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On the conformational preferability of 5,6-dihydro-4[*H*]-1,2-oxazines, their *N*-oxides and acyclic analogues

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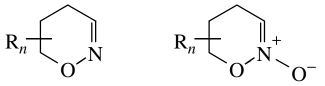
The most preferable conformation of 5,6-dihydro-4[*H*]-oxazines and their *N*-oxides is a distorted semi-chair, in which only the C(6) atom considerably deviates from the plane of the C=N bond, whereas 'planar' conformations, in which the O-alkyl group is at the *cis* position with respect to the free electron pair of the nitrogen atom or to the N→O fragment, are the most favourable for O-alkyl derivatives of acyclic oximes and alkyl nitronates, respectively.

Owing to their accessibility and diverse reactivity, 5,6-dihydro-4[*H*]-oxazines **1** and their *N*-oxides **2** (Figure 1) are widely used in organic synthesis, primarily in the directed syntheses of natural and biologically active compounds.[1] The high diastereoselectivity of many reactions involving these substrates[1–3] is also of considerable importance.



1 **2**

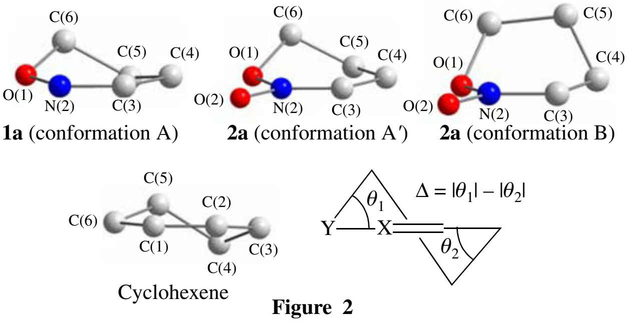
Figure 1

In order to analyse its origins, the factors determining the conformational preferability of compounds **1** and **2** should be found.

X-ray diffraction data for oxazines **1** and *N*-oxides **2** obtained from the Cambridge Structural Database (including our own data[2,4]) show that the above compounds in the crystalline state have a distorted semi-chair conformation (conformations A and A′, Figure 2), in which all the ring atoms except C(6) lie in virtually the same plane.[†] The grade of distortion of conformations A and A′ in comparison with the 'classical semi-chair' characteristic of cyclohexene can be approximated by the difference in the absolute torsion angles $\Delta = \theta_1 - \theta_2$ [where θ_1 is the dihedral angle C(3)–N(2)–O(1)–C(6) and θ_2 is the dihedral angle N(2)–C(3)–C(4)–C(5), see Figure 2].

We performed quantum-chemical calculations [B3LYP/6-31G(d)] for model unsubstituted oxazines **1a** and **2a**, as well as for cyclohexene. The results are presented in Table 1 and Figure 3. The calculation for oxazine **1a** revealed one stable conformation, which corresponds to conformation A observed by X-ray analysis for real objects. Two stable conformations A′ and B correspond to *N*-oxide **2a**, also in agreement with X-ray analysis results. Unlike cyclohexene used as a model, the difference in the absolute torsion angles Δ is considerable for all stable conformations of oxazines **1a** and **2a**.

The conformational stability of 5,6-dihydro-4[*H*]-1,2-oxazines is determined by the specifics of rotation about the N(2)–O(1) (angle θ_1) and C(3)–C(4) (angle θ_2) bonds. To elucidate the situation in more detail, it is expedient to separate these processes.



1a (conformation A) **2a** (conformation A′) **2a** (conformation B)

Cyclohexene

Figure 2

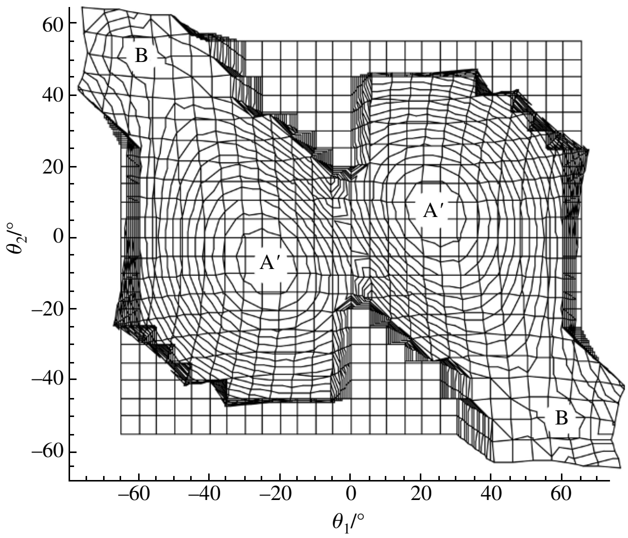


Figure 3 The surface of potentional energy of nitronate **2a**. The difference in the energies corresponding to the neighbouring isolines is 0.2 kcal mol^{-1}.

For this purpose, we performed a quantum-chemical calculation of rotation about the N–O bond for acyclic analogues of oxazines **1a** and **2a**, *i.e.*, the *O*-methyl ether of formaldoxime **3** and methyl methanenitronate **4** (Figure 4, curves *1* and *2*). It was found that the absolute energy minima for compounds **3** and **4** correspond to planar conformers A″ and A‴, in which the lone electron pair of the oxygen atom is anti-periplanar to the lone pair of nitrogen or to the N→O bond, respectively. In other words, the dihedral angle Me–O–N=C in the preferred conformations of **3** and **4** is close to 180°.

Note that the calculations of **3** and **4** also correlate with X-ray diffraction data.[‡] This situation is on the contrary to conformational preference for enols and esters (*e.g.*, **5** and **6** in Figure 4), in which the alkyl group in the most favourable conformation is at the *cis* position with respect to the C=O bond. Free rotation about the C–O bond in esters has been studied

Table 1 The calculated θ for model compounds **1a** and **2a**.

Compound	θ_1/°	θ_2/°	Δ/°
1a (A)	18.2	8.3	9.9
2a (A′)	24.3	6.5	17.8
2a (B)	53.7	–46.6	7.1

[†] Only one *N*-oxide is an exception. It exists in the semi-boat conformation, in which the C(5) and C(6) atoms deviate from the plane of the other four ring atoms (conformation B, Figure 2).

[‡] According to the data of the Cambridge Structural Database, almost all of O-alkyl derivatives of acyclic oximes and alkyl nitronates exist in crystals in a planar conformation with an anti-periplanar position of the lone electron pair of oxygen with respect to the lone pair of nitrogen or to the N→O bond.

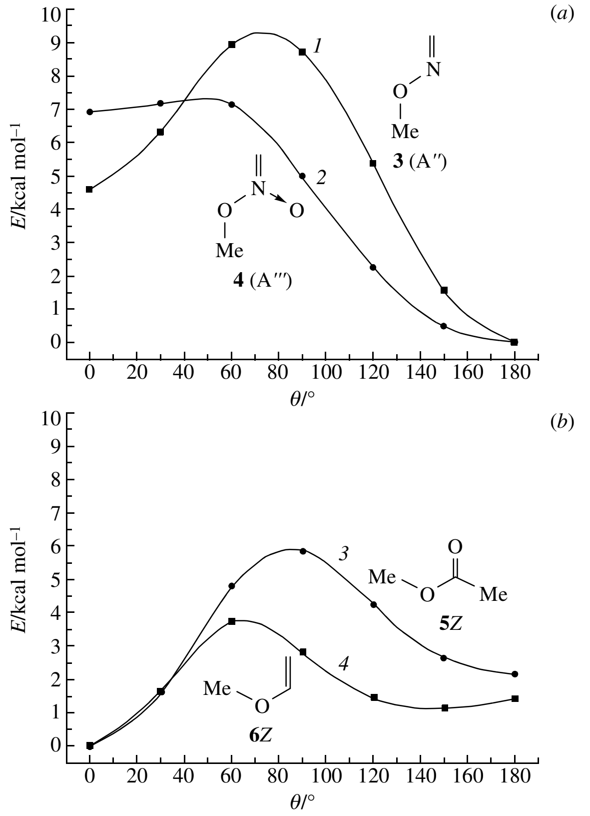


Figure 4 (*a*) θ is the dihedral angle Me–O–N=C; (*b*) θ is the dihedral angle Me–O–C=C or Me–O–C=O.

thoroughly, and the preference of '*Z*-conformation' was explained by the stabilising *n*–σ* interaction of the lone pair of the ester oxygen atom with the C=O bond.[5] However, the advantage of this conformation for derivatives **3** and **4** cannot be explained by stereoelectronic or steric interactions.

At the same time, both published data on the stereodynamics of esters **5** and our data for derivatives of acyclic oximes **3** and alkyl nitronates **4** can be explained in terms of the dipole–dipole interaction.[6] The predominating conformations for all these products (**3**–**6**) correspond to the minimised dipole moments of above molecules (Figure 5).

Obviously, the stability of a conformer is determined not only by its dipole moment but also by the contribution of *n*,π conjugation. However, the contribution of *n*,π conjugation in the planar conformers being compared (Figure 5) is virtually the same; hence, this effect can be neglected when considering their relative stability. On the other hand, attention should be paid to the fact that changes in the energies of oxime **3** and, especially, nitronate **4** due to variations in dihedral angle θ in the range 0–50° are insignificant (curves *1* and *2* in Figure 4). Most probably, such shapes of curves are due to the compensation of the effects discussed above. This interpretation is confirmed by the results of the Fourier analysis of curve *2* in Figure 4 (Figure 6); this analysis made it possible to assess the energy contributions of the dipole–dipole interaction and conjugation.

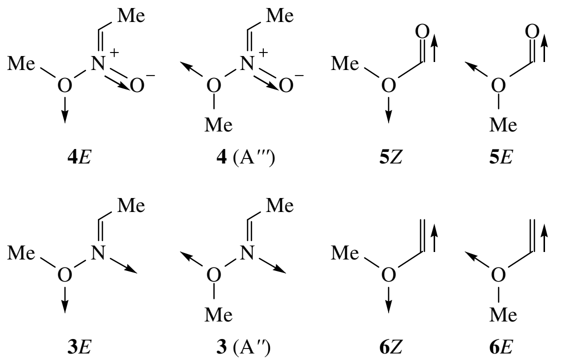


Figure 5

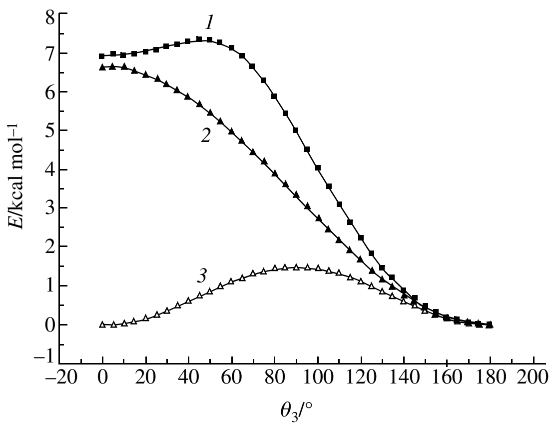


Figure 6 (*1*) Resulting function; (*2*) dipole–dipole interaction; (*3*) *n*–π conjugation.

The conformations A″ and A‴, which are most favourable for acyclic derivatives **3** and **4** ($\theta \approx 180°$), cannot occur in cyclic oxazines **1** and **2** for steric reasons. For these cyclic derivatives in the twist conformation, the absolute values of angle θ_1 responsible for the rotation about the N–O bond should lie near 0° in a narrow range not exceeding 50°. As noted above, this range is characterised by minimum changes in the energy of the conformers. Therefore, the overall rotation about the N(2)–O(1) and C(3)–C(4) bonds should occur in such a way as to minimise steric hindrances and decrease the dipole moments of oxazine derivatives. This is achieved by a considerable deviation of the C(6) atom from the plane along with a small deviation of the C(5) atom. In this case, the substituents at the *sp*^{3} carbon atoms of the oxazine ring acquire the most favourable *synclinal* conformation.

In conclusion, we have discussed the stereodynamic process in oxazines **1** and cyclic nitronates **2**, as well as in their acyclic analogues, *viz*., O-derivatives of oximes **3** and alkyl nitronates **4**. To explain the configurations of the dominant conformers, we used the concept of minimising the dipole moments.

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References

1 S. E. Denmark and J. J. Cottell, *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry toward Heterocycles and Natural Products*, Wiley, New York, 2002, pp. 83–168.
2 A. A. Tishkov, A. V. Lesiv, Yu. A. Khomutova, Yu. A. Strelenko, I. D. Nesterov, M. Yu. Antipin, S. L. Ioffe and S. E. Denmark, *J. Org. Chem.*, 2003, **68**, 9477.
3 V. O. Smirnov, S. L. Ioffe, A. A. Tishkov, Yu. A. Khomutova, I. D. Nesterov, M. Yu. Antipin, W. A. Smit and V. A.Tartakovsky, *J. Org. Chem.*, 2004, in press.
4 M. S. Klenov, A. V. Lesiv, Yu. A. Khomutova, I. D. Nesterov and S. L. Ioffe, *Synthesis*, 2004, 1159.
5 A. J. Kirby, *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*, Springer-Verlag, Berlin, 1983.
6 U. Brukert and N. L. Allger, *Molecular Mechanics*, ACS Monograph 177, American Chemical Society, Washingthon D.C., 1982.

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