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Conformational Analysis of 3-Methyltetrahydro-1,3-oxazine

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Abstract—Conformational analysis of 3-methyltetrahydro-1,3-oxazine has been performed using HF/6-31G(d), PBE/3z, and RI-MP2/λ2 simulation approximations. The potential energy surface contains eight minima. Interconversion of the axial and equatorial chair conformers (main minima) occurs via several independent pathways involving six twist forms. The preferred path presumes direct chair–chair transition via pyramidal inversion of the nitrogen atom.

Keywords: conformational analysis, tetrahydro-1,3-oxazine, computer simulation, conformer, interconversion, transition state

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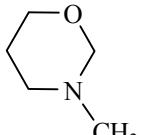
The interest to non-symmetric 1,3-heterocyclic analogs of cyclohexane, especially to tetrahydro-1,3-oxazines is due to their peculiar structural features [1–8] and valuable pharmacological properties [9–11] as well as to their wide application in fine organic synthesis [6, 12–19] and developing of new polymeric materials [20, 21]. Dipole moment measurements, NMR studies [1, 22, 23], and X-ray diffraction analysis [14] have led to conclusion that these compounds predominantly exist in the *chair* conformation with equatorial (C_e) or axial (C_a) orientation of the N-alkyl group. Ratio of the axial form decreases with growing conformational volume of the substituent at the nitrogen atom [3, 24–27]. In particular, results of DFT simulation and NMR spectroscopy study has demonstrated that methyl, ethyl, and propyl substituents in tetrahydro-1,3-oxazines take mainly the axial orientation in the gas phase and in low-polar solvents, whereas isopropyl and *tert*-butyl are located mainly in the equatorial position; in the more polar solvents, the conformational equilibrium is shifted towards the equatorial form [28]. According to dipole moment measurements, ratio of the C_e conformer in 3-methyltetrahydro-1,3-oxazine is 58%, corresponding to ΔG^0 of 0.2 kcal/mol [1]. Quantum-chemical simulation reported in [29] has revealed the electronic influence of the substituents at C^2 atom of tetrahydro-1,3-oxazine cycle on the preferential orientation of *N*-methyl group. On the other hand, the strong anomeric effect stabilizes the axial position of hydroxy group at nitrogen atom [30]. The important role of homoanomeric effects in governing the conformational behavior of a series of 1,3-diheterocyclohexanes has been deeply discussed in [31–33].

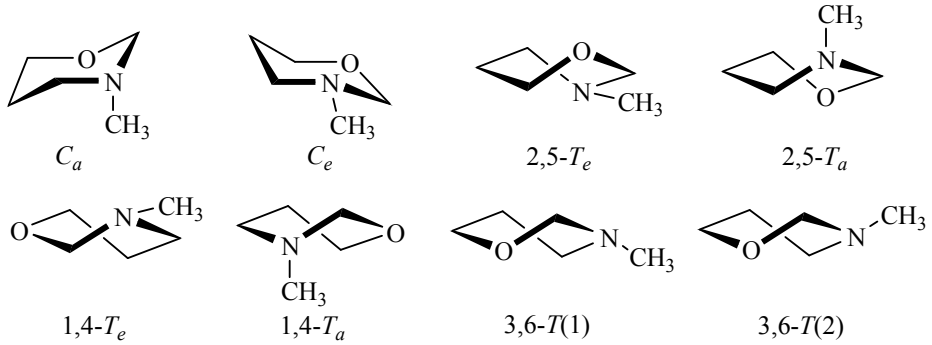
However, examples of comprehensive conformational analysis of molecules of the above-discussed class have been scarce so far. In particular, computer simulation in the frame of HF/6-31G(d) approximation has demonstrated that there are seven minima on the potential energy surface of unsubstituted tetrahydro-1,3-oxazine. The corresponding conformations were axial (global minimum) and equatorial *chair* and five flexible forms: two 1,4-*twist*- (1,4-*T*), two 2,5-*twist*- (2,5-*T*), and one 3,6-*twist*- (3,6-*T*) [34]. This work aimed to perform conformational analysis of 3-methyltetrahydro-1,3-oxazine **I** in the frame of the non-empirical HF/6-31G(d) approximation as implemented in HyperChem software [35], the hybrid DFT method PBE/3z, and the RI-MP2/λ2 method (the latter two available in PRIRODA software package [36]).



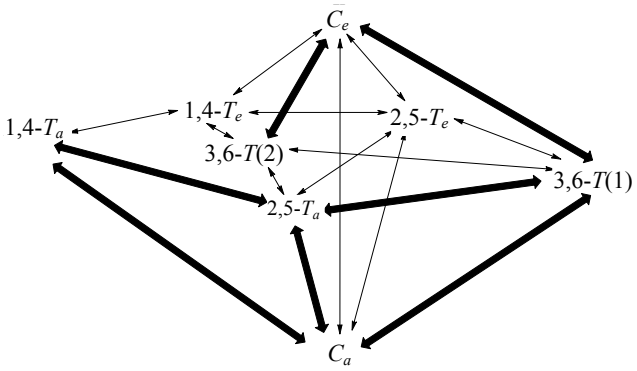
I

To do so, we performed scanning over single transannular torsion angles in the *chair* conformers and the flexible form seeking for the minima and the

corresponding transition barriers. The results evidenced a multicomponent equilibrium between the C_e and C_a conformers involving six of the flexible (*twist*) forms: 1,4-T_e, 1,4-T_a, 2,5-T_e, 2,5-T_a, 3,6-T(1), and 3,6-T(2).



According to the molecular graph shown below, the C_a *chair* could be directly converted into the C_e form and four of the *twist* forms. Equatorial *chair* could be directly converted into four *twist* conformers as well; the latter participated in the interconversions via different pathways.



As simulated with the HF/6-31G(d) and PBE/3z methods, the energy difference between the C_e and C_a forms did not exceed 0.4–0.5 kcal/mol, whereas in the frame of the RI-MP2/λ2 method these conformers are practically degenerated in energy (Table 1); the results were in good agreement with the experimental data [1, 37].

All the simulation methods showed that the 3,6-T(1) conformer was the most stable of all flexible forms, whereas the 3,6-T(2) conformer was the most labile. Noteworthily, the latter conformer was unstable in the case of unsubstituted tetrahydro-1,3-oxazine; in the course of energy minimization it was irreversibly converted into the 2,5-T_a form [34].

The following pairs of conformers could undergo interconversion via the pyramidal inversion of nitrogen atom through the transition state with planar N atom configuration: C_a and C_e, 1,4-T_a and 1,4-T_e, 2,5-T_a and 2,5-T_e (Scheme 1).

Scheme 1.

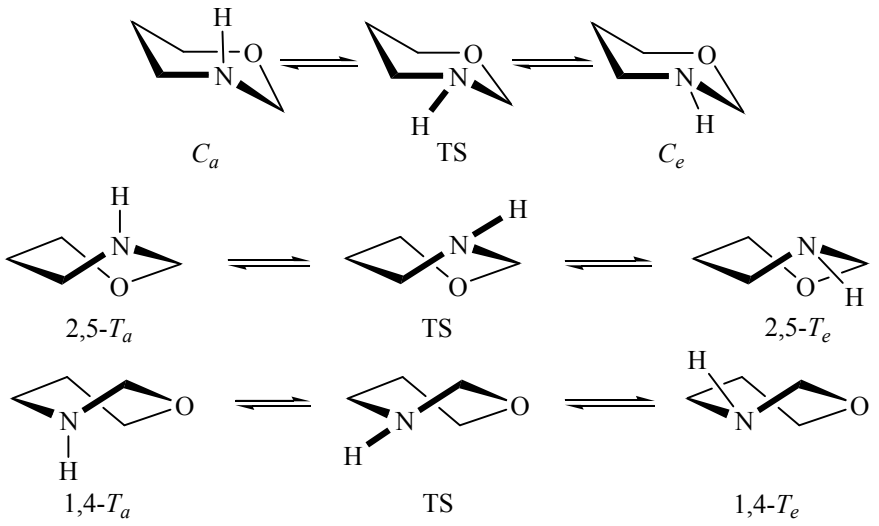
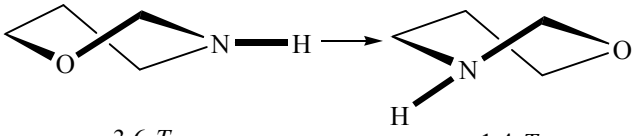


Table 1. Energy parameters of minima on the potential energy surface of compound **I**

Conformer	HF/6-31G(d)	PBE/3z				RI-MP2/λ2			
	ΔE^0 (0 K), kcal/mol	ΔE^0 (0 K), kcal/mol	ΔH^0_{298}, kcal/mol	ΔG^0_{298}, kcal/mol	ΔS^0_{298}, cal mol^{-1} K^{-1}	ΔE^0 (0 K), kcal/mol	ΔH^0_{298}, kcal/mol	ΔG^0_{298}, kcal/mol	ΔS^0_{298}, cal mol^{-1} K^{-1}
C_a	0	0.5	0.5	0.5	0.002	0.04	0.04	0.04	0.02
C_e	0.4	0	0	0	0	0	0	0	0
1,4-T_e	6.2	6.1	6.3	5.6	2.3	6.1	6.3	5.7	2.0
1,4-T_a	6.6	6.6	6.9	5.3	5.4	6.6	6.8	6.2	2.2
2,5-T_e	6.0	5.7	5.9	5.3	2.0	5.6	5.8	5.3	1.8
2,5-T_a	7.3	7.5	7.7	7.1	1.8	7.2	7.4	6.9	1.6
3,6-T(1)	5.5	5.5	5.6	5.2	1.4	5.4	5.5	5.1	1.3
3,6-T(2)	7.9	7.8	8.0	7.4	1.9	7.6	7.7	7.3	1.3

The data collected in Table 2 pointed at the relatively low barrier of the $C_e \leftrightarrow C_a$ inversion: 7.0 kcal/mol [HF/6-31G(d)] or 7.2 kcal/mol [RI-MP2/λ2]. That coincided with the experimental value of $\Delta G^{\neq}$ for the oxazine **I** (6.8 kcal/mol [38]). Two-dimensional slice of the potential energy surface illustrating the nitrogen atom pyramidal inversion is shown in Fig. 1.

In the case of the 3,6-*T* conformers such procedure was impossible. In the course of geometry optimization of the corresponding structure with the planar nitrogen configuration, it was irreversibly isomerized into the transition state corresponding to nitrogen configuration inversion in the 1,4-*twist* conformer.



3,6-*T* 1,4-*T*

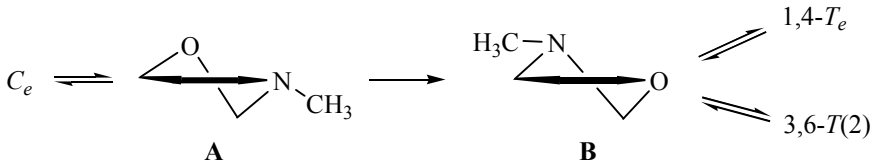
Scanning over the transannular torsion angles revealed several pathways of the C_e conformer conversion into the flexible forms. In particular, maximum at the bivariate slice of the potential energy surface of the $C_e \leftrightarrow$ 1,4-T_e transition corresponded to the *semi-chair* **A**, that was irreversibly transformed into the *semi-chair* **B** in the course of geometry optimization of the structure corresponding to the saddle point of the transition. Similar pathway enabled the $C_e \leftrightarrow$ 3,6-T(2) transition. Hence, conformation **B** should be regarded as transition state of the two parallel processes: $C_e \leftrightarrow$ 1,4-T_e and $C_e \leftrightarrow$ 3,6-T(2) (Scheme 2).

Furthermore, the C_e form was involved into the $C_e \leftrightarrow$ 3,6-T(1) and $C_e \leftrightarrow$ 2,5-T_e transitions, transition state in the both cases being different *semi-chair* modifications. Relative energy of the system as function of the scanning angle for the latter process is visualized in Fig. 2. At the same time, none of the scanning procedures revealed the $C_e \leftrightarrow$ 2,5-T_a and $C_e \leftrightarrow$ 1,4-T_a conformational transitions.

The C_a could be transformed into the 2,5-T_e, 2,5-T_a, 3,6-T(1), and 1,4-T_a conformers, transition states being the *sofa* conformation and different forms of the *semi-chair* (Scheme 3).

Noteworthily, the $C_a \leftrightarrow$ 3,6-T(1) and $C_a \leftrightarrow$ 1,4-T_a transformations occurred via the same transition state (1,4-*semi-chair*), whereas the $C_a \leftrightarrow$ 1,4-T_e and $C_a \leftrightarrow$ 3,6-T(2) transitions were found impossible (Scheme 4).

Scheme 2.



A **B**

Table 2. Energy parameters of transition states on the potential energy surface of compound **I** (relative to the conformer C_e) as determined by the PBE/3z method

Conformational transition	$\Delta E_0^{\neq}$ (0 K), kcal/mol	$\Delta H_{298}^{\neq}$, kcal/mol	$\Delta G_{298}^{\neq}$, kcal/mol	$\Delta S_{298}^{\neq}$, cal mol^{-1} K^{-1}
$C_e \rightleftarrows C_a$	5.7	5.5	5.7	–0.5
2,5-$T_e \rightleftarrows$ 2,5-T_a	10.8	10.9	10.1	2.6
1,4-$T_e \rightleftarrows$ 1,4-T_a	9.4	9.4	9.0	1.1
$C_e \rightleftarrows$ 1,4-T_e	10.3	10.2	9.9	0.7
$C_e \rightleftarrows$ 3,6-T(2)	10.3	10.2	9.9	0.7
$C_e \rightleftarrows$ 3,6-T(1)	12.2	12.2	11.3	3.1
$C_e \rightleftarrows$ 2,5-T_e	10.1	10.1	9.7	1.1
$C_a \rightleftarrows$ 2,5-T_e	10.8	10.6	10.6	0.2
$C_a \rightleftarrows$ 2,5-T_a	10.5	10.4	9.8	2.3
$C_a \rightleftarrows$ 3,6-T(1)	10.4	10.2	10.1	0.4
$C_a \rightleftarrows$ 1,4-T_a	10.4	10.2	10.1	0.4
1,4-$T_e \rightleftarrows$ 3,6-T(2)	8.4	8.2	8.6	–1.6
2,5-$T_e \rightleftarrows$ 3,6-T(1)	7.2	6.9	7.5	–1.8
1,4-$T_e \rightleftarrows$ 2,5-T_e	6.2	6.0	6.4	–1.3
1,4-$T_a \rightleftarrows$ 2,5-T_a	8.2	8.0	8.4	–1.2
2,5-$T_a \rightleftarrows$ 3,6-T(1)	8.2	8.0	8.4	–1.2
2,5-$T_a \rightleftarrows$ 3,6-T(2)	8.6	8.3	8.9	–1.9

The revealed pathways of interconversion of the flexible conformers can be represented by the Scheme 5.

Transition states of these processes correspond to various versions of the *boat* conformation, and the potential barriers are lower than those in the cases of interconversions of the *chair* conformers. The 3,6-*unsymmetrical boat* was a common transition state for the 2,5-$T_a \leftrightarrow$ 1,4-T_a and 2,5-$T_a \leftrightarrow$ 3,6-T(1) conversions (Table 2).

To conclude, the obtained results confirmed that oxazine **I** exist in the form of equilibrium mixture of the *chair* invertomers. Due to the lower activation

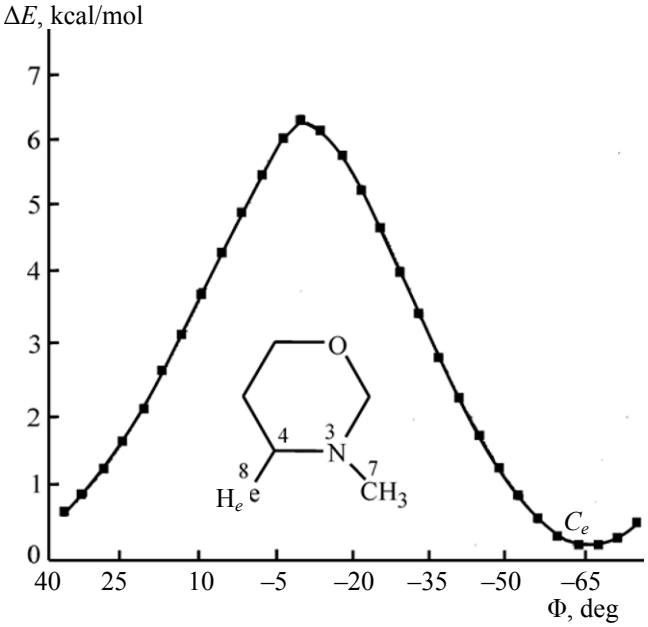


Fig. 1. Relative energy of compound **I** molecule as a function of the $C^7N^3C^4H_e^8$ torsion angle.

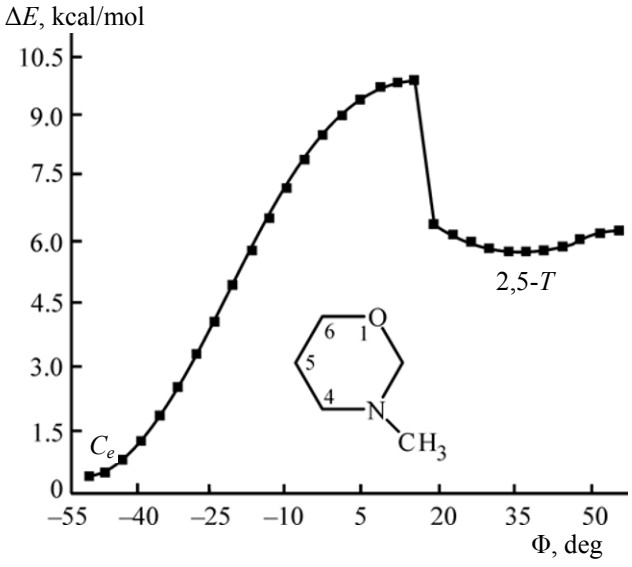
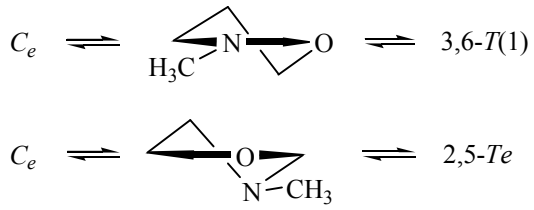
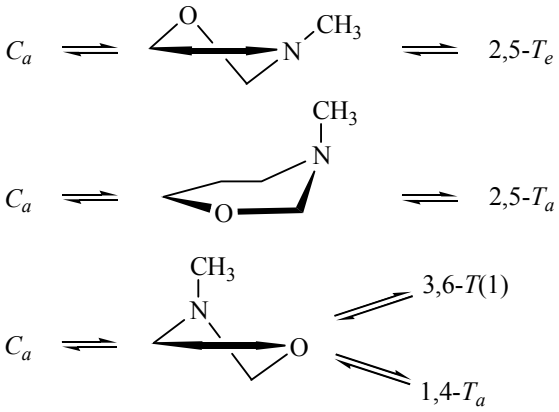


Fig. 2. Relative energy of compound **I** molecule as a function of the $O^1C^6C^5C^4$ torsion angle.

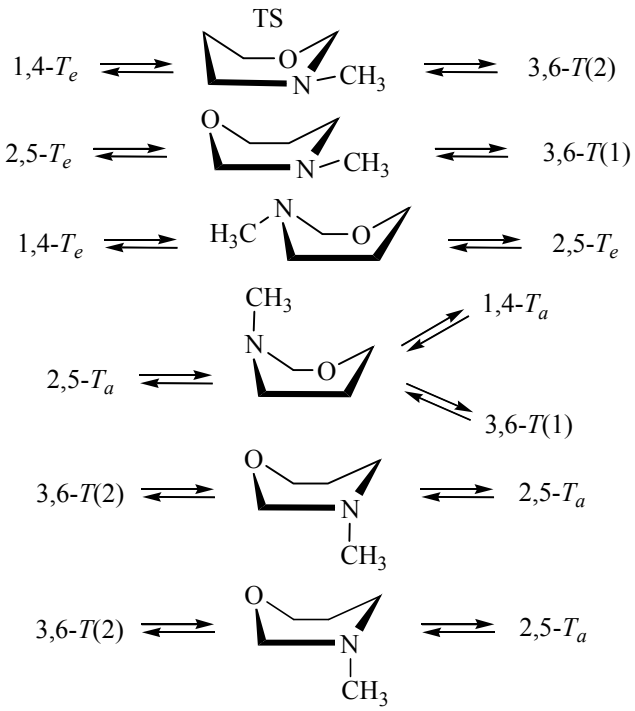
Scheme 3.



Scheme 4.



Scheme 5.



barrier, the direct transition $C_e \leftrightarrow C_a$ via pyramidal inversion of the nitrogen atom should be a dominating pathway; however, other pathways cannot be excluded basing on the simulation results.

EXPERIMENTAL

Pathways of the conformational transitions were determined by geometry optimization of the molecule after sequential change of one of the transannular torsion angles of the starting conformer, the scanning range was from ±70° to ±150°. The procedure was complete after minimization of the new form energy, corresponding to a stationary point at the bivariate slice of the potential energy surface (Figs. 1 and 2). Correspondence of the surface stationary points to the energy minima was confirmed by the absence of imaginary frequencies; correspondence of the point to the transition state was indicated by the presence of a single imaginary frequency in the Hessian matrix.

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