

Dynamic Conformational Behaviour of an Eleven-Membered Ring in the Solid State. X-ray Crystallographic Study of Cycloundecanone 4-Phenylsemicarbazone at 293 and 135 K

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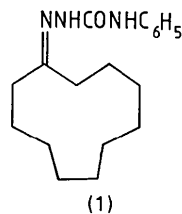
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Abstract. $C_{18}H_{27}N_3O$, $M_r = 301.46$, monoclinic, $P2_1/n$, $Z = 4$, $\lambda(\text{Cu } K\alpha) = 1.5418 \text{ \AA}$, $F(000) = 656$. At 293 K, $a = 5.617 (3)$, $b = 14.263 (2)$, $c = 21.925 (3) \text{ \AA}$, $\beta = 97.12 (2)^\circ$, $V = 1743 (1) \text{ \AA}^3$, $D_x = 1.15 \text{ Mg m}^{-3}$, $\mu = 0.57 \text{ mm}^{-1}$, $R = 0.10$ for 1237 independent reflections. At 135 K, $a = 5.546 (2)$, $b = 14.340 (2)$, $c = 21.147 (3) \text{ \AA}$, $\beta = 97.08 (2)^\circ$, $V = 1669 (1) \text{ \AA}^3$, $D_x = 1.20 \text{ Mg m}^{-3}$, $\mu = 0.60 \text{ mm}^{-1}$, $R = 0.065$ for 1653 independent reflections. The crystal structure is fully ordered at 135 K but is disordered at 293 K in the region occupied by the eleven-membered ring. At 135 K the eleven-membered ring exhibits the [335] conformation of cycloundecane, with C—C(sp^3)—C angles enlarged beyond tetrahedral, $112.9\text{--}118.4 (4)^\circ$. At room temperature the major component of the conformational mixture approximates to the [12323] conformation of cycloundecane derived by force-field calculations [Anet & Rawdah (1978). *J. Am. Chem. Soc.* **100**, 7810–7814].

Introduction. Eleven-membered rings are features of cytochalasins (Tamm, 1980), dolabellane diterpenoids (Matsuo, Kamio, Uohama, Yoshida, Connolly & Sim, 1988) and pyrrolizidine alkaloids (Robins, 1982). The conformations of cycloundecane (Anet & Rawdah, 1978), cycloundecene (Russell, 1981), cycloundeca-1,4-diene, cycloundeca-1,5-diene and cycloundeca-1,6-diene (Russell, Sim & Haufe, 1989) are therefore of some interest and have been investigated by force-field calculations. The calculations for cycloundecane delineated six conformations in an energy range of 11 kJ mol^{-1} , the two lowest-energy forms, [12323] and [335], being essentially identical in strain energy (Anet & Rawdah, 1978). The NMR spectra of cycloundecane (Anet, Cheng & Wagner, 1972) indicated that even as low as 120 K the hydrocarbon undergoes conformational exchange in solution and on the basis of their calculations Anet & Rawdah (1978) deduced that the conformational mixture in cycloundecane at low temperatures comprises the [12323] and [335] forms, with the latter predominating. X-ray crystallographic results are available for cycloundecanone (Groth,

1974) and its oxime (Groth, 1979) at *ca* 110 K and for cycloundecanone phenylsemicarbazone at 123 K (Groth, 1980); these establish that at low temperatures the solid cycloundecanone and the phenylsemicarbazone adopt the [335] conformation and the oxime the [12323] conformation. To obtain information about possible changes with temperature, the crystal structure of cycloundecanone phenylsemicarbazone (1) has been investigated at 293 and 135 K.



Experimental. Compound (1) was prepared by reaction of cycloundecanone with 4-phenylsemicarbazide. Colourless crystals, dimensions $0.2 \times 0.2 \times 0.4 \text{ mm}$. Enraf–Nonius CAD-4 diffractometer, $\text{Cu } K\alpha$ radiation. θ – ω scans. Cell dimensions from setting angles of 25 independent reflections with θ $17\text{--}25^\circ$ (293 K) and $18\text{--}28^\circ$ (135 K). At 293 K, 2136 intensities surveyed in range $1.5\text{--}55^\circ$, h $0\text{--}5$, k $0\text{--}14$, l $-21\text{--}21$; scan width $(1.0 + 0.3\tan\theta)^\circ$; max. counting time 120 s; 1790 independent reflections after deletion of 113 systematic absences and averaging of 233 pairs of equivalent reflections, $R_{\text{int}} = 0.020$, 1237 reflections with $I > 2.5\sigma(I)$. At 135 K, 2508 intensities surveyed in range $1.5\text{--}65^\circ$, h $0\text{--}6$, k $0\text{--}16$, l $-24\text{--}24$; scan width $(1.0 + 0.3\tan\theta)^\circ$; max. counting time 120 s; 2026 independent reflections after deletion of 146 systematic absences and averaging of 335 pairs of equivalent reflections, $R_{\text{int}} = 0.025$, 1929 reflections with $I > 2.5\sigma(I)$. The first crystal used at 135 K fractured after 1958 reflections and the second after 550 reflections. Two reference reflections monitored periodically showed no significant variation in intensity at either temperature. No absorption correction. Structures determined by direct phasing using MITHRIL (Gilmore, 1984).

At 293 K, atoms N(1), N(2), N(3), O(1), C(12), C(13), C(14), C(15), C(16), C(17), C(18) of the side chain and atoms C(1), C(2), C(9), C(10), C(11) of the eleven-membered ring were readily located, and after preliminary refinement the H atoms of the side chain and those at C(2), C(10), C(11) were also located. The difference electron-density maps indicated the most probable sites for C(3), C(4), C(5), C(6), C(7) and C(8), but with additional smaller peaks in this region which represented alternative atomic sites. Attempts were made to refine various models of the disordered region with partial occupation of atomic sites; all gave large thermal parameters and unsatisfactory bond lengths and angles, indicating considerable conformational disorder. Eventually it was decided to restrict calculations to the simplest model, using only the six largest peaks for atoms C(3)—C(8) to specify the major component of the conformational mixture and fixing the occupation parameters of all the atoms at 1.0. The H atoms in the disordered region were not located. Refinement of this simple model converged at $R = 0.10$, $wR = 0.13$, with $\Delta/\sigma < 0.5$, $w = 1/\sigma^2(|F_o|)$, final $\Delta\rho$ max. 0.41 , min. $-0.22 \text{ e } \text{Å}^{-3}$. The largest residual peaks in the final difference map were in the C(3)—C(8) region and confirmed that other conformations contribute to the disordered electron density, though to a lesser extent than the model used in the calculations.

At 135 K, only 11 significant peaks appeared in the region of the unit cell occupied by the cycloundecanone ring and after preliminary refinement of the C, N and O atoms all 27 H atoms were located unambiguously in a difference electron-density map. Full-matrix least-squares calculations on F with anisotropic thermal parameters for C, N and O atoms and isotropic parameters for H atoms converged at $R = 0.065$, $wR = 0.096$, with $\Delta/\sigma < 0.5$, $w = 1/\sigma^2(|F_o|)$, final Δ/ρ max. 0.29 , min. $-0.36 \text{ e } \text{Å}^{-3}$. Scattering factors from *International Tables for X-ray Crystallography* (1974, Vol. IV). Calculations on a SEL 32/27 computer with the *GX* system of programs (Mallinson & Muir, 1985).

Discussion. Atomic coordinates and molecular dimensions from the 135 K analysis are listed in Tables 1 and 2.* The molecular structures derived from the X-ray results at 293 and 135 K are illustrated by *ORTEP* diagrams (Johnson, 1965) in Figs. 1 and 2.

* Lists of structure factors, anisotropic thermal parameters and H-atom coordinates for the 135 K measurements and structure factors, atomic coordinates and anisotropic thermal parameters for the 293 K measurements have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 53298 (31 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 1. *Fractional atomic coordinates and equivalent isotropic thermal parameters (Å^2) for compound (1) at 135 K*

$$U_{eq} = (U_1U_2U_3)^{1/3}.$$

	<i>x</i>	<i>y</i>	<i>z</i>	U_{eq}
C(1)	-0.0373 (7)	0.3670 (3)	0.3938 (2)	0.024
C(2)	-0.0848 (8)	0.4691 (4)	0.3823 (2)	0.026
C(3)	0.0865 (9)	0.5190 (4)	0.3405 (2)	0.031
C(4)	0.0148 (9)	0.5156 (4)	0.2680 (2)	0.032
C(5)	0.0077 (8)	0.4201 (4)	0.2354 (2)	0.031
C(6)	0.2297 (7)	0.3600 (3)	0.2532 (2)	0.026
C(7)	0.2033 (8)	0.2622 (4)	0.2244 (2)	0.030
C(8)	0.0122 (8)	0.2010 (4)	0.2496 (2)	0.031
C(9)	0.0702 (8)	0.1766 (4)	0.3211 (2)	0.030
C(10)	-0.1370 (8)	0.1956 (4)	0.3616 (2)	0.028
C(11)	-0.2154 (7)	0.2966 (4)	0.3629 (2)	0.025
C(12)	0.5069 (7)	0.3567 (3)	0.4999 (2)	0.024
C(13)	0.6863 (7)	0.2035 (4)	0.5358 (2)	0.024
C(14)	0.9164 (8)	0.2338 (4)	0.5623 (2)	0.028
C(15)	1.0739 (7)	0.1695 (4)	0.5945 (2)	0.030
C(16)	1.0142 (9)	0.0773 (4)	0.5995 (2)	0.034
C(17)	0.7844 (9)	0.0462 (4)	0.5723 (2)	0.036
C(18)	0.6265 (8)	0.1098 (4)	0.5407 (2)	0.028
N(1)	0.1453 (6)	0.3321 (3)	0.4306 (1)	0.025
N(2)	0.3122 (6)	0.3947 (3)	0.4621 (1)	0.027
N(3)	0.5082 (6)	0.2607 (3)	0.5025 (2)	0.025
O(1)	0.6660 (5)	0.4071 (2)	0.5280 (1)	0.033

Table 2. *Interatomic distances (Å) and angles ($^\circ$) for compound (1) at 135 K*

C(1)—C(2)	1.503 (8)	C(1)—C(11)	1.504 (7)
C(1)—N(1)	1.299 (6)	C(2)—C(3)	1.550 (7)
C(3)—C(4)	1.538 (6)	C(4)—C(5)	1.531 (8)
C(5)—C(6)	1.512 (7)	C(6)—C(7)	1.528 (7)
C(7)—C(8)	1.522 (7)	C(8)—C(9)	1.546 (6)
C(9)—C(10)	1.540 (7)	C(10)—C(11)	1.514 (8)
C(12)—N(2)	1.375 (6)	C(12)—N(3)	1.379 (7)
C(12)—O(1)	1.234 (6)	C(13)—C(14)	1.398 (6)
C(13)—C(18)	1.390 (8)	C(13)—N(3)	1.405 (6)
C(14)—C(15)	1.389 (7)	C(15)—C(16)	1.369 (9)
C(16)—C(17)	1.405 (8)	C(17)—C(18)	1.378 (8)
N(1)—N(2)	1.399 (6)		
C(2)—C(1)—C(11)	119.4 (4)	C(2)—C(1)—N(1)	125.5 (4)
C(11)—C(1)—N(1)	115.1 (5)	C(1)—C(2)—C(3)	115.7 (4)
C(2)—C(3)—C(4)	117.0 (4)	C(3)—C(4)—C(5)	117.8 (5)
C(4)—C(5)—C(6)	115.0 (4)	C(5)—C(6)—C(7)	112.9 (4)
C(6)—C(7)—C(8)	115.2 (4)	C(7)—C(8)—C(9)	113.8 (4)
C(8)—C(9)—C(10)	115.2 (4)	C(9)—C(10)—C(11)	114.5 (4)
C(1)—C(11)—C(10)	118.4 (4)	N(2)—C(12)—N(3)	114.8 (4)
N(2)—C(12)—O(1)	120.8 (5)	N(3)—C(12)—O(1)	124.5 (4)
C(14)—C(13)—C(18)	119.0 (5)	C(14)—C(13)—N(3)	124.7 (5)
C(18)—C(13)—N(3)	116.2 (4)	C(13)—C(14)—C(15)	118.5 (5)
C(14)—C(15)—C(16)	122.3 (5)	C(15)—C(16)—C(17)	119.4 (5)
C(16)—C(17)—C(18)	118.6 (6)	C(13)—C(18)—C(17)	122.2 (5)
C(1)—N(1)—N(2)	117.4 (4)	C(12)—N(2)—N(1)	116.7 (4)
C(12)—N(3)—C(13)	127.1 (4)		

The X-ray analyses establish that the cycloundecanone derivative (1) adopts a single ordered conformation in the crystal at 135 K; at 293 K, in contrast, the compound is conformationally disordered and the major constituent of the conformational mixture differs from the 135 K conformation by rotation of a segment of the eleven-membered ring. The torsional angles for the eleven-membered ring were compared with the force-field angles calculated by Anet & Rawdah (1978) for the six low-energy conformations

of cycloundecane and this established that the 135 K conformation of compound (1) approximates closely to the [335] conformation of cycloundecane (Table 3), the differences between corresponding X-ray and force-field torsional angles ranging from 1 to 17° with a mean difference of 8°. The 293 K principal conformation is close to the [12323] conformation of cycloundecane, the differences between the X-ray and force-field torsional angles ranging from 0 to 32° with a mean difference of 12°. The comparison indicates that the conformational interconversion in crystals of compound (1) corresponds to the [335] \rightleftharpoons [12323] process deduced by Anet & Rawdah (1978) for cycloundecane in solution at temperatures above *ca* 120 K. The 293 K conformation also resembles the [121232][†] transition state for the interconversion of the [335] and [12323] conformations (Anet & Rawdah, 1978) with torsional angle differences of 0–50°, mean 14°. The best comparison for the 293 K conformation is actually with a confor-

Table 3. Torsional angles (°) and comparison of X-ray results for the eleven-membered ring of compound (1) at 135 and 293 K with force-field results for cycloundecane

	135 K	293 K	[335]	[12323]	[121232] [†]
11–1–2–3	–109.7 (6)	–72 (1)	–126	–58	–82
1–2–3–4	86.6 (5)	–60 (2)	97	–67	–60
2–3–4–5	–63.6 (5)	82 (3)	–55	75	102
3–4–5–6	–48.6 (5)	41 (3)	–66	65	–9
4–5–6–7	174.6 (6)	–144 (3)	172	–164	–149
5–6–7–8	–66.7 (5)	123 (2)	–61	91	139
6–7–8–9	–64.8 (5)	–101 (2)	–66	–80	–74
7–8–9–10	129.0 (6)	128 (2)	138	128	117
8–9–10–11	–60.9 (5)	–68 (2)	–62	–68	–69
9–10–11–1	–65.5 (5)	–68 (1)	–60	–75	–60
10–11–1–2	165.3 (6)	162 (1)	159	165	168

mation between the [12323] and [121232][†] forms; in this case the angular differences are 0–24°, mean 7°. For an isolated molecule of (1), the two lowest energy minima are the [335] and [12323] conformations and the potential-energy surface connecting these forms passes through the [121232][†] transition state (Anet & Rawdah, 1978). In the environment in a crystal, the forces exerted on a molecule are distributed in a locally unsymmetrical manner and the structure of a readily deformed molecule in the solid is not necessarily the same as the equilibrium structure of the isolated molecule; it is therefore not surprising to find that the 293 K major conformation of compound (1) in the crystal is distorted from the [12323] conformation in the direction of the transition state for conversion to the [335] conformation. A similar argument is at the basis of the correlation of crystallographic structural data with reaction paths (Bürgi & Dunitz, 1983).

The 135 K analysis and the previous 123 K analysis (Groth, 1980) are in excellent agreement and corresponding results for the torsional angles and bond angles of the eleven-membered ring differ by only 0.1–1.5°, mean 0.7°. It was essential, of course, to obtain low-temperature and room-temperature data from the same batch of crystals to exclude the possibility that conformational differences might be connected with the existence of polymorphic crystal modifications (Truter, 1983).

Other examples of conformational interconversions in solids have been detected by X-ray studies at several temperatures: nitrogen inversion and axial \rightleftharpoons equatorial interchange in 1,3,5-tribenzyl-1,3,5-triazacyclohexane (Sim, 1987a) and chair \rightleftharpoons boat interconversion in derivatives of bicyclo-[3.3.1]nonan-9-one (Sim, 1990).

The C–C(*sp*³)–C angles in the eleven-membered ring in (1) at 135 K range from 112.9 (4) to 118.4 (4)°, mean 115.6°. Though the corresponding H–C–H angles of 97.4 (45)–113.0 (39)° are subject to fairly large errors, the mean value of 105.9° is undoubtedly significantly smaller than tetrahedral.

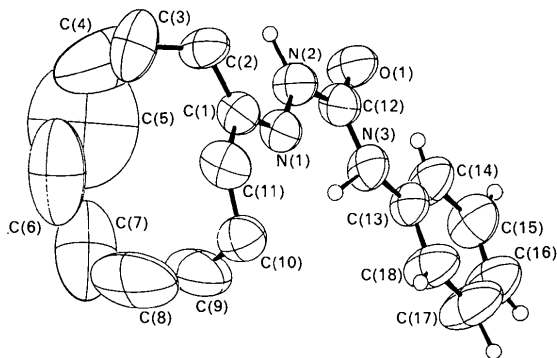


Fig. 1. Molecular structure and atomic numbering at 293 K. The thermal ellipsoids of the C, N and O atoms are drawn at the 50% probability level. The H atoms are represented by spheres of radius 0.1 Å.

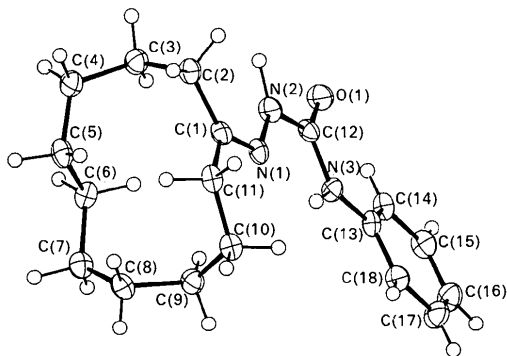


Fig. 2. Molecular structure and atomic numbering at 135 K. The thermal ellipsoids of the C, N and O atoms are drawn at the 50% probability level. The H atoms are represented by spheres of radius 0.1 Å.

For comparison, mean C—C(sp^3)—C and H—C(sp^3)—H angles for other large rings are 115.2 and 103.9° in cycloundecylmethyl 1-naphthylcarbamate (Russell & Sim, 1990) and 114.3 and 106.9° in *N*-(*p*-toluensulfonyl)azacyclotridecane (Sim, 1987*b*); in cyclodecane-1,6-diol the C—C—C angles are 113.4–120.1° and the H—C—H angles are 104.7–106.7° (Ermer, Dunitz & Bernal, 1973).

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Structural Studies of Mitomycins. IV. Structure of Albomitomycin A

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Abstract. [1*S*-(1 α ,2 α ,4 β ,5 β ,6 α ,6 α ,10 α *R*)]-2,3,6,6 α ,7,10-Hexahydro-1,2,5-metheno-5,8-dimethoxy-9-methyl-7,10-dioxo-1*H*,5*H*-imidazo[2,1-*f*]indol-6-ylmethyl carbamate, C₁₆H₁₉N₃O₆, $M_r = 351.36$, monoclinic, $P2_1$, $a = 10.605$ (1), $b = 8.342$ (2), $c = 9.4889$ (7) Å, $\beta = 106.416$ (7)°, $V = 805.2$ (3) Å³, $Z = 2$, $D_x = 1.45$ g cm⁻³, $Mo K\alpha$, $\lambda = 0.71073$ Å, $\mu = 1.296$ cm⁻¹, $F(000) = 372$, $T = 293$ K, $wR = 0.044$ for 1427 observed reflections with $F > 3\sigma(F)$. The title compound is one of the minor constituents from the fermentation broth of mitomycin A. The structure has a quite unusual fused-ring system for mitomycins. The quinone ring which is one of the important structural characteristics of the mitomycin family is reduced to a dihydroquinone in the title compound.

Introduction. Mitomycins are potent antitumour antibiotics and mitomycin C which is a member of the family has clinically been applied to various tumours successfully. Although mitomycin C is a prominent antitumor drug, we have been screening the minor constituents from the fermentation broth

of mitomycins since 1977 to discover more effective and less toxic compounds. Albomitomycin A was discovered from the fermentation broth of mitomycin A by *Streptomyces caespitosus* (Kono, Saitoh, Shirahata, Arai & Ishii, 1987). Albomitomycin A is almost colourless as suggested by its name. Since the colours of most mitomycins are very deep the unusual pale colour of albomitomycin A implies that it should have a quite unique skeleton. If albomitomycin A has a new skeleton we may develop a new chemistry of mitomycins to discover more potent compounds. Therefore we have undertaken its structure determination. Since the compound was isolated as a minor constituent the sample was very small. In addition the structure is quite different from other members of the mitomycin family. Therefore it was extremely difficult to elucidate the chemical structure by normal spectroscopic methods (Kono, Saitoh, Shirahata, Arai & Ishii, 1987). The chloroform solution, which was left in a refrigerator for days, unexpectedly gave a few prismatic crystals and by use of these crystals we have successfully determined the unique structure unequivocally by X-ray analysis. The crystals were pale violet due to a trace amount of mitomycin A in the crystals.

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