

ELECTRON DIFFRACTION STUDY OF MOLECULAR STRUCTURE OF MEBICAR

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The structure of the mebicar molecule has been studied by gas-phase electron-diffractometry using quantum chemical calculations. An eclipsed conformation along the C–C bond (torsion angle $\varphi(\text{H}-\text{C}-\text{C}-\text{H}) = 10^\circ$) and flattened *semi-chair* conformations of cyclic fragments have been found. The bond lengths (r_g) and angles ($\angle\alpha$) show the following average values: $r(\text{C}-\text{C})$ 1.576(3) Å, $r(\text{C}-\text{N})$ 1.460(3) Å, $r(\text{C}(\text{O})-\text{N})$ 1.390(4) Å, $r(\text{C}=\text{O})$ 1.211(5) Å, $r(\text{C}-\text{H})$ 1.090(5) Å, $\angle\text{CCN}$ 103.0(5)°, $\angle\text{CNC}(\text{O})$ 112.2(1)°, $\angle\text{CNC}$ 122.4(1)°. The dihedral angle between the cyclic fragments is 116.6°.

Keywords: gas-phase electron diffraction, geometrical structure, eclipsed conformation along the C–C bond, 2,4,6,8-tetramethyl-2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-dione, mebicar.

Mebicar — 2,4,6,8-tetramethyl-2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-dione — started to be used in clinical practice in 1978 as a daytime tranquilizer [1]. It is common knowledge that incorporation of substituents and heteroatoms into cyclopentane causes pseudorotation to disappear and stabilizes the *envelope* or *semichair* conformers. Increased angular strain leads to cycle flattening, whereas increased torsion strain leads to greater deviation from the flat structure. The sum of the values of the bond angles $\angle\text{CCN}$, $\angle\text{CNC}$, and $\angle\text{NC}(\text{O})\text{N}$ of the acyclic analogs of mebicar (ethylamine [2] and tetramethylurea [3, 4], $2 \cdot 115 + 2 \cdot 117.5 + 120 = 585^\circ$) is appreciably higher than the largest possible value for five-membered cycles (540°). Thus formation of the mebicar molecule is accompanied by substantial deformation of bond angles, which favors the flat conformation of the rings. A similar effect must be exerted by the π systems of the $-\text{N}(\text{CH}_3)\text{C}(\text{O})\text{N}(\text{CH}_3)-$ fragments. However, the eclipse arising along the carbon–carbon bond (Fig. 2a) in the flat conformation (and also in the *envelope* conformation, Fig. 4b) is a destabilizing factor.

Thus the shape of the mebicar molecule is determined by balance between counteracting factors, which hinders the prediction of conformation and demonstrates the necessity for an experimental structural research.

EXPERIMENTAL

A mebicar sample was synthesized by a procedure described in [6]. Electron diffraction patterns were obtained on a modernized ER-100M electron diffractometer (accelerating voltage 50 kV, evaporator nozzle temperature 160°C). The Kodak Electron Image Film SO-163 was used for recording. Three films have been obtained for each of the nozzle–film distances 169 mm and 375 mm. At the same time, electron diffraction patterns were recorded for benzene to refine the scattered electron wavelength. The photographic patterns obtained were digitized on an MFS-12000CX scanner calibrated

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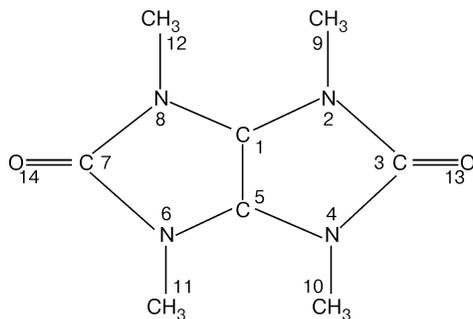


Fig. 1. Mebicar.

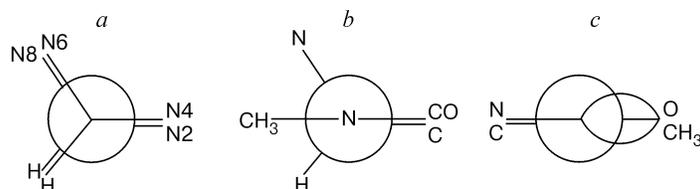


Fig. 2. Newman projections of mebicar for flat conformation of cyclic fragments along the bonds: *a*) C–C, *b*) C–N, *c*) N–C(O). The twisted bond concept [5] was used to depict the C=O double bond.

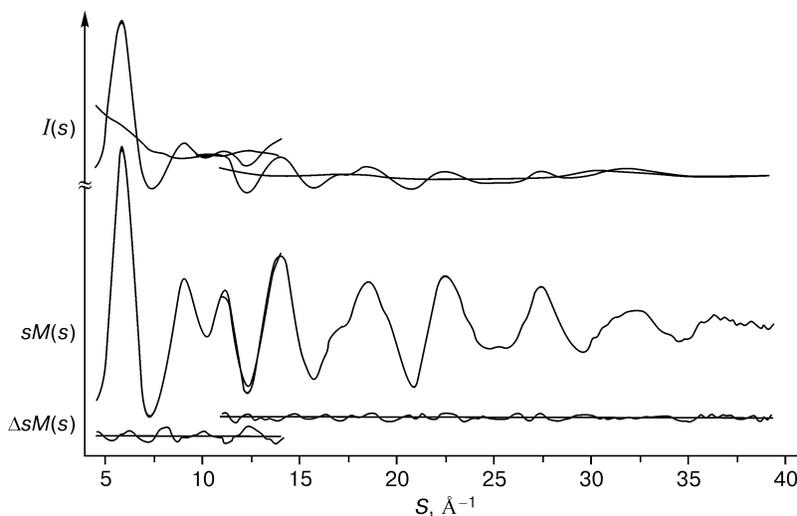


Fig. 3. Experimental intensity $I(s)$, background, molecular intensity function $sM(s)$, and difference curves $\Delta sM(s)$ ($\Delta sM(s) = sM(s)^{\text{exp}} - sM(s)^{\text{theor}}$) calculated for model *a* of the mebicar molecule for large and small nozzle-to-plate distances.

against a photometric wedge. Primary treatment of the photographic patterns (search for the center of the diffraction pattern and transformation of two-dimensional intensity $I(x, y)$ to one-dimensional $I(s)$, $s = 4\pi/\lambda \sin(\Theta/2)$, λ is the electron wavelength, Θ is the scattering angle) was performed by the procedure of [7]. The background on the intensity curves (Fig. 3) was drawn with a cubic spline [8]. To calculate the radial distribution curve, the experimental molecular intensity function $sM(s)$ in the experimentally unrecorded intervals (from 0 to $s_{\text{min}} = 4.6 \text{ \AA}^{-1}$ and from $s_{\text{max}} = 39.2 \text{ \AA}^{-1}$ to 100 \AA^{-1}) was complemented with a theoretical model and divided by the g function of the atomic pair with maximum contribution (C–N). It can be demonstrated [9] that the radial distribution curve in this case will approximate the sum of the Gaussian peaks (Fig. 5).

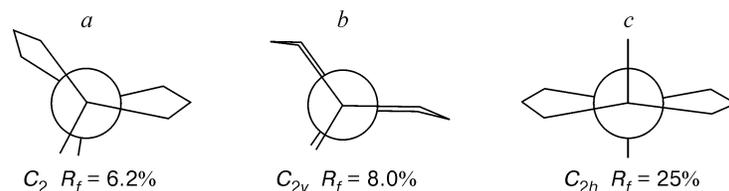


Fig. 4. Checked models of the mebicar molecule: *a* — *gauche-semichair-semichair*, C_2 ; *b* — *envelope-envelope*, C_{2v} ; *c* — *trans-semichair-semichair*, C_{2h} .

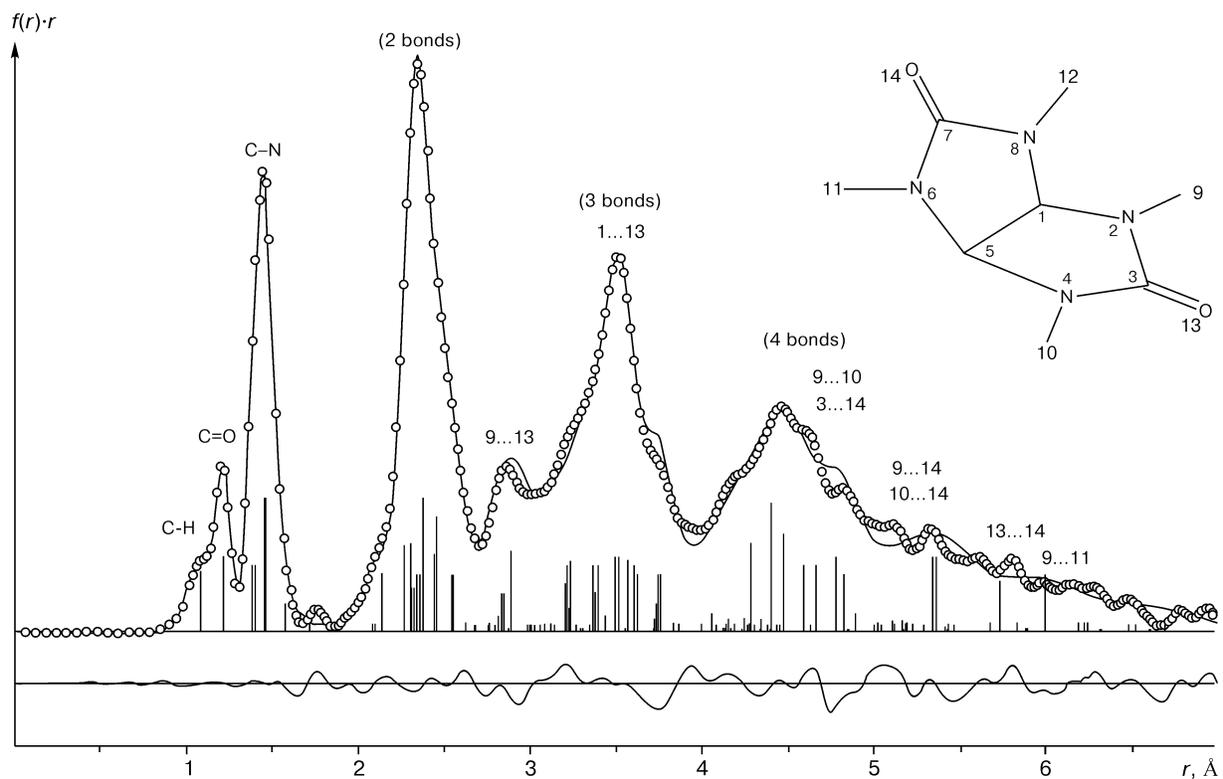


Fig. 5. Radial distribution curve for mebicar.

STRUCTURAL ANALYSIS

The structure of the mebicar molecule was described in terms of three groups of internuclear distances ($C-C$, C_1-N_2 , C_5-N_4 , C_9-N_2 , $C_{10}-N_4$), (C_3-N_2 , C_3-N_4), and ($C=O$, $C-H$) and five groups of bond angles ($\angle C_5C_1N_2$, $\angle C_1C_5N_4$), ($\angle C_1N_2C_3$, $\angle C_3N_4C_5$), ($\angle C_1N_2C_9$, $\angle C_3N_2C_9$, $\angle C_3N_4C_{10}$, $\angle C_5N_4C_{10}$), $\angle N_2C_1N_8$, and $\angle NCH$. The small differences between the parameters within the groups were taken from quantum chemical data (B3LYP/6-31G(*d*), Table 1). The elements of the dispersion and covariation matrix were up to 0.5 for simultaneously varied parameter groups. An attempt to adjust separately the $C-C$ bond length led to high dispersion in determining this parameter (1.569(22) Å). Since the resulting value was close to the group value for this bond (1.576(3) Å), this parameter was subsequently adjusted together with the $C-N$ bonds. The oxygen atoms were located on the continuation of the median of the $N-C(O)-N$ triangle. For methyl groups, C_{3v} local symmetry was taken. The rotational orientation of the methyl groups and the direction of inversion of the nitrogen bonds were fixed in accordance with the results of quantum chemical calculations.

The vibration amplitudes and corrections for the shrinkage effect were calculated by the procedure of [10] using the force field obtained in quantum chemical calculations and were not varied. For refined parameters, tripled standard deviation

TABLE 1. Experimental (r_g , \angle_α) and Theoretical (B3LYP/6-31G(d), r_e , \angle_c) Structural Parameters of the Mebicar Molecule [internuclear distances r and mean square vibration amplitudes l (Å) and angles (deg)]

Bond	r_g	r_e	l	Angle	\angle_α	\angle_c
C–C	1.576(3)	1.564	0.0543	N ₂ C ₁ C ₅	103.0(5)	103.2
C ₁ –N ₂	1.467	1.455	0.0516	C ₁ C ₅ N ₄	102.9	103.0
C ₅ –N ₄	1.453	1.441	0.0495	C ₁ N ₂ C ₃	111.6(3)	111.4
C ₉ –N ₂	1.462	1.450	0.0462	C ₃ N ₄ C ₅	112.8	112.7
C ₁₀ –N ₄	1.458	1.446	0.0484	C ₁ N ₂ C ₉	122.5	122.4
C ₃ –N ₂	1.395(4)	1.392	0.0481	C ₃ N ₂ C ₉	120.0	119.9
C ₃ –N ₄	1.386	1.384	0.0466	C ₅ N ₄ C ₁₀	124.8	124.7
C=O	1.211(5)	1.220	0.0377	C ₃ N ₄ C ₁₀	122.2	122.1
C–H	1.090	1.095	0.0777	N ₂ C ₃ N ₄	108.7*	107.7
N ₂ ...N ₈	2.432*	2.467	0.0689	N ₂ C ₁ N ₈	114.2(1.6)	116.8
N ₂ ...N ₆	3.174*	3.202	0.118	C ₃ ...X...C ₇ **	116.6*	123.7
N ₄ ...N ₈	3.388*	3.411	0.158	NCH	114(3)	107.5
				HCCH	10.0*	

$R_f = 6.2\%$

*Dependent parameters.

**X is the middle of the C–C bond.

is given in parentheses. The C_2 (*gauche-semichair-semichair*), C_{2v} (*envelope-envelope*), and C_{2h} (*trans-semichair-semichair*) models (Fig. 4) were checked in the course of structural analysis. Model *a* was found to be the only model that fits the data of electron diffraction experiment. The experimental and calculated structural parameters of this model are presented in Table 1.

DISCUSSION OF RESULTS

Of three models (Fig. 4) selected for checking and adjusting the structural parameters, model *c* does not fit the data of electron diffraction experiment ($R_f = 25\%$). In addition, an unreasonably large value of bond angles $\angle N_2C_1N_8 = 151^\circ$ is necessary to provide the *trans*-conformation of the five-membered fragments.

Model *b* is also in appreciably worse agreement with experimental data ($R_f = 8.0\%$) compared with model *a*. Quantum chemical computation of model *b* leads to an internal energy that is only 120 cal/mole higher than the energy of the *a* conformer. However, calculation of normal vibration frequencies using a quantum chemical force field revealed an imaginary frequency for model *b*. This indicates that model *b* is not a conformer. Conceivably, this is a transition state between two enantiomeric forms of conformer *a*.

Coincidence in every detail between the experimental radial distribution curve (Fig. 5, circles) and the theoretical curve for model *a* with C_2 symmetry (*semichair-semichair*) indicates that this model approximates the mebicar molecular conformation.

Partial removal of eclipse along the C–C bond (Fig. 6) does not completely eliminate the torsion strain, which manifests itself as appreciable elongation of the C–C bond (1.576(3) Å) compared with the value of 1.533(3) Å typical for normal saturated hydrocarbons [5]. The molecule is also characterized by angular strain, which manifests itself as difference between the endocyclic bond angles and the analogous parameters of acyclic compounds ($\angle CCN = 103^\circ$ vs 115° in ethylamine [2], $\angle NC(O)N = 108.7^\circ$ and $\angle CNC = 112^\circ$ vs 119.8° and 114.4° in tetramethylurea [3]). The sum of angles in the pentagonal fragments is 539° , which differs only slightly from 540° in a flat pentagon.

The bond lengths in the mebicar molecule are close to the values of analogous parameters for structurally related

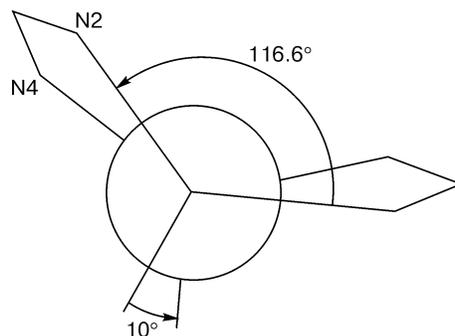


Fig. 6. Newman projection of the mebicar molecule along the C–C bond.

molecules. By averaging the values of chemically equivalent N–C(O) bond lengths (not equivalent in symmetry, Table 1), we obtain 1.390 Å (1.397(4) Å for tetramethylurea [3]). The endocyclic and exocyclic C–N bonds not involved in conjugation are close to each other (1.45–1.47 Å) and do not differ appreciably from the C–N bond in ethylamine (1.470(3) Å [2]) and tetramethylurea (1.461(2) Å [3]). The C=O internuclear distance (1.211(5) Å) is slightly shorter than the analogous parameter of tetramethylurea (1.240(5) Å [3]).

The bonding system of nitrogen atoms is considerably flattened as in the case of tetramethylurea, for which practically flat conformation [3, 4] was found. The sum of the $\angle\text{CNC}$ bond angles differs from 360° by 5.9° (N2, N6 atoms, Fig. 6) and 0.2° (N4, N8 atoms). The N2 and N6 atoms are closer to the neighboring ring (Fig. 6, Table 1) and their slightly greater pyramidalicity is probably due to steric strain. The bonds of the N2 and N6 atoms are inverted in directions of the maximum mutual separation of the methyl groups. The nitrogen atoms with a more flattened bonding system also have shorter C–N internuclear distances (N2 and N6: 1.395(4) Å, 1.462(3) Å, 1.467(3) Å; N4 and N8: 1.386(4) Å, 1.453(3) Å, 1.458(3) Å), which is in perfect agreement with the conjugation concept.

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