of 0 and π values. Karle maps were computed for all but the all-positive set, and one of the maps led to peak positions which could be interpreted as chemically meaningful.

An alternative approach to the solution of the phase problem is the application of the tangent formula of Karle & Karle (1968, 1969) to a starting set of either 6 or 7 reflexions with 'known' phases which are then used to generate phases of additional reflexions. The generated phases are expanded and refined by repeated cyclic application of the tangent formula until a consistent set is obtained. Phases from this set are used to calculate a Karle map.

To facilitate examination of these maps we have used a technique whereby the values at the grid point are printed out in a condensed format, with each section on one sheet of paper only. The map is also stored on magnetic tape which is searched for the highest peaks. Interatomic distances between a specified number of these peaks are calculated and listed. The structure can usually be examined by using this information without need for replotting any maps by hand.

For *cis-trans-cis-cyclodeca-2,4,8-triene-1,6-dione* a starting set of six phases was used, three of which were origin determining (Table 1). Seven phase sets were generated for the possible sign combinations of the remaining three reflexions and some of the corresponding Karle maps were computed. None of the maps could be interpreted.

As the next stage in the application of the tangent formula method, 4 non-origin defining reflexions were

Table 1. Starting phases to compute a correct phase set or *cis-trans-cis-cyclodeca-2,4,8-triene-1,6-dione* by use of the tangent formula

Reflexion	E	Phase		
1 $\bar{3}$ 5	4.46	0	origin	
4 3 2	3.47	0	defining	
4 5 $\bar{3}$	2.78	π		
1 $\bar{2}$ 7	3.32	π	a	
5 3 1	3.65	π	b	symbolic phases
2 $\bar{4}$ 4	3.38	0	c	
2 $\bar{8}$ 0	2.81	π	d	

selected (Table 1) and 15 phase sets generated. The program calculated various criteria for these sets including the so called R_{Karle} value

$$\frac{\sum | |E_h| - |E_h|_{\text{calc}} |}{\sum |E_h|},$$

the average value of $\alpha = |E_h|(A^2 + B^2)^{1/2}$, where

$$A = \sum_{\mathbf{k}} |E_{\mathbf{k}}| |E_{\mathbf{h}-\mathbf{k}}| \cos(\varphi_{\mathbf{k}} + \varphi_{\mathbf{h}-\mathbf{k}})$$

$$B = \sum_{\mathbf{k}} |E_{\mathbf{k}}| |E_{\mathbf{h}-\mathbf{k}}| \sin(\varphi_{\mathbf{k}} + \varphi_{\mathbf{h}-\mathbf{k}}),$$

the average consistency

$$t = \frac{(A^2 + B^2)^{1/2}}{\sum_{\mathbf{k}} |E_{\mathbf{k}}| |E_{\mathbf{h}-\mathbf{k}}|}$$

(taking the average over all the input reflexions E_h), and

$$R_{\text{Drew}} = \frac{\sum_h |E_h| (1 - t_h)}{\sum_h |E_h|}.$$

The set with the lowest R_{Karle} value gave a map from which the entire structure, other than the hydrogen atoms was evident. It is our impression from this and other structures we have recently determined that the R_{Karle} value is the most sensitive indication of the correctness of a phase set.

In the calculations which led to a successful solution, a phase was accepted as determined if $\alpha > 10.0$ (0.983 probability). The refinement of phases converged after 20 cycles with 279 of the 281 phases for reflexions with $|E| > 1.306$ being determined. The lowest R_{Karle} value was 0.19 with an average value of $\alpha = 201$.

The positions of all atoms other than hydrogen atoms were located from the properly phased Karle map. The maximum shift in peak position after refinement was 0.18 Å for oxygen atom O(11). There were some spurious peaks on the map but these were about half as high as peaks corresponding to the carbon and oxygen positions. Distances and angles between the latter peaks were chemically reasonable.

The parameters derived from the Karle map were refined, first isotropically and then anisotropically, by full-matrix least-squares calculations. On convergence

a difference-Fourier synthesis was calculated and the coordinates of the hydrogen atoms were located. Refinement was continued with anisotropic thermal parameters for the carbon and oxygen and isotropic thermal parameters for the hydrogen atoms. The refinement results are summarized in Table 2.

Table 2. Summary of refinement of cis-trans-cis-cyclodeca-2,4,8-triene-1,6-dione

Step	R
1. Structure factor calculation using positions from correctly phased Karle map.	34.0%
2. Two cycles of isotropic least-squares refinement of C and O positions, using 1385 terms.	18.7%
3. Two cycles of anisotropic least-squares with C and O.	14.6%
4. Hydrogen atoms from Fourier included.	13.1%
5. Four cycles, C and O anisotropic, and H isotropic	5.2%

The following form factors were used: for C and H, Table 3.3.1A, *International Tables for X-ray Crystallography* (1962); for O, values from Cromer & Mann (1968). Corrections for extinction were included in the refinement by use of Larson's (1970) equation (22), by which the calculated structure factor is given by

$$F_c^* = K|F_c|(1 + 2r^*|F_c|^2(1 + \cos^2 2\theta)/(1 + \cos^2 \theta))^{-1/4}$$

where F_c is given by the usual structure-factor equation. The final extinction parameter r^* was $1.96(34) \times 10^{-5}$. Weights were assigned to individual reflections on the basis of counting statistics. Reflexions with $I < 2\sigma$ were treated as 'less thans' and were not used in the refinement. The final $R = \sum ||F_o| - |F_c^*|| / \sum F_o$ was 5.2%. The final weighted R was 2.8%. The final atomic positions are listed in Table 3, the thermal parameters in Table 4 and the observed and calculated structure factors in Table 5.

Table 3. Fractional atomic coordinates and e.s.d.'s for cis-trans-cis-cyclodeca-2,4,8-triene-1,6-dione

	x	y	z
C(1)	0.4929 (3)	0.2992 (2)	1.0886 (3)
C(2)	0.4849 (3)	0.1885 (2)	1.2334 (3)
C(3)	0.3466 (4)	0.1102 (2)	1.2208 (3)
C(4)	0.1783 (4)	0.1148 (2)	1.0502 (3)
C(5)	0.2240 (4)	0.1520 (2)	0.8472 (3)
C(6)	0.0262 (4)	0.1901 (2)	0.6913 (3)
C(7)	-0.0071 (4)	0.3150 (2)	0.5901 (3)
C(8)	0.2005 (3)	0.3781 (2)	0.5816 (3)
C(9)	0.3126 (3)	0.4048 (2)	0.7422 (3)
C(10)	0.2712 (3)	0.3738 (2)	0.9798 (3)
O(11)	0.6820 (2)	0.3352 (1)	1.0694 (2)
O(12)	-0.1177 (3)	0.1312 (1)	0.6606 (2)
H(13)	0.598 (3)	0.180 (1)	1.352 (3)
H(14)	0.354 (3)	0.045 (1)	1.342 (3)
H(15)	0.017 (3)	0.098 (1)	1.101 (3)
H(16)	0.385 (3)	0.168 (1)	0.803 (3)
H(17)	-0.069 (3)	0.321 (1)	0.436 (3)
H(18)	-0.136 (3)	0.344 (1)	0.672 (3)
H(19)	0.250 (3)	0.408 (1)	0.434 (3)
H(20)	0.447 (3)	0.450 (1)	0.705 (3)
H(21)	0.137 (3)	0.339 (1)	1.014 (3)
H(22)	0.261 (3)	0.445 (1)	1.051 (3)

The least-squares refinement, Fourier map calculations, and distance and angle calculations were made by using updated versions of programs by Larson, Cromer & Roof (1964, 1965). Programs by Larson (1969) were used in making the symbolic-addition calculations, and a program originally written by Drew (1967) and extensively modified by Larson & Motherwell (1968) was used in performing the tangent-formula calculations. A program written by Coppola & Fawcett (1968) was used for the data reduction.

Molecular geometry and description of structure

The analysis has established the conformation of the molecule as cis-trans-cis-cyclodeca-2,4,8-triene-1,6-di-

Table 4. Thermal parameters for cis-trans-cis-cyclodeca-2,4,8-triene-1,6-dione

Anisotropic parameters are for the expression
 $T_J = \exp [-(h^2\beta_{11} + k^2\beta_{22} + l^2\beta_{33} + hk\beta_{12} + hl\beta_{13} + kl\beta_{23})]$

	$\beta_{11} \times 10^4$	$\beta_{22} \times 10^4$	$\beta_{33} \times 10^4$	$\beta_{12} \times 10^4$	$\beta_{13} \times 10^4$	$\beta_{23} \times 10^4$
C(1)	283 (6)	70 (1)	230 (5)	-75 (5)	-60 (11)	-53 (5)
C(2)	342 (8)	76 (2)	253 (5)	-51 (6)	-184 (12)	3 (6)
C(3)	396 (8)	67 (2)	269 (6)	-53 (6)	-155 (13)	29 (6)
C(4)	358 (8)	60 (1)	291 (6)	-82 (6)	-158 (13)	19 (5)
C(5)	364 (8)	52 (1)	299 (6)	-68 (6)	-126 (13)	-24 (5)
C(6)	441 (8)	83 (2)	251 (5)	-143 (7)	-170 (13)	-14 (6)
C(7)	365 (8)	76 (2)	275 (6)	-72 (7)	-171 (14)	13 (6)
C(8)	341 (8)	69 (2)	231 (5)	-54 (6)	-10 (12)	7 (5)
C(9)	288 (7)	62 (1)	259 (5)	-49 (6)	-5 (12)	0 (5)
C(10)	279 (7)	57 (1)	243 (5)	-68 (6)	-41 (11)	-22 (5)
O(11)	291 (5)	102 (1)	403 (5)	-149 (4)	-108 (9)	-17 (4)
O(12)	783 (8)	115 (1)	510 (6)	-368 (6)	-654 (13)	87 (5)

$B(\text{\AA}^2)$

H(13)	2.3 (4)	H(18)	2.6 (5)
H(14)	3.5 (5)	H(19)	1.4 (4)
H(15)	2.3 (4)	H(20)	2.2 (4)
H(16)	1.7 (4)	H(21)	1.5 (4)
H(17)	2.6 (4)	H(22)	3.6 (4)

one. Perspective views of the structure are shown in Fig. 1, together with the torsion angles for the C-C bonds. Individual bond distances and angles are given in Fig. 2. Standard deviations of the bond lengths are $\sigma(\text{C}-\text{C})=0.002$, $\sigma(\text{C}-\text{O})=0.002$, and $\sigma(\text{C}-\text{H})=0.02$ Å, and of the angles, $\sigma(\text{C}-\text{C}-\text{C})=0.2^\circ$, $\sigma(\text{C}-\text{C}-\text{O})=0.2^\circ$, $\sigma(\text{C}-\text{C}-\text{H})=1.0^\circ$, and $\sigma(\text{H}-\text{C}-\text{H})=1.4^\circ$.

The carbon ring-skeleton can be thought of as an extreme distortion of the stable cyclodecane conformation with C(2) and C(7) as type I atoms (Dunitz & Ibers, 1968) (Fig. 3). This distortion is necessitated by the steric requirement about the three double bonds. The torsion angles (Fig. 1) are approximately symmetri-

cal about a twofold axis passing through the midpoints of bonds C(2)–C(3) and C(7)–C(8). There is, however no indication that the carbon skeleton has a mirror symmetry as in cyclodecane (Dunitz & Ibers, 1968) and in all-*cis*-1,6-dichlorodeca-1,3,6,8-tetraene (Kennard, Watson, Fawcett & Kerr, 1971).

Of the three double-bonds, the greatest deviation from planarity occurs about the *trans* double C(4)–C(5) bond with a torsion angle of 160° . This is consistent with chemical observations that *trans* double bonds in medium-ring olefins are subject to considerable steric strain (Prelog, Schenker & Gunthardt, 1952; Prelog, Schenker & Kung, 1953; Aebi, Barton & Lindsey, 1953).

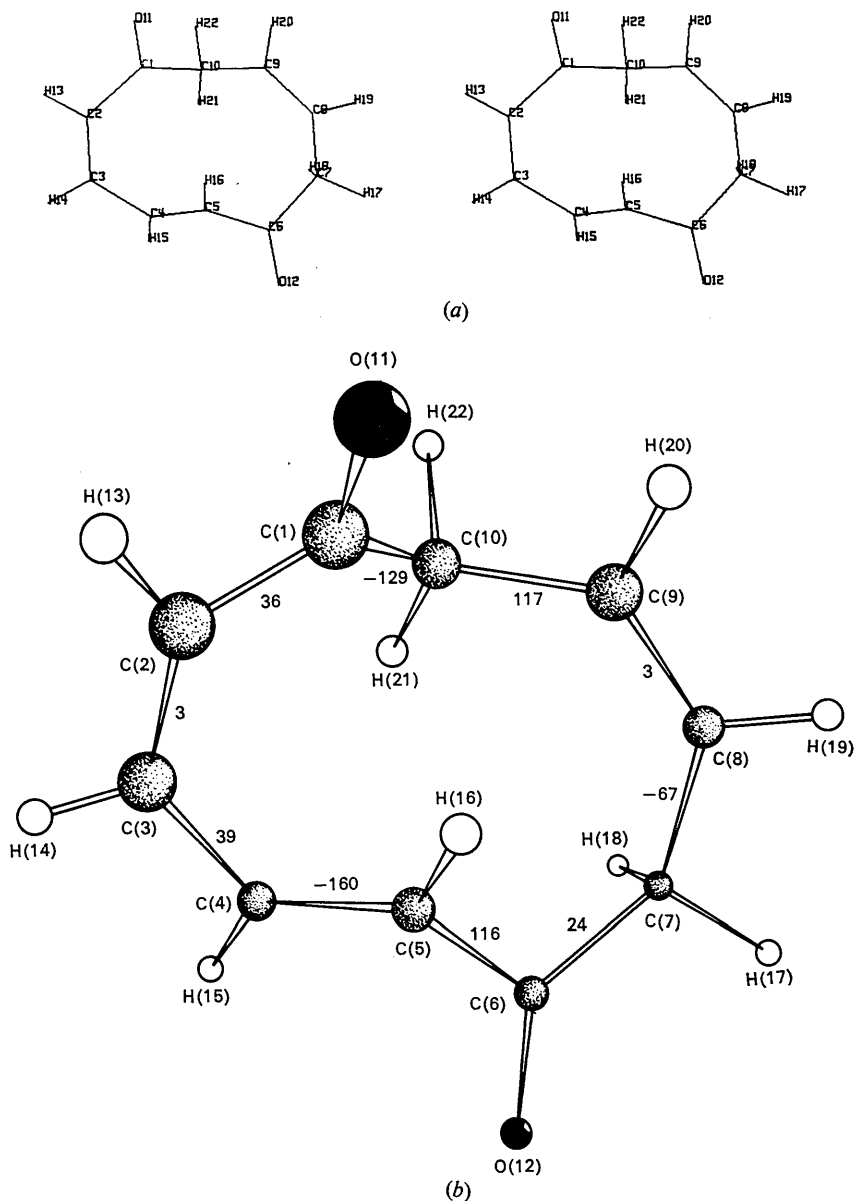


Fig. 1. (a) Stereo drawing of the molecular structure of *cis-trans-cis*-cyclodeca-2,4,8-triene-1,6-dione. (b) Perspective view of *cis-trans-cis*-cyclodeca-2,4,8-triene-1,6-dione showing the torsion angles and numbering scheme.

6 gives a variety of transannular intramolecular distances.

Table 6. *Some intramolecular distances for cis-trans-cis-cyclodeca-2,4,8-triene-1,6-dione*

C(1)–C(4)	3.11 Å	C(6)–H(21)	3.08 Å
C(1)–C(5)	3.12	C(7)–H(21)	2.90
C(1)–H(16)	2.74	C(8)–H(16)	2.73
C(2)–C(5)	3.03	C(9)–H(16)	2.77
C(2)–H(16)	2.86	C(10)–H(16)	2.85
C(3)–H(21)	2.92	C(10)–H(18)	3.17
C(4)–C(10)	3.20	H(15)–H(21)	3.04
C(4)–H(21)	2.64	H(16)–H(21)	2.80
C(5)–C(8)	2.93	H(18)–H(21)	2.69
C(5)–C(9)	3.12		
C(5)–C(10)	2.98		
C(5)–H(21)	2.61		

As expected, the distortion about the *cis*-double bonds in *cis-trans-cis*-cyclodeca-2,4,8-triene-1,6-dione is small. The four carbon atoms about each *cis*-double bond are coplanar within 0.009 Å (root mean square of the distances of the four atoms from the best plane defined by the atoms). The most significant distortion about the *cis*-double bonds is the deviation by 8° of H(13) from the plane of C(1)–C(2)–C(3): it is below the plane as seen in Fig. 1. This value is significant since it is about five times the expected standard deviation. The explanation of this bending is not obvious,

but perhaps it is a distortion to reduce the C(2)–C(3)–C(4)–C(5) torsion angle to facilitate conjugation of the C(2)–C(3) and C(4)–C(5) double bonds. The C(3)–C(4) bond length of 1.451 ± 0.004 Å is significantly shorter than the expected single-bond value. This shortening indicates that conjugation does occur although the torsion angle about this bond 39°.

The packing of the *cis-trans-cis*-cyclodeca-2,4,8-triene-1,6-dione in the crystal is illustrated in Fig. 4. The molecules are held together in the lattice by van der Waals forces only, and examination of the intermolecular contacts showed no unusually close distances.

We thank Professor Sondheimer and Dr P. J. Mulligan for suggesting the problem and providing us with the crystals used in the analysis. The work in Cambridge was supported by the Medical Research Council and the Office for Scientific and Technical Information.

We thank John Wiley & Sons for permission to reproduce Fig. 3.

References

- AEBI, A., BARTON, D. W. R. & LINDSEY, A. S. (1953). *J. Chem. Soc.* p. 3123.
 CANIS, P. & DUNITZ, J. D. (1967). *Helv. Chim. Acta*, **50**, 2379.
 COPPOLA, J. C. & FAWCETT, K. (1968). Private communication.

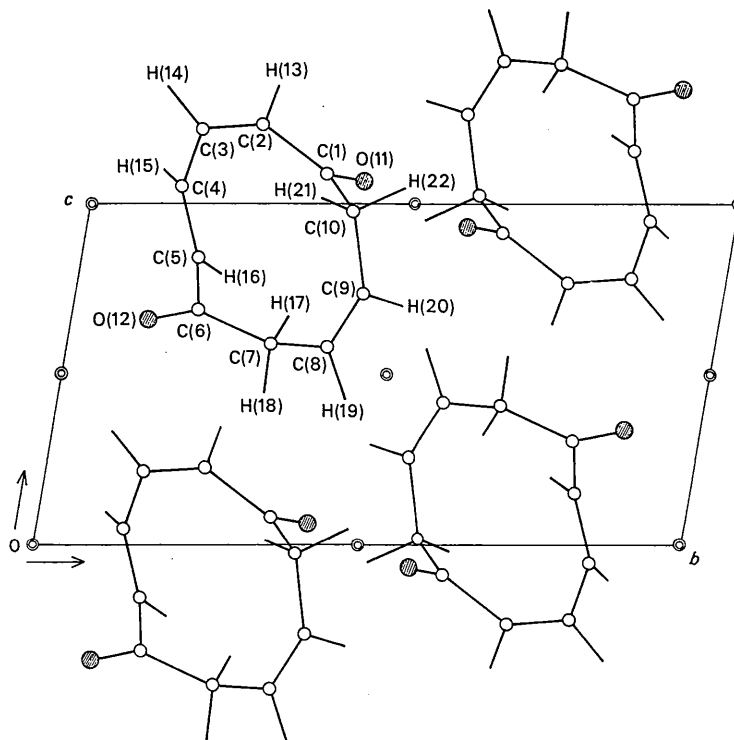


Fig. 4. Projection of the crystal structure of *cis-trans-cis*-cyclodeca-2,4,8-triene-1,6-dione down a^* onto the bc plane, illustrating the molecular packing. The positive a axis extends from the plane of the page towards the reader.

- CROMER, D. & MANN, J. (1968). *A24*, 321.
 DREW, M. (1967). Private communication.
 DUNITZ, J. D. & IBERS, J. A. (1968). *Perspectives in Structural Chemistry*, Vol. II, New York: John Wiley.
International Tables for X-ray Crystallography (1962). Vol. III, Birmingham: Kynoch Press.
 KARLE, J. & KARLE, I. L. (1966). *Acta Cryst.* **21**, 849.
 KARLE, J. & KARLE, I. L. (1968). *Acta Cryst.* **B24**, 182.
 KARLE, J. & KARLE, I. L. (1969). *Acta Cryst.* **B25**, 428.
 KENNARD, O., WATSON, D. G., FAWCETT, J. K. & KERR, K. A. (1971). *Tetrahedron*. In the press.
 LARSON, A. C. (1969). Private communication.
 LARSON, A. C. (1970). *Proceedings of IUCR Summer School on Crystallographic Computing*. Ottawa, 1969.
 LARSON, A. C., CROMER, D. T. & ROOF, R. B. JR (1964, 1965), USAEC Los Alamos Sci. Lab. reports LA-3310, 3309, 3259, 3198, 3233.
 LARSON, A. C. & MOTHERWELL, W. D. S. (1968). Private communication.
 MCCLURE, R., SIM, G., COGGON, P. & MCPHAIL, A. T. (1970). *Chem. Comm.* p. 128.
 MULLIGAN, P. & SONDEIMER, F. (1967). *J. Amer. Chem. Soc.* **89**, 7118.
 PRELOG, V., SCHENKER, K. & GUNTARDT, H. H. (1952). *Helv. Chim. Acta.* **35**, 1602.
 PRELOG, V., SCHENKER, K. & KUNG, W. (1953). *Helv. Chim. Acta*, **36**, 471.
 ROGERS, D. & SMART, M. (1969). *Acta Cryst.* **A25**, 5149

Acta Cryst. (1971). **B27**, 1123

The Crystal Structure of a 1:1 Nicotine–Salicylic Acid Complex (Nicotinyl Salicylate)

BY H. S. KIM AND G. A. JEFFREY

Department of Crystallography, University of Pittsburgh, Pittsburgh, Pa. 15213, U.S.A.

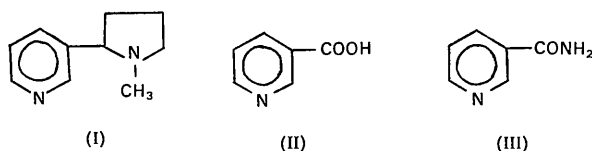
(Received 6 July 1970)

Crystals of the 1:1 complex of nicotine–salicylic acid, $C_{10}N_2H_{14} \cdot C_7H_6O_3$, are monoclinic, space group $P2_1$, with two formula units in a unit cell, $a = 7.673$ (2), $b = 11.355$ (6), $c = 9.580$ (2) Å, $\beta = 109.34$ (8)°, $D_m = 1.270$ g.cm⁻³ at 20°C. The structure was solved by direct methods using tangent formula phase refinement from 1411 intensities measured with Cu $K\alpha$ radiation on a FACS I automatic diffractometer. The parameters were refined anisotropically to a final R of 0.053. All hydrogen atoms were located on difference synthesis. The quaternary ammonium cation of the nicotine forms a molecular complex with a salicylate anion through a $N^+(H) \cdots O^-$ hydrogen-bond of 2.627 Å. The conformational angle between the best planes of the puckered pyrrolidine and planar pyridine ring of the nicotinyl ion is 77°. In the salicylate anion, the carboxylate group is slightly out of the plane of the ring, by 0.1 Å. As in the free acid, the hydroxyl forms a strong internal hydrogen-bond with a carboxyl oxygen, with a $O(-H) \cdots O$ distance of 2.544 Å.

Introduction

The poisonous alkaloid, nicotine, was first isolated from tobacco by Posselt & Reimann (1828). It is a colorless oily liquid, boiling under atmospheric pressure at 246°C, is levorotatory, soluble in water, and oxidizes in contact with air. The formula (I), α -pyridyl-*N*-methyl-pyrrolidine, was proposed by Pinner (1893), and confirmed by syntheses (Pictet & Crepieux, 1895; Späth & Bretschneider, 1928).

The parent compound has not been studied in the solid state, but crystal structures have been reported for nicotinic acid (II), and nicotinamide (III) (Wright & King, 1953, 1954), familiarly known as the vitamin niacin.



The crystalline complex of nicotine with salicylic acid provides both a means for a structural study of this important molecule and for examining the way in which it can form a hydrogen-bonded complex with an organic acid. As such, this investigation forms part of a general study of hydrogen-bonded complexes, which has included glucose–urea (Snyder & Rosenstein, 1971) and glucitol–pyridine (Kim, Jeffrey & Rosenstein, 1971).

The physiological action of nicotine and chemically related compounds has, not surprisingly, been the subject of research for nearly a century. In 1951, Taylor proposed that the quaternary ammonium cation is the active molecular species at body pH; this is supported by the fact that the monomethiodide has comparable activity (Barlow & Dobson, 1955; Gillis & Lewis, 1956). It also seems likely that it is this cation which occurs naturally in the tobacco plant in combination with maleic and citric acids. This work has confirmed that the salicylic acid complex is, in fact, a molecular crystal of nicotinyl salicylate (IV).