===

Theoretical Study of Alkaline Methanolysis of Alicyclic Epoxy Derivatives

S. I. Okovityi, E. L. Platitsyna, and L. I. Kas'yan

Dnepropetrovsk State University, Nauchnyi per. 13, Dnepropetrovsk, 320625 Ukraine

Abstract—The structures of epoxycycloalkane molecules and strains therein were calculated using the MM2MX procedure. Opening of the oxirane ring in these compounds in alkaline methanolysis was simulated by the PM3 method. The calculations were performed both for the gas phase and with account taken of solvent effect in macroscopic and supermolecular approximations. A model was developed, which takes into consideration contributions of electronic and steric factors in the supermolecular approximation. The calculated values of $\Delta H^{\neq}$ showed a good agreement with the experimental rate constants of the corresponding reactions.

Epoxy compounds are readily formed in living bodies via enzymatic processes. They are obtained on a laboratory or industrial scale with the aid of accessible oxidants [1, 2]. Numerous compounds belonging to this group are characterized by high reactivity with respect to various nucleophiles, such as amines, water, alcohols, etc. Reactions of epoxy derivatives, as well as their formation, are convenient models for studying important biological processes, specifically those responsible for carcinogenesis. Therefore, these reactions persistently attract interest and are extensively studied by both experimental and theoretical methods.

A specific group of epoxy derivatives consists of compounds in which the oxirane ring is fused to an alicyclic fragment. Steric strains inherent to the latter should considerably affect the reactivity of the oxirane ring toward nucleophiles. We previously reported on the methanolysis of epoxycycloalkanes [3], and kinetic parameters of these reactions in various media were presented in [4]. The greatest activity was found for epoxycyclohexane (**III**) in the presence of both sulfuric acid and sodium methoxide. Some compounds, e.g., epoxycyclooctane, epoxy-cyclododecane, and *exo*-epoxynorbornane (**VI**), undergo opening of the oxirane ring only in acid medium [3, 4]. We also revealed considerably different reactivities of two stereoisomeric epoxy derivatives: *exo*- (**VI**) and *endo*-epoxynorbornane (**V**); the *exo* isomer is more reactive in acid medium, and the *endo* isomer, in neutral and basic media.

More recent MINDO/3 quantum-chemical calculations [5], analysis of spectral parameters [6] and basicity [7] of epoxycycloalkanes, and theoretical [8] and experimental assessment of strain in their molecules by thermochemical methods [9] demonstrated a clear relation between the strain and electron density distribution in their molecules [10]. However, some important problems concerning the reactivity of epoxy derivatives remained unresolved.

The goal of the present study was to obtain quantitative data on reactions of epoxycycloalkanes **I**–**VII** with methanol. Compounds **VIII** and **IX** were studied for comparison.
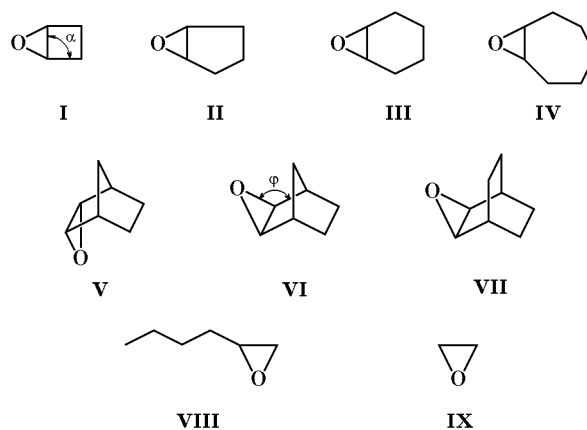
The mechanism of gas-phase opening of the oxirane ring in the parent compound **IX** and its closest homolog (methyloxirane) was studied in sufficient

detail using reactions with NH_3, F^-, Cl^-, SH^-, NH_2^-, and H^- as nucleophiles, as well as by semiempirical [11, 12] and nonempirical quantum-chemical methods involving extended basis sets and taking into account electronic correlation in terms of the Meller–Plesset second-order perturbation theory [13, 14]. It was found that in alkaline and neutral media the reaction is a bimolecular nucleophilic substitution process in which the oxirane oxygen atom is a nucleofuge [15]. Also, the advantage of the rear attack by nucleophile, typical of the S_N2 mechanism, was demonstrated relative to the frontal attack [16]. Theoretical studies of the solvent effects using the Germer solvaton model [13] and supermolecular approximation [17] were performed only for the parent compound, oxirane itself. No quantum-chemical studies of methanolysis of epoxycycloalkanes were reported.

We performed molecular-mechanics calculations of the structure and strain of epoxycycloalkanes using the MM2MX force field which was obtained by supplementing the standard MM2 force field [18] with parameters of the oxirane ring taken from [19]. The electron density distribution in epoxycycloalkane molecules and parameters of their reactions with methanol were calculated by the PM3 semiempirical method [20]. The solvent effects were taken into account in the macroscopic approximation using the COSMO procedure [21] ($\varepsilon = 32.66$; this value corresponds to the dielectric constant of methanol) and also in the supermolecular approximation where the solvate shell was simulated by introduction of methanol molecules. Transition states were localized by preliminarily scanning the potential energy surface. The nature of critical points was established by calculating the force constant matrix where transition states are characterized by the presence of one negative value; for prereaction complexes, all values are positive.

Epoxy derivatives **II**, **III**, and **V**–**VII** were calculated previously [8] using the standard MM2 force field. However, the lack of parameters of the oxirane

Table 1. Some geometric parameters of the molecule of oxirane (**IX**)

Parameter	MM2	MM2MX	Experiment [22]
$l(C-O)$, Å	1.435	1.439	1.436
$l(C-C)$, Å	1.505	1.478	1.472
$l(C-H)$, Å	1.087	1.089	1.082
$\alpha(COC)$, deg	63.2	61.8	61.7
$\alpha(HCH)$, deg	115.04	115.3	116.7

ring resulted in distortion of the structures (Table 1) and considerable overestimation of the deformation energy of bond angles [8]. We thought it reasonable to calculate the whole series of compounds **I**–**IX** using the MM2MX force field [9]. The data of [9], where compounds **VI** and **IX** were calculated, as well as the data in Table 2, show a good agreement between the calculated enthalpies of formation (MM2MX) and experimental results of thermochemical studies [9].

Table 2 shows that the strain energy of epoxycycloalkanes varies over a wide range, from 126.78 to 224.86 kJ/mol), and increases in the series **III** < **II** < **IV** < **VII** < **V** < **I**. The major contribution to the overall steric energy of molecules **I**, **V**, and **VI** is that of the angular strain resulting from deformation of the bond angle α (contiguous to the oxirane ring). Molecules of the other epoxycycloalkanes are characterized by the major contribution of the torsion strain. Compounds **I**–**VII** conform to the relation found in [8]: decrease in the angle α is accompanied by deviation of the epoxy fragment from the ring plane: the dihedral angle ϕ ($C^1C^2C^3O$) shows the following correlation with α: $\alpha = (261 \pm 28) - (1.3 \pm 0.2)\phi$; $r = 0.950$, $n = 7$ (Table 3).

According to our previous data [4] and those obtained in this work (Tables 2, 3), increase in the strain energy of epoxycycloalkanes is accompanied by increase in the LUMO energy and the order of the $C-O$ bond (in the series **III**, **III**, **IV**, **VII**). Our PM3 results (Table 3), as well as the parameters calculated in [4] by the MINDO/3 procedure, indicate a good agreement between the E_{LUMO} values and orders of the $C-O$ bonds of epoxycycloalkanes **II**–**IV** and epoxybicyclo[2.2.2]octane (**VII**), on the one hand, and the kinetic data [4], on the other. In keeping with the kinetic data, the rate of alkaline methanolysis decreases in the following series: **III** > **II** > **IV** > **VII**. However, the calculated bond orders and LUMO energies do not reflect some specific features of the methanolysis of 1,2-epoxyhexane (**VIII**) and stereoisomeric epoxynorbornanes **V** and **VI**. Compound **VIII** is the most reactive among epoxy derivatives **I**–**VIII**, and the calculation gives the greatest order of the $C-O$ bond in **VIII** (0.9703). The orders of the $C-O$ bond in molecules **V** and **VI** are 0.9654 and 0.9638, respectively; according to [4], *exo*-isomer **VI** is stable to sodium methoxide ([MeO$^-$] = 6.21 M) for 20 h at 60°C, whereas under the same conditions *endo*-isomer **V** undergoes slow methanolysis at a rate of 0.036 l mol^{-1} s^{-1} [4].

The above may be explained by a considerable contribution of steric factor to the reaction. Therefore,

Table 2. Contributions of different interactions and strains to steric energy, enthalpies of formation, and strain energies of molecules **I**–**VII**, calculated by the MM2MX method (kJ/mol)

Parameter	I	II	III	IV	V	VI	VII
Total steric energy	160.82	73.33	68.27	86.93	151.81	142.51	122.35
Distortion of bond lengths	3.68	1.54	1.66	1.89	4.87	4.75	4.51
Distortion of bond angles	96.10	22.55	10.78	16.22	71.47	69.21	18.04
Cross term (bonds–angles)	−5.45	−1.11	−0.12	0.33	−4.14	−3.82	−1.16
Torsion strain	65.42	46.20	44.47	54.06	67.22	59.36	72.95
Van der Waals 1,4-interactions	4.95	9.36	19.48	23.50	17.90	17.42	37.75
Other van der Waals interactions	−0.98	−1.55	−4.13	−5.32	−2.11	−1.00	−6.20
Dipole–dipole interactions	−2.90	−3.66	−3.86	−3.75	−3.33	−3.40	−3.55
Strain energy	224.86	134.61	126.78	142.68	206.32	196.83	173.91
Enthalpy of formation							
MM2MX	8.33	−106.01	−137.92	−146.13	−54.22	−63.73	−110.75
MMX	34.14	−86.94	−120.83	−124.18	−21.09	−32.13	−78.28
MM2 [8]	–	−90.09	−123.23	–	−33.23	−42.11	−93.35
experiment [9]	–	−97.1	−138.0	−152.3	–	−53.90	–

proper description of the chemical behavior of oxirane derivatives requires detailed knowledge of the mechanism of oxirane ring opening, including localization of transition states and prereaction complexes and simulation of the reaction conditions (specifically, the effect of the solvent). Table 4 contains geometric parameters of transitions states and enthalpies of activation ($\Delta H^{\neq}$) for alkaline methanolysis of compounds **I**–**IX**. The activation barriers for the gas-phase reactions are well consistent with such parameters of the initial epoxy compounds as the strain energy and the order of the C−O bond: increasing strain in the alicyclic fragment in the series of epoxycycloalkanes **I**–**VII** is accompanied by increase in the enthalpy of activation.

Among geometric parameters of transition states the most illustrative are the bond angles O^1CO^2 (β) and O^1CCO^2 (γ), where O^1 is the oxirane oxygen atom, and O^2 is the oxygen atom of methoxide ion. The first of these angles decreases as $\Delta H^{\neq}$ rises: from 167.9° for oxirane (**IX**) to 144.0° for the most strained *endo*-epoxynorbornane (**V**):

$$\Delta H^{\neq} = -(1.4 \pm 0.2)\beta + (332 \pm 24); \ r = 0.95, \ n = 9.$$

An analogous correlation is observed between $\Delta H^{\neq}$ and γ. The existence of such correlations is closely related to the S_N2 character of the reaction under study: the corresponding angles in a classical bimolecular substitution reaction approach 180°. Deviation from this value reduces overlap of molecular orbitals, and the activation barrier increases (Fig. 1).

The C−O bonds in the epoxy fragment of molecule **III** are nonequivalent (see the corresponding orders of bonds in Table 3). We examined the potential energy surfaces (PES) for two alternative reactions involving attack by methoxide ion on the C^1 and C^2 atom. In keeping with the concepts developed in [22], favorable attack by methoxide ion (X = MeO⁻) on C^1 gives rise to mild transition from the *half-chair* conformation of the initial epoxy compound to the *chair* conformer of the product. Alternative attack on C^2 is unfavorable, for it leads to formation of the

**Table 3.** Calculated parameters and relative rate constants of methanolysis of compounds **I**–**IX**

Comp. no.	E_{LUMO}, eV	Angle, deg		Order of C−O bond	k_{rel}[a]
		α	ϕ		
I	2.1415	90.6	120.1	0.9650	–
II	2.3628	108.3	110.3	0.9603	0.41
III	2.3591	120.8	103.6	0.9583[b]	1.00
				0.9595[c]	
IV	2.4061	121.6	106.7	0.9605	15.5×10^{-3}
V	2.3392	104.5	116.0	0.9654	0
VI	2.4188	104.6	116.9	0.9638	0
VII	2.4857	111.0	112.6	0.9630	5.52×10^{-3}
VIII	2.3628	–	–	0.9703	5.96
IX	2.3862	–	–	0.9705	–

[a] Sodium methoxide concentration 1.667 M (20°C) [4].
[b] Order of the C^1−O bond.
[c] Order of the C^2−O bond.
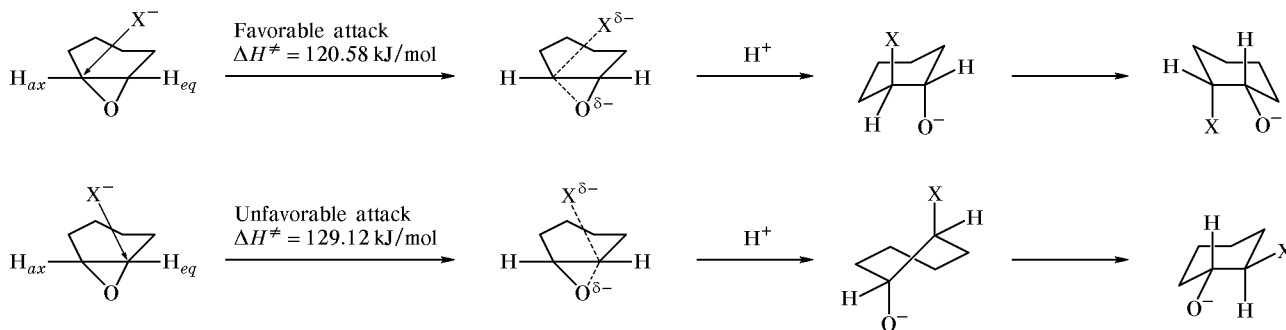
asymmetric *boat* conformer with higher energy (Scheme 1). Thus the conclusion drawn in [23] is supported, according to which conformational factor contributes most to regioselectivity of opening of the oxirane ring in epoxycyclohexane, whereas stereo-electronic and steric effects are less important.

Epoxy compounds **II–IV**, **VII**, and **VIII** show a satisfactory correlation between the calculated values of $\Delta H^{\neq}$ (Table 4) and logarithms of the rate constants given in [4]:

$$\log k_{\mathrm{rel}} = -(0.31 \pm 0.03)\,\Delta H^{\neq} + (37.4 \pm 6.7);$$

$$r = 0.95, \quad n = 5.$$

However, the calculations performed for the gas phase incorrectly predict greater reactivity of *exo*-epoxynorbornane (**VI**) relative to its *endo* isomer **V**. This may be due to underestimation of steric factor whose contribution considerably increases in reactions of epoxy derivatives with solvated methoxide ion.
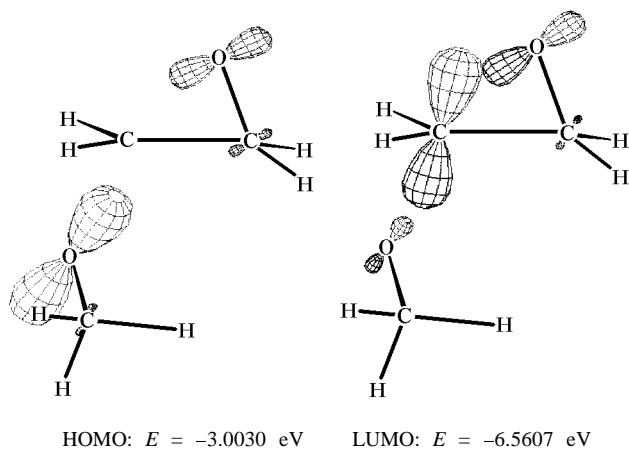

HOMO: $E = -3.0030$ eV   LUMO: $E = -6.5607$ eV

Fig. 1. Structure and energies of frontier molecular orbitals of the transition state in alkaline methanolysis of oxirane (**IX**).

Taking into account that experimental data on alkaline methanolysis of epoxycycloalkanes were obtained in methanol which is a fairly polar solvent capable of forming hydrogen bonds, we performed a theoretical study of the solvent effect on the process.

Table 4 gives the prinicipal geometric parameters and $\Delta H^{\neq}$ values for alkaline hydrolysis of compounds **I–IX**, calculated in the macroscopic approximation using the COSMO procedure [22]. The corresponding transition states are characterized by lower degree of O^2-C bond formation and greater degree of $C-O^1$ bond cleavage, as compared with the gas-phase calculations, i.e., the transition states are "looser." In this case, the *endo* isomer of epoxynorbornanes turns out to be more reactive; however, the difference in the activation barrier is as small as 2.38 kJ/mol, which is not quite consistent with the experimental data [4]. In addition, the $\Delta H^{\neq}$ values for compounds **VII** and **VIII** are considerably underestimated.

The supermolecular approximation provides a more appropriate desription of specific solvation and reaction mechanisms, where solvent molecules are considered to be reagents. Successful application of the supermolecular approach requires that the necessary and sufficient number of solvent molecules be specified. While studying the reaction of oxirane (**IX**) with methanol [17], the most acceptable results were obtained when the first solvate shell of methoxide ion contained four solvent molecules (methanol) and the less basic oxirane oxygen atom was solvated with one methanol molecule, i.e., the model $CH_3O^-(CH_3OH)_n$ + oxirane$(CH_3OH)_m$ ($n = 4$, $m = 1$) was used. The same model was used to examine alkaline methanolysis of epoxy derivatives **I–VIII**.

The principal geometric and activation parameters for methanolysis of compounds **I–VIII**, calculated in terms of the supermolecular approximation, are given in Table 4. Here, the correlation between the $\Delta H^{\neq}$ values and the angles β and γ was retained. Also,

Table 4. Calculated geometric parameters of transition states for opening of the oxirane ring and the corresponding activation barriers for compounds **I–IX**

Compound no.	Bond length, Å		Angle, deg			$\Delta H^{\neq}$, kJ/mol
	$C-O^1$	$C-O^2$	CCO^1	β	γ	
I	1.779	2.071	76.1	147.8	−157.6	133.55
II	1.775	2.005	76.6	150.9	−158.5	129.91
III[a]	1.787	2.000	76.8	152.5	159.6	120.58
IV	1.837	2.036	79.3	148.8	162.8	134.08
V	1.854	2.058	80.3	144.0	−142.7	141.24
VI	1.876	2.064	81.5	144.4	−144.9	135.60
VII	1.867	2.043	81.2	148.0	−148.5	136.20
VIII	1.737	1.982	74.1	159.3	175.1	115.23
IX	1.740	1.995	74.5	167.9	175.6	108.74
Macroscopic approximation						
I	1.841	2.193	79.0	142.3	−153.1	149.66
II	1.832	2.142	79.1	145.8	−157.6	156.98
III[a]	1.826	2.101	78.7	148.1	−151.7	150.37
IV	1.873	2.124	81.3	147.8	−151.5	127.32
V	1.893	2.155	82.2	139.3	−137.2	169.74
VI	1.981	2.292	87.0	137.0	−136.8	172.05
VII	1.903	2.152	82.8	144.0	−144.5	132.97
VIII	1.775	2.014	75.9	159.5	176.1	149.62
IX	1.772	2.065	76.1	154.7	179.5	128.24
Supermolecular approximation						
II	1.950	2.088	85.5	147.5	16.1	179.79
III[a]	1.890	2.046	82.2	145.0	157.8	163.43
IV	1.892	2.030	82.3	143.3	155.5	188.28
V	2.046	2.298	91.1	143.7	138.8	205.23
VI	2.078	2.205	92.8	134.5	124.3	214.85
VII	2.015	2.190	89.4	138.4	134.3	198.76
VIII	1.871	1.993	81.1	158.1	174.8	148.82
IX	1.862	1.991	81.3	156.0	179.6	141.46

[a] For the reaction at C^1 (favorable attack); the value of $\Delta H^{\neq}$ for gas-phase attack on C^2 is equal to 129.12 kJ/mol.

a satisfactory correlation exists between the calculated $\Delta H^{\neq}$ values and logarithms of the experimental relative rate constants ($\log k_{rel}$):

$$\Delta H^{\neq} = -(0.2 \pm 0.04)\beta + (195 \pm 24);$$
$$r = 0.91, \quad n = 8;$$

$$\Delta H^{\neq} = -(0.7 \pm 0.1)\gamma + (278 \pm 18);$$
$$r = 0.96, \quad n = 8;$$

$$\log k_{rel} = -(0.14 \pm 0.02)\Delta H^{\neq} + (23.1 \pm 3.4);$$
$$r = 0.96, \quad n = 5.$$

Both supermolecular and macroscopic calculations of stereoisomeric epoxynorbornanes which do not react with sodium methoxide under the given conditions predict the largest values of $\Delta H^{\neq}$. It should be noted that the activation barrier to the reaction of *endo* isomer **V**, calculated in the supermolecular approximation, is lower by 9.62 kJ/mol than the corresponding barrier calculated for *exo* isomer **VI**. Comparison of these results with those obtained by calculations for the gas phase shows that steric factor is actually determining for the reactivity of strained epoxynorbornanes **V** and **VI**. Just this factor is taken into account in terms of the supermolecular approach,

according to which solvent molecules are included in the explicit form. As a result, the effective volume of the reagent considerably increases (Fig. 2).
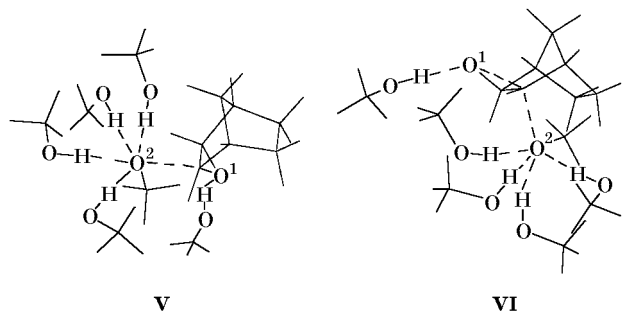

V **VI**

Fig. 2. Structure of transition states in the methanolysis of stereoisomeric epoxynorbornanes **V** and **VI**, calculated in the supermolecular approximation ($n = 4$, $m = 1$).

REFERENCES

1. Dryuk, V.G., Kartsev, V.G., and Voitsekhovskaya, M.A., *Oksirany – sintez i biologicheskaya aktivnost'* (Oxiranes. Synthesis and Biological Activity), Moscow: Bogorodskii Pechatnik, 1999.

2. Kas'yan, L.I., Seferova, M.F., and Okovityi, S.I., *Alitsiklicheskie epoksidnye soedineniya. Metody sinteza* (Alicyclic Epoxy Compounds. Methods of Synthesis), Dnepropetrovsk: Dnepropetr. Gos. Univ., 1996.

3. Kas'yan, L.I., Stepanova, N.V., Belyakova, T.A., Kunanets, V.K., Lutsenko, A.I., and Zefirov, N.S., *Zh. Org. Khim.,* 1984, vol. 20, no. 11, pp. 2295–2301.

4. Kas'yan, L.I., Gorb, L.G., Seferova, M.F., Chernousov, D.A., Svyatkin, V.A., and Boldeskul, I.E., *Zh. Org. Khim.,* 1990, vol. 26, no. 1, pp. 3–10; Kas'yan, L.I., *Doctoral (Chem.) Dissertation,* 1989.

5. Kas'yan, L.I., Gorb, L.G., Stepanova, N.V., and Zefirov, N.S., *Zh. Org. Khim.,* 1986, vol. 22, no. 5, pp. 893–897.

6. Kas'yan, L.I., Stepanova, N.V., Galafeeva, M.F., Boldeskul, I.E., Trachevskii, V.V., and Zefirov, N.S., *Zh. Org. Khim.,* 1987, vol. 23, no. 1, pp. 122–126.

7. Kas'yan, L.I., Gorb, L.G., Seferova, M.F., Tomalak, N.V., Il'chenko, N.N., Boldeskul, I.E., and Dryuk, V.G., *Zh. Org. Khim.,* 1989, vol. 25, no. 12, pp. 2473–2478.

8. Kas'yan, L.I., Seferova, M.F., and Porubleva, L.V., *Zh. Org. Khim.,* 1992, vol. 28, no. 3, pp. 449–460.

9. Kozina, M.P., Timofeeva, L.P., Luk'yanova, V.A., Pimenova, S.M., and Kas'yan, L.I., *Zh. Fiz. Khim.,* 1988, vol. 62, no. 5, pp. 1203–1207.

10. Kas'yan, L.I., Gnedenkov, L.Yu., Stepanova, N.V., Sitnik, I.V., and Zefirov, N.S., *Zh. Org. Khim.,* 1986, vol. 22, no. 1, pp. 215–216.

11. Ford, G.P. and Smith, C.T., *J. Comput. Chem.,* 1989, vol. 10, no. 4, pp. 568–592.

12. Ford, G.P. and Smith, C.T., *J. Chem. Soc., Chem. Commun.,* 1987, no. 2, pp. 44–45.

13. Glad, S.S. and Jensen, F., *J. Chem. Soc., Perkin Trans. 2,* 1994, pp. 871–876.

14. Gronet, S. and Lee, J.M., *J. Org. Chem.,* 1995, vol. 60, no. 14, pp. 4488–4497.

15. Parker, R.E. and Isaaks, N.S., *Chem. Rev.,* 1959, vol. 59, pp. 737–799; Prilezhaeva, E.N., *Reaktsiya Prilezhaeva. Elektrofil'noe okislenie* (The Prilezhaev Reaction. Electrophilic Oxidation), Moscow: Nauka, 1974.

16. Fujimoto, H., Hataue, I., Koga, N., and Yamasaki, T., *Tetrahedron Lett.,* 1984, vol. 25, no. 46, pp. 5339–5342.

17. Okovityi, S.I., Platitsyna, E.L., and Kas'yan, L.I., *Vestn. Dnepropetr. Gos. Univ., Ser. Khim.,* 1998, no. 2, pp. 132–135.

18. *Molecular Mechanics,* Burkert, U. and Allinger, N.L., Eds., Washington, DC: ACS, 1982.

19. Podlogar, B.L. and Raber, D.J., *J. Org. Chem.,* 1989, vol. 54, no. 21, pp. 5032–5035.

20. Stewart, J.J.P., *J. Comput. Chem.,* 1989, vol. 10, no. 2, pp. 209–220.

21. Klamt, A., *J. Phys. Chem.,* 1995, vol. 7, pp. 2224–2235.

22. Hirose, C., *Bull. Chem. Soc. Jpn.,* 1974, vol. 47, no. 6, pp. 235–244.

23. Kirk, D.N., *Chem. Ind.,* 1973, no. 3, pp. 109–116.