

Conformational Study of the 1-Azabicyclo[3.3.1]nonan-2-one System. Molecular-mechanics Calculations and X-Ray Structure of 5-Phenyl-1-azabicyclo[3.3.1]nonan-2-one

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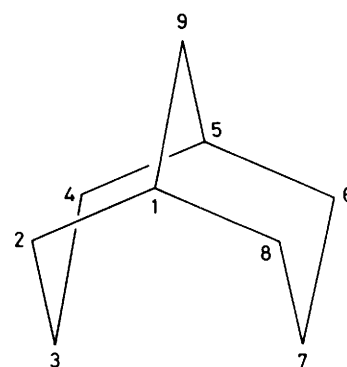
Molecular-mechanics calculations for 5-methyl-1-azabicyclo[3.3.1]nonan-2-one indicate that the boat-chair conformation is more stable than the twin-boat conformation by 4.0 kJ mol⁻¹. An *endo* methyl substituent at position 7 causes the twin-boat conformation to be favoured by 5.2 kJ mol⁻¹. The boat-chair conformation of 5-phenyl-1-azabicyclo[3.3.1]nonan-2-one has been characterized by X-ray crystal-structure analysis. The bridgehead amide is appreciably distorted from planarity, with N(1) displaced by 0.36 Å from the plane of C(2), C(8), and C(9). The crystal structure provides an example of enantiomeric disorder: on average, each molecular site is occupied by 0.8 of a molecule of one configuration and 0.2 of the mirror-image molecule. Crystallographic data are $a = 12.253(3)$, $b = 8.372(2)$, $c = 11.665(3)$ Å, $Z = 4$, space group $Pca2_1$. X-Ray intensity measurements were made on a four-circle diffractometer and least-squares adjustment of the atomic parameters converged at R 0.050 for 1 023 reflections.

Three possible conformations, twin-chair (1), boat-chair (2), and twin-boat (3), can be considered for derivatives of bicyclo[3.3.1]nonane. Various X-ray studies have established that molecules lacking *endo*-substituents at positions 3 and 7 generally adopt a modified twin-chair conformation in which the rings are somewhat flattened so that the C(3)···C(7) separation is *ca.* 3.1 Å and the H···H 3,7-separation *ca.* 1.9 Å.¹⁻⁶ Other X-ray studies have confirmed that molecules with bulky *endo*-substituents at positions 3 or 7 adopt the boat-chair conformation.⁷ 9-Oxa-3,7-dithiabicyclo[3.3.1]nonane⁸ and 3-benzyl-7-methyl-3,7-diazabicyclo[3.3.1]nonan-9-one⁹ also adopt the boat-chair conformation and this has been ascribed to lone-pair repulsions between the 3 and 7 positions in the twin-chair conformation.

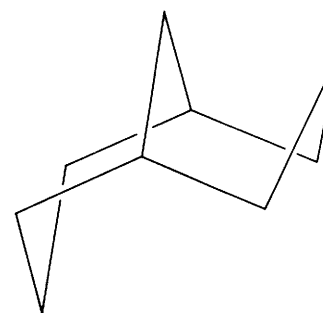
Investigation of bicyclo[3.3.1]nonane by electron diffraction has demonstrated the presence of *ca.* 5% of the boat-chair conformer at 65 °C and *ca.* 25% at 400 °C and these results are consistent with an energy difference of *ca.* 10 kJ mol⁻¹ between the twin-chair and boat-chair forms.¹⁰ Other experiments indicate that the twin-chair conformer is more stable than the boat-chair conformer by *ca.* 13 kJ mol⁻¹.¹¹ Molecular-mechanics calculations with the force field developed by White and Bovill¹² favour the twin-chair form by 12 kJ mol⁻¹,⁴ in good agreement with the experimental results. Allinger's MM2 force field gives a similar value (10 kJ mol⁻¹)^{10,13} and other calculations give estimates of 6, 10, and 16 kJ mol⁻¹.¹⁴ The twin-boat form of the hydrocarbon is calculated to be a further 23 (WB) or 11 (MM2) kJ mol⁻¹ less stable than the boat-chair form.

Molecular models of bridgehead amides of type (4) suggest that effective p - π overlap requires the adoption of the boat-chair conformation. Spectroscopic results for (4)¹⁵ and the 5-phenyl derivative (5)¹⁶ support this assignment of conformation.

An X-ray examination of (5) was undertaken to provide details of the molecular conformation. The crystal structure was determined by direct-phasing procedures and the atomic co-ordinates adjusted by full-matrix least-squares calculations. The analysis was complicated by the discovery of enantiomeric disorder; R and S molecules are not confined to unique sites in the unit cell but substitute to a limited extent so that, on average, each molecular site is occupied by 0.8 of a molecule of one configuration and 0.2 of the mirror image molecule.



(1)



(2)

Such disorder is not common, but is not unknown. 1-*p*-Bromophenylsulphonyloxymethyl-5-methylbicyclo[3.3.1]nonan-9-ol, one of the first bicyclo[3.3.1]nonane derivatives to be studied by X-ray crystallography, provides an excellent example of the effect.¹

The molecular structure of (5) is shown in Figure 1 and the torsion angles defining the ring conformations are in Table 1.

The N atom in (5) is displaced by 0.36 Å from the plane of C(2), C(8), and C(9). Departures from planarity in amides are

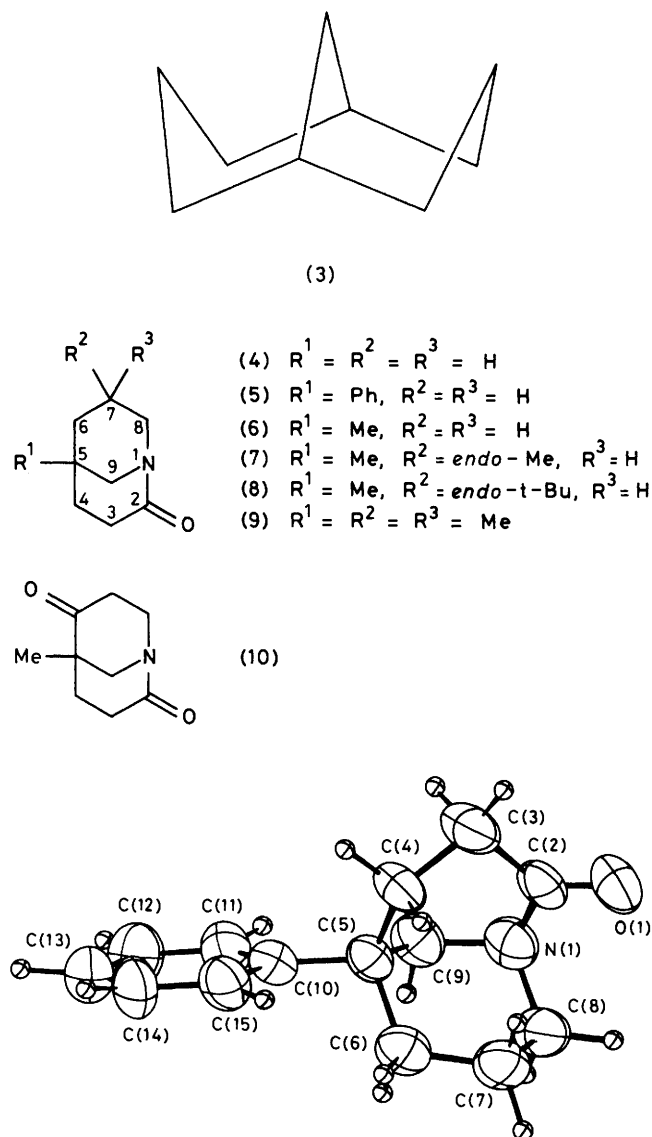


Figure 1. The molecular structure of 5-phenyl-1-azabicyclo[3.3.1]nonan-2-one. The thermal ellipsoids of the C, N, and O atoms are drawn at the 50% probability level. The H atoms are represented by spheres of radius 0.1 Å

well documented but are usually much smaller than in (5); in β -lactams, for example, displacements of *ca.* 0.2 Å have been reported.¹⁷ The out-of-plane distortions of an amide group can be partitioned among out-of-plane bending at the nitrogen (χ_N) and the carbonyl carbon (χ_C) and twisting around the N-CO bond (τ).¹⁸ The values of these parameters in (5) are $\chi_N -48.8^\circ$, $\chi_C 5.9^\circ$, and $\tau 200.8^\circ$ (*i.e.* a twist of 21°). For comparison, the *trans*-amide in caprylolactam is subject to some strain by its presence in a nine-membered ring and the conformational parameters indicate a substantial degree of out-of-plane distortion, $\chi_N 21.5^\circ$, $\chi_C -5.5^\circ$, $\tau 162.0^\circ$.¹⁸ In the tertiary amide 4-diethylcarbamoylcyclohex-1-ene-5-carboxylic acid¹⁹ the amide is free from ring constraints and the out-of-plane bending at N is substantially lower, $\chi_N 14^\circ$, $\chi_C 5^\circ$, $\tau -169^\circ$.

The N-CO bond length in (5), 1.374(7) Å, is rather longer than the corresponding distance in caprylolactam¹⁸ and 4-diethylcarbamoylcyclohex-1-ene-5-carboxylic acid,¹⁹ 1.34 Å, and the C=O bond length in (5), 1.201(6) Å, is shorter than the

Table 1. Torsion angles for the boat-chair (BC) conformer of 5-phenyl-1-azabicyclo[3.3.1]nonan-2-one (*X*-ray: column BC_x) and the boat-chair (BC) and twin-boat (BB) conformers of 5-methyl-1-azabicyclo[3.3.1]nonan-2-one (molecular mechanics: columns BC_{MM} and BB_{MM})

	BC _x (°)	BC _{MM} (°)	BB _{MM} (°)
C(9)-N-C(2)-C(3)	-0.8	10.2	2.0
C(3)-C(4)-C(5)-C(9)	-4.2	-5.5	-28.7
N-C(2)-C(3)-C(4)	54.2	48.2	46.7
C(2)-C(3)-C(4)-C(5)	-49.9	-48.5	-29.7
C(2)-N-C(9)-C(5)	-59.3	-67.1	-63.0
C(4)-C(5)-C(9)-N	58.2	58.7	73.1
C(9)-C(5)-C(6)-C(7)	50.3	52.3	-18.3
C(9)-N-C(8)-C(7)	-65.1	-70.5	-44.7
C(5)-C(6)-C(7)-C(8)	-47.2	-46.7	60.2
C(6)-C(7)-C(8)-N	50.9	49.7	-27.4
C(6)-C(5)-C(9)-N	-60.2	-62.5	-45.7
C(8)-N-C(9)-C(5)	73.5	79.3	87.6

distance in caprylolactam, 1.23 Å and 4-diethylcarbamoylcyclohex-1-ene-5-carboxylic acid, 1.24 Å. These results must reflect the decreased *p*- π overlap in (5). The C=O stretching frequency in (5) is at 1695 cm⁻¹ whereas the unstrained *N*-methyl-2-piperidone absorbs at 1650 cm⁻¹, consistent with a shorter and stronger C=O bond in (5).

The conformational preferences of various derivatives of 1-azabicyclo[3.3.1]nonan-2-one were investigated by molecular-mechanics calculations using the amide force field developed by White and Guy.²⁰ The generation and initial optimization of the conformations were performed with a high-performance refreshed graphics system (Megatek MGS-7000). Energy minimization was accomplished by pattern search, block-diagonal, and full-matrix Newton-Raphson procedures.²¹ Torsion angles derived for boat-chair and twin-boat forms of 5-methyl-1-azabicyclo[3.3.1]nonan-2-one (6) are presented in Table 1 and comparison of the results for the boat-chair conformer with the *X*-ray results for (5) shows that calculated and observed C-C-C-C and N-C-C-C angles agree very well, with an average difference of only 1.9°. The agreement for C-N-C-C angles is not quite so good, the mean difference being 7.1°. The molecular-mechanics calculations yield a model in which the N atom is displaced by 0.39 Å from the plane of C(2), C(8), and C(9), and the conformational parameters χ_N , χ_C , and τ have values of -35.1, 20.7, and 197.4°. Comparison with the *X*-ray results of 0.36 Å, -48.8, 5.9, and 200.8° indicates that the amide force field successfully reproduces the large departure from planarity and the twist about the N-CO bond but overestimates out-of-plane bending at the carbonyl C atom and underestimates that at the N atom. The discrepancies are not unexpected, since experimental results for such a heavily distorted amide as (5) were not available during the parameterization of the force field. The experimental results in Table 1 will be important for further improvement of the peptide force field.

The *X*-ray and molecular-mechanics results in Table 1 show that because of the constraints of the rigid chair ring, the boat ring in the boat-chair conformer of (5) or (6) is only slightly skewed. On the other hand, the twin-boat conformer has appreciably skewed-boat rings. The boat-chair and twin-boat conformers of (6) are shown in Figure 2.

The boat-chair conformation of (6) is calculated to be 4.0 kJ mol⁻¹ more favourable than the twin-boat conformation. No energy minimum could be located in the vicinity of a twin-chair conformation. The geometries and energies of several derivatives of (6) with substituents at position 6 or 7 were also

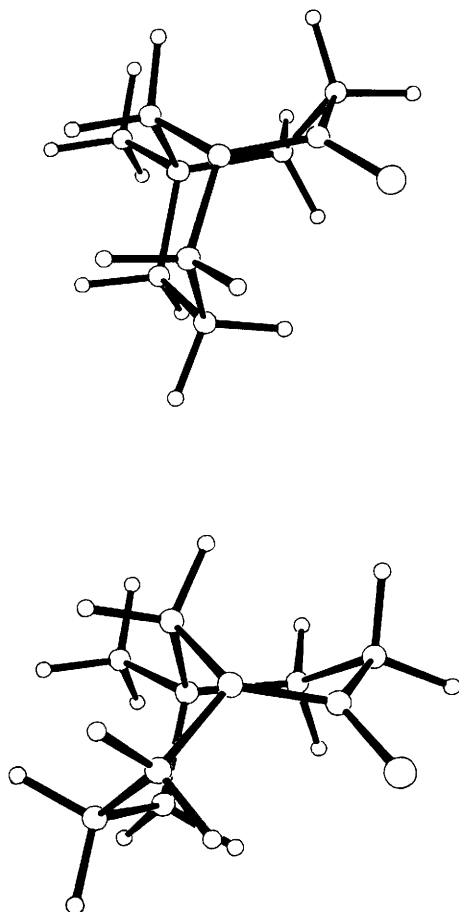


Figure 2. Boat-chair and twin-boat conformations of 5-methyl-1-azabicyclo[3.3.1]nonan-2-one, derived by molecular-mechanics calculations

calculated and in no instance could energy minima corresponding to a twin-chair conformation be located. In (7), the *endo*-methyl group at C(7) leads to the twin-boat conformation being favoured over the boat-chair conformation by 5.2 kJ mol⁻¹. When the bulk of the 7-*endo* group is increased by replacing methyl by *t*-butyl (8), the twin-boat conformation becomes the only definable energy minimum. We conclude that synthesis of a 7-*endo*-substituted 1-azabicyclo[3.3.1]nonan-2-one will provide access to the interesting twin-boat conformation.

When the 7-position is disubstituted, (9), the boat-chair conformation is again favoured, to the extent of 3.3 kJ mol⁻¹; in this case the steric congestion between the 7-*endo* methyl group and the axial H atom at C(4) in the boat-chair form is preferable to that between the C(7)-methyl and the C(9)-H in the twin-boat form.

Previous calculations have shown that a carbonyl group at C(2) leads to a reduction in the energy difference between twin-chair and boat-chair conformations of bicyclo[3.3.1]nonane derivatives.⁴ Accordingly, we investigated the effect of incorporation of a carbonyl group at C(6) in the 1-azabicyclo[3.3.1]nonan-2-one system. Calculations for compound (10) indicate that the boat-chair conformation is still preferred over the twin-boat form in this case, but only to the extent of 1.8 kJ mol⁻¹. Since errors in high-quality molecular-mechanics calculations are of the order of 2 kJ mol⁻¹ it would be of interest to prepare and examine (10) to see whether the twin-boat conformer can be detected.

Experimental

Crystal Data.—5-Phenyl-1-azabicyclo[3.3.1]nonan-2-one (5), C₁₄H₁₇NO, *M* = 215.30, orthorhombic, *a* = 12.253(3), *b* = 8.372(2), *c* = 11.665(3) Å, *U* = 1 197 Å³, *D_c* = 1.20 g cm⁻³, *Z* = 4, *F*(000) = 464, μ(Mo-*K*_α) = 0.81 cm⁻¹, μ(Cu-*K*_α) = 5.94 cm⁻¹, systematic absences *0kl*: *l* = 2*n* + 1, *h0l*: *h* = 2*n* + 1, space group *Pca*2₁ (C₂_v⁵, No. 29).

Crystallographic Measurements.—Cell dimensions were derived from least-squares treatment of the setting angles of 25 reflections measured on an Enraf-Nonius CAD4 diffractometer with Cu-*K*_α radiation. Two sets of intensity measurements were obtained: set 1 with Mo-*K*_α radiation and set 2 with another crystal and Cu-*K*_α radiation. For set 1, reflections *hkl* were surveyed in the range θ ≤ 27° and 641 satisfied the criterion *I* > 2.5σ(*I*). For set 2, reflections *hkl* and *hk̄l* were surveyed in the range θ ≤ 72° and equivalent reflections were averaged (*R*_{int} 0.037) to yield 1 023 reflections, which satisfied the criterion *I* > 2.5σ(*I*).

Structure Analysis.—With data set 1, the crystal structure was elucidated by a version of MULTAN adapted for the Glasgow University ICL 2976 computer by Dr. C. J. Gilmore. After preliminary least-squares adjustment of the co-ordinates of the C, N, and O atoms, the H atoms were located in a difference electron-density distribution and included in subsequent structure-factor calculations constrained to ideal positions with C-H 1.08 Å. Refinement with anisotropic thermal parameters for the C, N, and O atoms then converged at *R* 0.092, *R_w* 0.098 with weights *w* ∝ 1/σ²(|*F*|). A difference electron-density distribution contained a number of small peaks in the region of the molecule but these could not be interpreted as solvent molecules or misplaced atoms. The molecular dimensions were satisfactory. Nevertheless, the final value of *R* is rather high, indicating that there are errors either in the intensity data or in the calculated model.

Another crystal was selected and intensity set 2 collected with Cu-*K*_α radiation. When equivalent reflections *hkl* and *hk̄l* were averaged, the result obtained for *R*_{int} (0.037) indicated that these intensities are of normal high accuracy. Least-squares adjustment of the atomic parameters with these intensity data converged at *R* 0.108, *R_w* 0.097, indicating a deficiency in the calculated model. A difference synthesis again showed various small peaks close to the C, N, and O atomic sites and careful consideration of these eventually suggested some disorder in the crystal and a model to account for this: the *R* and *S* enantiomeric molecules are not completely segregated at unique sites, related by the glide planes of space group *Pca*2₁, but occur to a limited extent (*ca.* 25%) at the sites of their mirror images. The peaks in the difference map were allocated to the appropriate C, N, and O atoms of the minor enantiomeric component and included in further least-squares calculations in which the site occupation parameters (*K*) of the major and minor molecular components were allowed to adjust subject to the constraint *K*(major component) + *K*(minor component) = 1. For atoms C(3), C(5), and C(10–15) of the phenyl ring, the major and minor sites are too close to be separated and single sites were adopted for these atoms, with *K* = 1. The H atoms of the major component were constrained to ideal positions with a common thermal parameter (*U* = 0.09) and the H-atom contributions of the minor component were neglected. These calculations converged at *R* 0.050, *R_w* 0.053, with weights *w* ∝ 1/σ²(|*F*|). The final values obtained for the site occupation parameters are *K*(major component) = 0.802, *K*(minor component) = 0.198.

Fourier and least-squares calculations were performed with

Table 2. Fractional atomic co-ordinates with standard deviations in parentheses for (5)

Atom	x	y	z
O(1)	0.483 2(2)	1.148 4(4)	0.553 3(—)
N(1)	0.315 7(3)	1.084 0(5)	0.487 1(4)
C(2)	0.418 0(5)	1.047 5(6)	0.527 5(5)
C(3)	0.443 8(3)	0.871 4(5)	0.524 8(4)
C(4)	0.424 2(4)	0.812 4(6)	0.401 0(5)
C(5)	0.310 9(2)	0.864 3(4)	0.352 7(4)
C(6)	0.322 8(4)	0.996 5(6)	0.256 5(5)
C(7)	0.369 0(5)	1.157 4(6)	0.295 5(5)
C(8)	0.312 6(6)	1.214 4(6)	0.404 4(6)
C(9)	0.251 4(4)	0.947 7(5)	0.447 8(4)
C(10)	0.254 0(3)	0.724 3(4)	0.298 0(4)
C(11)	0.153 3(3)	0.670 1(5)	0.334 9(5)
C(12)	0.100 8(4)	0.543 0(6)	0.281 0(6)
C(13)	0.151 6(5)	0.466 2(5)	0.188 0(6)
C(14)	0.250 9(5)	0.518 2(5)	0.151 0(5)
C(15)	0.303 1(3)	0.647 5(5)	0.204 2(5)
N(1')	0.440 1(12)	1.063 8(18)	0.382 1(14)
C(2')	0.464 2(18)	1.028 1(25)	0.496 6(24)
C(4')	0.331 4(14)	0.799 3(23)	0.482 4(18)
C(6')	0.220 6(17)	1.002 2(28)	0.347 8(24)
C(7')	0.247 0(24)	1.144 2(30)	0.410 3(26)
C(8')	0.366 8(24)	1.195 0(34)	0.365 3(33)
C(9')	0.407 5(16)	0.933 3(23)	0.302 8(19)

Table 3. Bond lengths (Å) and angles (degrees) for (5)

O(1)—C(2)	1.201(6)	C(5)—C(10)	1.506(5)
N(1)—C(2)	1.374(7)	C(6)—C(7)	1.530(8)
N(1)—C(8)	1.457(7)	C(7)—C(8)	1.523(9)
N(1)—C(9)	1.460(6)	C(10)—C(11)	1.383(6)
C(2)—C(3)	1.508(7)	C(10)—C(15)	1.404(6)
C(3)—C(4)	1.545(7)	C(11)—C(12)	1.393(7)
C(4)—C(5)	1.560(6)	C(12)—C(13)	1.406(9)
C(5)—C(6)	1.583(7)	C(13)—C(14)	1.362(9)
C(5)—C(9)	1.500(6)	C(14)—C(15)	1.402(7)
N(1)—C(2)—O(1)	122.4(4)	C(3)—C(2)—O(1)	123.6(5)
C(8)—N(1)—C(2)	114.7(5)	C(9)—N(1)—C(2)	115.2(4)
C(3)—C(2)—N(1)	113.7(4)	C(9)—N(1)—C(8)	111.3(4)
C(7)—C(8)—N(1)	107.8(5)	C(5)—C(9)—N(1)	109.5(4)
C(4)—C(3)—C(2)	107.4(4)	C(5)—C(4)—C(3)	112.8(4)
C(6)—C(5)—C(4)	111.6(3)	C(9)—C(5)—C(4)	107.2(4)
C(10)—C(5)—C(4)	110.4(3)	C(9)—C(5)—C(6)	104.1(3)
C(10)—C(5)—C(6)	106.6(4)	C(7)—C(6)—C(5)	116.0(4)
C(10)—C(5)—C(9)	116.8(3)	C(11)—C(10)—C(5)	122.4(4)
C(15)—C(10)—C(5)	119.2(3)	C(8)—C(7)—C(6)	110.9(5)
C(15)—C(10)—C(11)	118.3(4)	C(12)—C(11)—C(10)	121.5(5)
C(14)—C(15)—C(10)	120.2(4)	C(13)—C(12)—C(11)	119.5(5)
C(14)—C(13)—C(12)	119.6(5)	C(15)—C(14)—C(13)	120.9(5)

the program SHELX. Molecular diagrams were prepared with the program ORTEP.

Atomic co-ordinates are listed in Table 2. Bond lengths and angles for the principal molecule are in Table 3. Observed and

calculated structure amplitudes, thermal parameters, hydrogen atom positions, and additional details of the molecular geometry, together with co-ordinates, geometries and ORTEP diagrams for compounds (6)—(10) from the molecular-mechanics calculations are listed in Supplementary Publication No. SUP 23715 (74 pp.).*

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* For details of the Supplementary Publications Scheme see Instructions for Authors, *J. Chem. Soc., Perkin Trans. 2*, 1983, Issue 1.