CEDA. Following the completion of the structure refinement, the reflection data were given to Dr G. M. Sheldrick who solved the structure with some difficulty with the *SHELX* system (Sheldrick, 1985). He has suggested that the difficulties in solving the structure with *MULTAN* and *MITHRIL* were probably associated with the molecular pseudo-symmetry.

This work was supported by the Naval Sea System Command (task 61153NSR024-03), by the National Science Foundation (CHe-84-02155) for purchase of the MicroVAX System, through the facilities of the University's Computer Science Center and by the National Institutes of Health (GM-3492 to A. D. Podjarny). We thank Drs G. H. Cohen, D. R. Davies, A. D. Podjarny, G. M. Sheldrick, P. B. Sigler and E. M. Westbrook for useful discussions and encouragement.

References

Ammon, H. L. & Bhattacharjee, S. K. (1982). *Acta Cryst.* B38, 2718–2721.

Ammon, H. L. & Bhattacharjee, S. K. (1984). *Acta Cryst.* C40, 487–490.

Ammon, H. L., Bhattacharjee, S. K., Hall, S. R. & Skelton, B. (1983). *Acta Cryst.* C39, 1565–1568.

Bhat, T. N. (1984). *Acta Cryst.* A40, C-15.

Bhat, T. N. (1985). Abstract H1, American Crystallographic Association Annual Meeting, Stanford, California, USA.

Bhat, T. N. (1988). *J. Appl. Cryst.* **21**, 279–281.

Bhat, T. N. & Cohen, G. H. (1984). *J. Appl. Cryst.* **17**, 244–248.

Gilmore, C. J. (1983). *MITHRIL*. Program for the automatic solution of crystal structures from X-ray data. Univ. of Glasgow, Scotland.

Hope, W. & Gassman, J. (1968). *Acta Cryst.* B24, 97–107.

International Tables for X-ray Crystallography (1974*a*). Vol. IV, pp. 99–101. Birmingham: Kynoch Press. (Present distributor Kluwer Academic Publishers, Dordrecht.)

International Tables for X-ray Crystallography (1974*b*). Vol. IV, pp. 149–150. Birmingham: Kynoch Press. (Present distributor Kluwer Academic Publishers, Dordrecht.)

Johnson, C. K. (1971). *ORTEP*II. Report ORNL-3794. Oak Ridge National Laboratory, Tennessee, USA.

Jones, T. A. (1978). *J. Appl. Cryst.* **11**, 268–272.

Main, P., Fiske, S. J., Hull, S. E., Lessinger, L., Germain, G., Declercq, J.-P. Woolfson, M. M. (1980). *MULTAN. A System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Diffraction Data*. Univs. of York, England, and Louvain, Belgium.

Molecular Structure Corporation (1986). *TEXSAN. TEXRAY Structure Analysis System*. MSC, 3304 Longmire Drive, College Station, TX 77840, USA.

Pflugrath, J. W., Saper, M. A. & Quiocho, F. A. (1984). In *Methods and Applications of Crystallographic Computing*, edited by S. Hall & I. Ashiaka, pp. 404–407. Oxford: Clarendon Press.

Podjarny, A. D., Bhat, T. N. & Zwick, M. (1987). *Annu. Rev. Biophys. Biophys. Chem.* **16**, 351–373.

Sheldrick, G. M. (1976). *SHELX76*. Program for crystal structure determination. Univ. of Cambridge, England.

Sheldrick, G. M. (1985). In *Crystallographic Computing* 3, edited by G. M. Sheldrick, C. Krueger & R. Goodhard, pp. 184–189. Oxford: Clarendon Press.

Tulinsky, A. (1985). *Methods Enzymol.* **115**, 77–89.

Wang, B. C. (1985). *Methods Enzymol.* **115**, 90–112.

Acta Cryst. (1990). C46, 116–119

Structure of 5-Hydroxy-5-phenyl-7-azatricyclo[7.4.0.0^{2,7}]trideca-2,9(1),10,12-tetraen-8-one by the Consistent Electron Density Approach

By T. Narayana Bhat*

Laboratory of Molecular Biology, National Institutes of Health, Bethesda, Maryland 20892, *USA*

Herman L. Ammon

Department of Chemistry and Biochemistry and Centre for Advanced Research in Biotechnology, University of Maryland, College Park, Maryland 20742, *USA*

and Paul H. Mazzocchi and Mazuaki Oda

Department of Chemistry and Biochemistry, University of Maryland, College Park, Maryland 20742, *USA*

(*Received* 11 *October* 1988; *accepted* 20 *April* 1989)

Abstract. $C_{18}H_{15}NO_2$, $M_r = 277·3$, monoclinic, $P2_1/n$, $a = 7·408$ (2), $b = 22·311$ (7), $c = 8·613$ (2) Å, $\beta = 103·53$ (3)°, $V = 1384$ (1) Å^3, $Z = 4$, $D_x = 1·33$ g cm^{-3}, λ(Mo $K\alpha$) = 0·71069 Å, $\mu = 0·94$ cm^{-1}, $F(000) = 594$, $T = 293$ K, 2229 unique diffractometer data, 963 with $I > 3\sigma(I)$, $R = 0·050$. Structure solution was by the consistent electron density approach

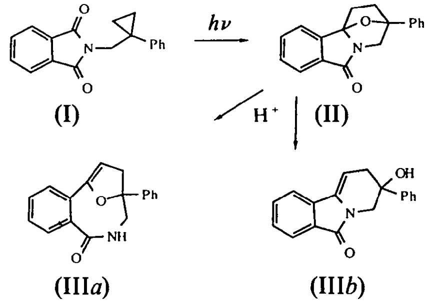
---

* Present address: Département d'immunologie, Institut Pasteur, 75724 Paris CEDEX 15, France.

0108-2701/90/010116-04$03.00

which combines the concepts of the OMIT map and density modification procedures. The benzolactam portion of the molecule is highly planar; most bond lengths and angles have typical values.

Introduction. In the course of an investigation of the photochemically induced electron transfer chemistry of phenylcyclopropane-substituted phthalimides, the irradiation of (I) with a 450 watt Hanovia mercury lamp through Pyrex resulted in the formation of a 43% yield of a single product identified as (II) by spectroscopic analysis. In solution, (II) underwent slow decomposition to (III), whereas the addition of a trace of acid resulted in a smooth conversion to (III). There were two probable structures for (III): (III*a*), which would result from protonation of the carbonyl oxygen atom followed by ring opening and deprotonation, and (III*b*), which would arise from protonation of the other oxygen atom followed by ring opening and deprotonation. The spectroscopic characteristics of these candidates were sufficiently similar that an X-ray crystallographic determination was undertaken.



We previously used the consistent electron density approach (CEDA) (Bhat, 1984) to solve the structure of a $C_{10}H_8N_{10}O_{18}F_4$ compound (IV) in the acentric space group *Pc* (Bhat & Ammon, 1987, 1990), and elected to attempt a structure solution of (III), which crystallizes in the centric space group $P2_1/n$, with the CEDA. The steps used in the CEDA to determine phases for the two compounds differ somewhat for the following reasons: (*a*) acentric *vs* centric space group; (*b*) the objective of the work on (IV) was to investigate the structure solution potential from a model built on a medium resolution map, while the work on (III) involved the use of *E* values in a CEDA.

Experimental. 0·1 × 0·2 × 0·3 mm crystal from ethanol; Enraf–Nonius CAD-4 diffractometer, Mo radiation with incident-beam graphite monochromator, cell parameters from 25 reflections automatically centered in the range $6{\cdot}7 < \theta < 12{\cdot}1°$, 2θ–θ scan at variable speed of 1·10–5·49° $\min^{-1}$, θ scan range of $(1{\cdot}2 + 0{\cdot}35\tan\theta)°$, scan range was recorded in 96 steps and subsequently processed with a modified Lehmann & Larsen (1974) procedure (Ammon, 1986), 18 steps on either side of the central peak were taken as background with the central peak width varied starting at 36 steps, θ range for data collection = 2–24°, index range of $h = -8$ to 8, $k = 0$ to 25, $l = 0$ to 9, seven standards measured at intervals of 2 h of crystal X-ray exposure, standard intensity variation from −2·4 to 0·2%, average variation of −0·6%, 2479 total data measured (includes standards and systematically absent reflections), 2229 unique data, 963 data with $I > 3\sigma(I)$. Structure solution by the CEDA (described below). Structure refinement by full-matrix least squares with anisotropic temperature factors for carbon, nitrogen and oxygen and isotropic terms for hydrogen, minimization of $\sum[(|F_o| - |F_c|)/\sigma(|F_o|)]^2$, final *S*, *R* and weighted *R* value of 1·40, 0·050 and 0·050, $w = 1/\sigma^2(F_o)$, min. and max. values in final difference map of −0·19 and 0·24 e Å^{-3}, max. shift/e.s.d. = 0·37. Scattering factors from *International Tables for X-ray Crystallography* (1974). The crystallographic calculations were performed on a MicroVAX II computer with the *TEXSAN* (Molecular Structure Corporation, 1987) system of programs. Atomic coordinates are listed in Table 1.*

Table 1. *Fractional coordinates and B_{eq} values, with e.s.d.'s, for the carbon, nitrogen and oxygen atoms in* (III*b*)

	x	y	z	B_{eq}*(Å^2)
O1	0·6707 (5)	−0·0617 (2)	−0·3991 (4)	3·8 (2)
O2	0·5634 (5)	0·1371 (2)	−0·4028 (4)	3·3 (2)
N	0·7588 (5)	0·0292 (2)	−0·2778 (4)	2·7 (2)
C1	0·7058 (7)	−0·0292 (3)	−0·2806 (7)	3·1 (3)
C2	0·7025 (7)	−0·0434 (2)	−0·1122 (6)	2·7 (2)
C3	0·6517 (7)	−0·0961 (3)	−0·0490 (7)	3·8 (3)
C4	0·6543 (8)	−0·0959 (3)	0·1129 (7)	4·1 (3)
C5	0·7089 (8)	−0·0457 (3)	0·2049 (6)	4·1 (3)
C6	0·7612 (7)	0·0063 (3)	0·1417 (6)	3·5 (3)
C7	0·7559 (7)	0·0072 (3)	−0·0217 (6)	3·0 (3)
C8	0·7934 (7)	0·0555 (3)	−0·1237 (5)	2·7 (3)
C9	0·8418 (7)	0·1111 (3)	−0·1010 (6)	3·2 (3)
C10	0·8630 (8)	0·1518 (3)	−0·2341 (6)	3·3 (3)
C11	0·7557 (7)	0·1281 (2)	−0·3974 (5)	2·8 (2)
C12	0·7916 (8)	0·0613 (2)	−0·4152 (6)	3·0 (3)
C13	0·8148 (8)	0·1620 (2)	−0·5324 (6)	3·2 (3)
C14	0·9934 (8)	0·1572 (3)	−0·5542 (6)	4·0 (3)
C15	1·047 (1)	0·1892 (3)	−0·6746 (7)	4·8 (3)
C16	0·923 (1)	0·2253 (3)	−0·7748 (7)	5·2 (4)
C17	0·744 (1)	0·2299 (3)	−0·7559 (8)	6·1 (4)
C18	0·691 (1)	0·1985 (3)	−0·6341 (7)	4·7 (3)

$^*B_{eq} = \frac{8}{3}\pi^2\sum_i\sum_j U_{ij}a_i^*a_j^*\mathbf{a}_i.\mathbf{a}_j.$

---

* Lists of structure factors, anisotropic temperature factors and H-atom parameters have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 52172 (10 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

The steps used in the CEDA for (III) are described below:

(*a*) Initial phases and map. A starting *E* map, ρ_1, was calculated with random phase angles for all 202 reflections with $E > 1$. The phase angles were generated without regard to space-group symmetry restrictions (*i.e.* effective space group was $P1$).

(*b*) Density modification. All values more negative than $-0{\cdot}55$ r.m.s. in ρ_1 were set to the lower threshold value of $-0{\cdot}55$ r.m.s.

(*c*) OMIT map calculation. OMIT map ρ_2 was formed from the density-modified map ρ_1. The calculations were carried out in the acentric space group $P2_1$ (equivalent positions of x, y, z and $\frac{1}{2} - x, \frac{1}{2} + y, \frac{1}{2} - z$) which enhances phase angle refinement of the CEDA by not restricting the new values to 0 or 180°. The effective $P2_1$ space group was used in steps (*b*)–(*d*). The maps were computed with an *a*, *b*, *c* grid sampling of $30 \times 90 \times 36$ and the dimensions of the electron density volume-element box were $7 \times 22 \times 8$ grid divisions. A 'neutral volume' surrounding each box was established by extending each grid dimensions by four, which gave an effective box size of $15 \times 30 \times 16$ for use in map levelling. Only the new electron density in the $7 \times 22 \times 8$ volume-element box contributed to the formation of an OMIT map. A more detailed discussion of the calculation of OMIT maps is given by Bhat (1988).

(*d*) OMIT map→density modification→OMIT map cycle. The density modification and OMIT map steps (*b* and *c*) were repeated 35 times with the OMIT map ρ_2 from step (*c*) serving as the initial map ρ_1 in density modification step (*b*).

(*e*) 0/180° phase angle restriction. OMIT map (ρ_2) of the final step (*c*) was converted into a centric map (ρ_3) in space group $P2_1/n$ by the use of half of map ρ_2 and the $-x$, $-y$, $-z$ symmetry operation. Fourier inversion of centric map ρ_3 gave phase set φ_3.

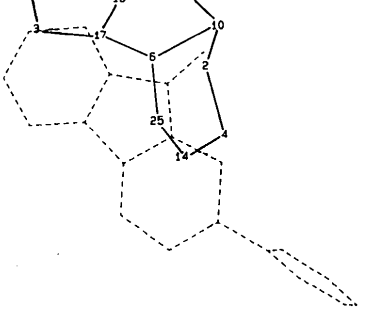


Fig. 1. Initial CEDA-derived (solid lines) and the final refined (dashed lines) models. The atom numbers refer to the peak height sequence in the CEDA phased *E* map.

Table 2. *Intramolecular distances* (Å) *and angles* (°) *with e.s.d.'s for* (III*b*)

O1—C1	1·229 (6)	C7—C8	1·456 (7)
O2—C11	1·428 (5)	C8—C9	1·294 (7)
N—C1	1·360 (6)	C9—C10	1·499 (7)
N—C8	1·418 (6)	C10—C11	1·539 (6)
N—C12	1·451 (6)	C11—C12	1·528 (7)
C1—C2	1·491 (7)	C11—C13	1·535 (7)
C2—C7	1·377 (7)	C13—C18	1·378 (7)
C2—C3	1·384 (7)	C13—C14	1·383 (7)
C3—C4	1·391 (7)	C14—C15	1·392 (7)
C4—C5	1·377 (8)	C15—C16	1·367 (8)
C5—C6	1·377 (8)	C16—C17	1·372 (9)
C6—C7	1·399 (7)	C17—C18	1·393 (8)
C1—N—C8	113·6 (4)	N—C8—C7	104·0 (4)
C1—N—C12	124·1 (5)	C8—C9—C10	122·7 (5)
C8—N—C12	122·1 (4)	C9—C10—C11	111·5 (5)
O1—C1—N	125·8 (5)	O2—C11—C12	109·3 (4)
O1—C1—C2	129·3 (5)	O2—C11—C13	111·4 (4)
N—C1—C2	104·9 (5)	O2—C11—C10	106·2 (4)
C7—C2—C3	122·9 (5)	C12—C11—C13	108·5 (4)
C7—C2—C1	108·0 (5)	C12—C11—C10	111·2 (4)
C3—C2—C1	129·1 (5)	C13—C11—C10	110·2 (4)
C2—C3—C4	116·8 (6)	N—C12—C11	109·4 (4)
C5—C4—C3	120·9 (6)	C18—C13—C14	118·4 (6)
C4—C5—C6	122·0 (5)	C18—C13—C11	120·5 (5)
C5—C6—C7	117·8 (6)	C14—C13—C11	121·1 (5)
C2—C7—C6	119·6 (5)	C13—C14—C15	120·7 (6)
C2—C7—C8	109·6 (4)	C16—C15—C14	120·3 (7)
C6—C7—C8	130·8 (5)	C15—C16—C17	119·6 (7)
C9—C8—N	121·4 (5)	C16—C17—C18	120·2 (7)
C9—C8—C7	134·6 (5)	C13—C18—C17	120·7 (6)

(*f*) OMIT map→density modification→OMIT map recycling. Map ρ_4, calculated with the *E* values and centric phase set φ_3, was used as ρ_1 in the density modification step (*b*) and steps (*b*)–(*f*) were repeated (eight cycles) until two successive sets of the φ_3 phases were identical.

A molecular model for the planar three-ring system of (III*b*) was fitted to the 27 highest peaks in the final *E* map ρ_4 (all reflections $E > 1$; Fig. 1). Bond distances varied from 1·1–1·8 Å. Structure refinements with restraints on bond distances with the *SHELX76* system (Sheldrick, 1976), followed by difference maps, revealed the remaining atoms. The final cycles of least-squares refinement were performed with the *TEXSAN* system (Molecular Structure Corporation, 1987) to an *R* factor of 0·050. For reflections with $E > 1{\cdot}0$, the difference between the initial CEDA-derived and final (refined model) phases averaged 49° at 2·5 Å. These have been subsequently improved and extended to 1·5 Å; the final phase error is 16° to 2·5 Å and 52° to 1·5 Å and this phase determination is *ab initio* in the sense that it did not involve a subjective model building step based on the chemical formula of the compound. Bond distances and angles are given in Table 2.

Discussion. The CEDA supplemented by the stereochemical information of the expected chemical structure has been used to solve the structure of (*a*) a 21-atom (C, N, O) compound in a centric space group, (*b*) a 42-atom compound in an acentric space group (Bhat & Ammon, 1987, 1990). In developing this method a number of test structures have been studied (Bhat, 1984). The phases obtained by the CEDA are not as accurate as those usually obtained from the traditional direct methods. However, the CEDA is different from the direct methods. It should be emphasized that we have not attempted, at this time, to optimize the phase determination/refinement potential of the CEDA. The solution of two structures with the CEDA is encouraging, and we plan further investigations to explore the potential of the concept and improve the phase accuracy. One obvious extension would be maximum entropy refinement of the CEDA-derived electron density map.

The crystallographic determination has shown that the structure of the photochemical reaction product is (III*b*). An *ORTEP* (Johnson, 1965) drawing is shown in Fig. 2. The three-fused-ring fragment is planar with an average deviation of 0·027 Å from the 13-atom least-squares plane with the exclusion of C11. C11 deviates by 0·628 Å from this plane and reflects the extent to which the azacyclohexene ring is puckered. The phenyl group linked at C11 is approximately perpendicular to the 13-atom plane with an angle of 87·5°. The C11—C13 conformation minimizes non-bonded interactions between the phenyl moiety and the adjacent azacyclohexene ring, and the configuration at C7 with an *exo*-phenyl and *endo*-hydroxyl further reduces phenyl–azacyclohexene interactions. This phenyl *vs* hydroxyl configuration arises from the structure of precursor (II).

Bond lengths in (III*b*) are typical of the values found in many naphthalimides and in the few published isoindolinone structures [*e.g.* 2-(3-methyl-1-oxoisoindolin-2-yl)butyramide; Carlstrom, Hacksell, Jonsson & Soderholm, 1983]. However, the C8—C9 distance of 1·294 Å in the azacyclohexene is substantially shorter than one usually finds for a carbon—carbon double bond linked to an amino function.

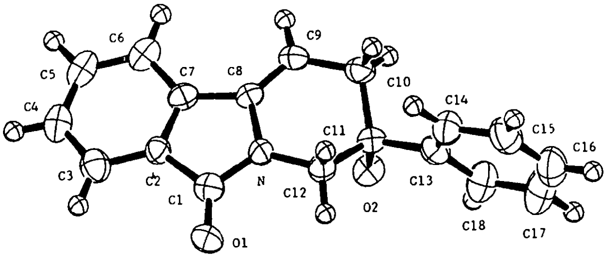


Fig. 2. *ORTEP* drawing for (III*b*). The carbon, nitrogen and oxygen atoms are depicted as 50% ellipsoids; hydrogen atoms are drawn as spheres with $B = 1{\cdot}5$ Å^2.

The only short intermolecular contact of O1···O2 = 2·174 (5) Å (O2 at $1-x$, $-y$, $-1-z$) almost certainly indicates the presence of a hydroxyl···carbonyl hydrogen bond. Unfortunately, the hydroxyl hydrogen atom could not be located in a difference electron density map.

It should be noted that the structure solution by the CEDA for (III*b*) was not carried out because a more traditional initial approach by the direct methods has failed. Rather, we have used this structure solution as a test to gain experience with CEDA. Following the completion of the structure refinement, the structure was easily solved with the *MITHRIL* (Gilmore, 1983) link of the *TEXRAY* system (Molecular Structure Corporation, 1987).

We thank Dr D. R. Davies for encouragement and fruitful discussions. This work was supported by a National Science Foundation grant (CHE-84-02155) which provided a portion of the funds for purchase of a diffractometer/computer system, and by a National Institutes of Health Shared Instrumentation Award (RR-03354) for purchase of a graphics workstation system.

References

Ammon, H. L. (1986). *CAD4PROFILE*. Program for reflection profile analysis. Univ. of Maryland, College Park, Maryland, USA.

Bhat, T. N. (1984). *Acta Cryst.* **A40**, C15.

Bhat, T. N. (1988). *J. Appl. Cryst.* **21**, 279–281.

Bhat, T. N. & Ammon, H. L. (1987). *Acta Cryst.* **A43**, C-285.

Bhat, T. N. & Ammon, H. L. (1990). *Acta Cryst.* **C45**, 112–116.

Carlstrom, D., Hacksell, I., Jonsson, N. A. & Soderhom, M. (1983). *Acta Chem. Scand. Ser. B*, **37**, 769–773.

Gilmore, C. J. (1983). *MITHRIL*. Program for the automated solution of crystal structures from X-ray data. Univ. of Glasgow, Scotland.

International Tables for X-ray Crystallography (1974). Vol IV. Birmingham: Kynoch Press. (Present distributor Kluwer Academic Publishers, Dordrecht.)

Johnson, C. K. (1965). *ORTEP*. Report ORNL-3794. Oak Ridge National Laboratory, Tennessee, USA.

Lehmann, M. S. & Larsen, F. K. (1974). *J. Appl. Cryst.* **9**, 243–244.

Molecular Structure Corporation (1987). *TEXSCAN*. *TEXRAY Structure Analysis System*, version 2.0. Molecular Structure Corporation, The Woodlands, Texas, USA.

Sheldrick, G. M. (1976). *SHELX76*. Program for crystal structure determination. Univ. of Cambridge, England.