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SYNTHESIS AND PROPERTIES OF AZOLES AND THEIR DERIVATIVES. 68.* [2+3] CYCLOADDITION OF 2-NITRO-1-PROPENE TO (*Z*)-C,N-DIPHENYLNITRONE RELATIVE TO AM1 AND AM1/COSMO QUANTUM-CHEMICAL CALCULATIONS**

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Semiempirical AM1 and AM1/COSMO calculations were used to examine possible pathways for the [2+3] cycloaddition of 2-nitro-1-propene to (Z)-C,N-diphenylnitrone. These reactions proceed in the gas phase through a concerted mechanism. The effect of toluene or nitromethane as a dielectric medium results in the appearance of zwitterionic intermediates on pathways leading to 3,4-cis- and 3,4-trans-4-methyl-4-nitro-2,3-diphenylisoxazolidines.

Keywords: nitroalkenes, nitrones, [2+3] cycloaddition, semiempirical AM1 quantum-chemical method.

The [2+3] cycloaddition of nitrones to simple alkenes proceeds through a concerted mechanism [2]. However, in the case of strong electrophilic alkenes or considerable shielding of one of the reaction sites, a stepwise mechanism involving formation of a dipolar intermediate may compete with the concerted mechanism [3, 4]. In this regard, in a continuation of a study of the mechanism of (4+2) π-electron cycloadditions [5-11], we investigated the reaction pathways of the [2+3] cycloaddition of 2-nitro-1-propene (**1**) to (*Z*)-C,N-diphenylnitrone (**2**). The formation of four regioisomeric and stereoisomeric diarylnitroisoxazolidines **3-6** is possible in the reaction.

The mechanism of this reaction has not yet been subjected to kinetic investigation. Nitropropene **1** satisfies the above-mentioned criteria. The global electrophilicity of this compound (ω = 2.47 eV) is characteristic for strong π-electron-deficient dipolarophiles [12], while the reaction sites are considerably shielded due to the presence of the nitro and methyl groups at the same vinyl carbon atom.

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* For Communication 67 see [1].

** Dedicated to the memory of Professor Genrikh Avgustovich Shvekhgeimer, our friend and teacher.

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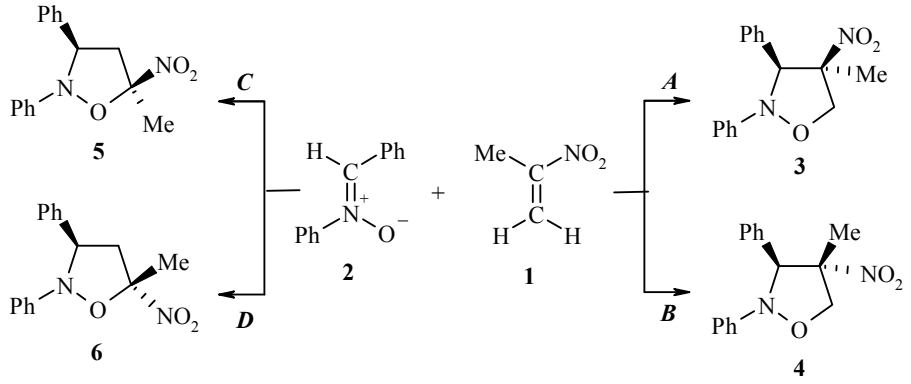

Calculations of the possible reaction pathways were carried out with complete optimization of the geometric parameters using the MOPAC 93 program [13] by the standard AM1 method, as in the case of cycloaddition reactions studied in our previous work [5-8]. The effect of the dielectric medium (toluene and nitromethane) was calculated using the COSMO procedure [14] with NSPA = 42 and RSOLV = 1. The geometrical and energy characteristics of the critical structures corresponding to pathways ***A-D*** are given in Table 1, while the corresponding reaction activation parameters are given in Table 2.

The energy profiles of reactions ***A-D*** in the gas phase are very similar (Fig. 1). Movement of the reaction system along the reaction coordinate from reagents (**1 + 2**) to the corresponding transition states (**TS**) always occurs through shallow local minima (structures **LM**) without overcoming the activation barriers. We should note that structures **LM** are not oriented complexes.

The existence of **LM** on pathways ***A*** and ***B*** is related to a decrease in the enthalpy of the reaction system (ΔH), respectively, by 5.9 and 5.4 kcal/mol, while the corresponding decreases for pathways ***C*** and ***D*** are 4.9 and 6.3 kcal/mol (Table 2). These structures, however, are related exclusively to enthalpy considerations. Consideration of the entropy factor ($T\Delta S$) leads to the circumstance that, at 308 K, the differences in the Gibbs free energy (ΔG) of the corresponding **LM** structures and supermolecule **1 + 2** acquire positive values.

Hence, such structures cannot be stable intermediates at this temperature. There is no charge transfer between the reagents comprising **LM** ($t = 0.0$). The formation of **LM** is probably related to dispersion interactions [16, 17] characteristic of the polar reagent molecules.

The structures of **TS** of reactions ***A-D*** are similar. The formation of new σ-bonds in these structures is synchronous but at different rates. In particular, the distances between the reaction sites C(3) and C(4) in $\mathbf{TS}_{\boldsymbol{A}}$ and $\mathbf{TS}_{\boldsymbol{B}}$ are, respectively, 2.534 and 2.854 Å, while the distances between the atoms C(5) and O(1) are only 1.822 and 1.551 Å (Table 1, Fig. 2). The dipole moments of both **TS** are greater than 6 D, while the charge transfer between the reagents formed them is 0.20 and 0.44 e, respectively (Table 1). These findings indicate the polar nature of both **TS**. However, according to the accepted terminology [18], reactions ***A*** and ***B*** may be considered as concerted processes with normal orbital control.

The **TS** of reactions ***C*** and ***D*** are characterized by much less asymmetry. This is indicated by the distances between the atoms C(3) and C(4) and also between C(5) and O(1) in $\mathbf{TS}_{\boldsymbol{C}}$ and $\mathbf{TS}_{\boldsymbol{D}}$: 2.031 and 2.139 Å, respectively, in $\mathbf{TS}_{\boldsymbol{C}}$ and 2.017 and 2.146 Å, respectively, in $\mathbf{TS}_{\boldsymbol{D}}$. The charge transfer in both cases does not exceed 0.08 e (Table 1).

The calculated activation energies ΔG (Table 2) indicate that reaction ***B*** is favored in the gas phase. The energy barriers on the alternative pathways are more than 5 kcal/mol higher. Unfortunately, there are no experimental results presently related to this problem.

After overcoming the energy barriers, further motion of the reaction system along the reaction coordinates in all four directions lead directly to valleys of the corresponding cycloadducts. This finding unequivocally indicates the concerted nature of reactions ***A-D*** in the gas phase.

TABLE 1. Characteristics of Critical Structures in the [2+3] Cycloaddition of 2-Nitro-1-propene (**1**) to Diphenylnitrone (**2**) from AM1 and AM1/COSMO Calculations

ε	Structure*	*r*, Å					∠ CNO, deg	*t*, e*[2]	μ, D	H_{308}, kcal/mol	S_{308}, cal/(mol·K)
		O(1)–N(2)	N(2)–C(3)	C(3)–C(4)	C(4)–C(5)	C(5)–O(1)					
1.0	**1 + 2**	1.228	1.339	—	1.342	–	124.4	—	—	92.0	171.6
	LM$_A$	1.229	1.337	5.966	1.341	3.265	125.9	0.00	9.01	86.1	109.9
	TS$_A$	1.267	1.359	2.534	1.405	1.822	119.4	0.20	6.71	112.5	112.8
	3	1.346	1.504	1.581	1.546	1.450	108.1	0.05	4.23	67.3	111.3
	LM$_B$	1.228	1.337	4.992	1.342	3.341	126.2	0.00	1.32	86.5	109.7
	TS$_B$	1.301	1.336	2.854	1.442	1.551	122.3	0.44	7.82	108.8	117.3
	4	1.349	1.502	1.580	1.548	1.449	108.5	0.05	2.34	67.2	111.1
	LM$_C$	1.228	1.337	4.830	1.341	4.023	126.2	0.00	8.05	87.1	113.0
	TS$_C$	1.232	1.403	2.031	1.405	2.139	117.7	0.08	7.52	116.6	114.7
	5	1.371	1.507	1.545	1.539	1.443	107.4	0.09	5.57	64.7	111.9
	LM$_D$	1.227	1.338	5.350	1.342	4.380	125.9	0.00	3.33	85.7	107.2
	TS$_D$	1.231	1.403	2.017	1.405	2.146	117.3	0.08	5.92	112.9	111.7
	6	1.351	1.506	1.546	1.539	1.450	108.4	0.05	4.27	62.8	115.3
2.3	**1 + 2**	1.231	1.336	—	1.343	—	125.8	—	—	79.2	169.0
	LM$_A$	1.233	1.335	5.968	1.342	3.276	125.7	0.00	10.16	76.8	110.2
	TS$_A$	1.282	1.330	3.517	1.409	1.719	124.3	0.35	11.47	98.4	116.5
	I$_A$	1.320	1.327	3.661	1.454	1.506	122.0	0.59	15.03	94.2	116.9
	TS'$_A$	1.314	1.350	2.605	1.462	1.515	119.6	0.50	10.57	99.7	114.2
	3	1.365	1.498	1.578	1.549	1.447	108.1	0.10	2.75	61.1	108.3
	LM$_B$	1.232	1.335	4.951	1.342	3.369	126.0	0.18	1.41	77.7	109.8
	TS$_B$	1.281	1.327	3.546	1.408	1.745	124.3	0.34	8.99	95.2	113.2
	I$_B$	1.320	1.325	3.445	1.457	1.508	123.0	0.60	11.87	92.8	116.6
	TS'$_B$	1.311	1.342	2.660	1.459	1.521	120.7	0.50	9.16	96.8	117.9
	4	1.349	1.500	1.579	1.544	1.454	108.0	0.07	3.31	58.4	114.7
	LM$_C$	1.233	1.335	5.097	1.342	4.313	125.8	0.00	10.24	76.9	110.9
	TS$_C$	1.230	1.405	1.997	1.407	2.168	117.6	0.10	9.00	108.0	115.4
	5	1.371	1.507	1.545	1.538	1.441	107.7	0.10	6.64	56.7	108.7
	LM$_D$	1.232	1.335	5.347	1.342	4.407	125.8	0.00	4.21	76.8	107.4
	TS$_D$	1.230	1.405	1.993	1.406	2.173	117.4	0.10	7.14	104.8	112.0
	6	1.352	1.506	1.545	1.539	1.449	108.4	0.07	4.94	54.6	112.2
38.2	**1 + 2**	1.244	1.330	—	1.345	—	125.2	—	—	62.8	166.6
	TS$_A$	1.275	1.328	3.858	1.399	1.866	123.8	0.27	14.90	79.1	108.1
	I$_A$	1.331	1.327	3.745	1.478	1.472	121.4	0.69	20.24	68.1	117.5
	TS'$_A$	1.324	1.366	2.445	1.480	1.494	116.4	0.37	11.76	83.0	114.0
	3	1.364	1.496	1.579	1.546	1.448	108.7	0.11	3.85	50.6	114.7
	TS$_B$	1.274	1.329	3.763	1.400	1.871	123.9	0.27	10.40	79.2	110.6
	I$_B$	1.330	1.326	3.594	1.480	1.473	122.1	0.69	15.59	69.1	113.9
	TS'$_B$	1.320	1.363	2.447	1.478	1.498	117.4	0.52	10.49	80.2	114.0
	4	1.350	1.501	1.578	1.543	1.458	108.0	0.10	4.32	48.2	111.8
	TS$_C$	1.198	1.412	1.916	1.412	2.888	122.3	0.37	16.32	94.4	118.4
	5	1.371	1.508	1.544	1.539	1.436	107.9	0.10	8.38	45.5	109.2
	TS$_D$	1.201	1.410	1.904	1.410	2.822	122.5	0.34	13.17	92.4	116.7
	6	1.353	1.507	1.545	1.538	1.447	108.4	0.09	5.96	43.7	112.4

* **I$_A$** and **I$_B$** – intermediates (see Fig. 3).

*[2] Charge transfer calculated using the Leray equation [15].

TABLE 2. Activation Characteristics of the [2+3] Cycloaddition of 2-Nitro-1-propene (**1**) to Diphenylnitrone (**2**) from AM1 and AM1/COSMO Calculations (T = 308°K)

ε	Transition	ΔH	ΔS	ΔG	ΔH	ΔS	ΔG	ΔH	ΔS	ΔG	ΔH	ΔS	ΔG
		A			*B*			*C*			*D*		
1.0	**1+2→LM**	-5.9	-61.7	12.5	-5.44	-61.9	13.0	-4.9	-58.6	12.6	-6.3	-64.4	12.9
	1+2→TS	20.6	-58.8	38.1	16.8	-54.2	33.0	24.6	-56.9	41.5	20.9	-59.9	38.8
2.3	**1+2→LM**	-2.4	-58.8	15.1	-1.6	-59.2	16.1	-2.3	-58.1	15.0	-2.4	-61.6	16.0
	1+2→TS	19.2	-52.5	34.8	16.0	-55.8	32.6	28.8	-53.6	44.8	25.6	-57.0	42.6
	1+2→I	14.9	-52.1	30.5	13.5	-52.4	29.1	—	—	—	—	—	—
	1+2→TS'	20.5	-54.8	36.8	17.6	-51.1	32.8	—	—	—	—	—	—
38.2	**1+2→TS**	16.3	-58.6	33.8	16.4	-56.0	33.1	31.7	-48.2	46.03	29.7	-49.9	44.5
	1+2→I	5.4	-49.2	20.0	6.34	-52.7	22.1	—	—	—	—	—	—
	1+2→TS'	20.2	-52.6	35.9	17.4	-52.7	33.1	—	—	—	—	—	—

* ΔH and ΔG, kcal/mol, ΔS, cal/(mol·K).

The use of toluene (ε = 2.3) as the solvent significantly alters the calculated energy profiles of reactions ***A*** and ***B*** (Fig. 3). In both cases, four critical points are found between the minima of the reagents and products, corresponding to structures $\mathbf{LM}_A$ and $\mathbf{LM}_B$, transition states $\mathbf{TS}_A$ and $\mathbf{TS}_B$, intermediates $\mathbf{I}_A$ and $\mathbf{I}_B$, as well as transition states $\mathbf{TS'}_A$ and $\mathbf{TS'}_B$.

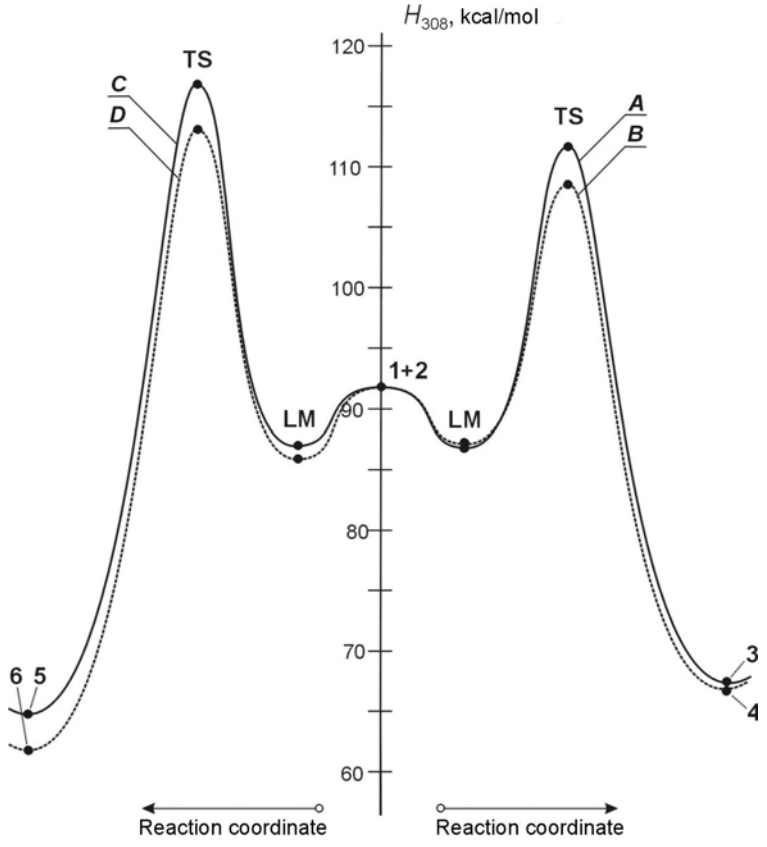

Fig. 1. Energy profiles of the [2+3] cycloaddition of 2-nitro-1-propene (**1**) to (*Z*)-C,N-diphenylnitrone in the gas phase.

A detailed analysis of the geometry of structures $\mathbf{LM}_A$ and $\mathbf{LM}_B$ indicates that these structures are not oriented complexes in either the solvent or gas phase. The enthalpy of the reaction system is reduced less by the formation of $\mathbf{LM}_A$ and $\mathbf{LM}_B$ than in the case of the gas phase (Table 2). As in the gas phase, no charge transfer is observed in toluene between the reagents forming **LM** (Table 1).

Moving along the coordinates of reactions ***A*** and ***B*** from valleys $\mathbf{LM}_A$ and $\mathbf{LM}_B$ toward the valleys of products **3** and **4**, we observe transition states $\mathbf{TS}_A$ and $\mathbf{TS}_B$. The structure of these states is more asymmetrical in the solvent than in the gas phase (Table 1). In particular, the C(5)–O(1) bond length in $\mathbf{TS}_A$ is 1.719 Å, while the distance between reaction sites C(3) and C(4) is 3.517 Å. For $\mathbf{TS}_B$, these values are equal to 1.745 and 3.546 Å, respectively. The charge transfer between the reagent fragments in $\mathbf{TS}_A$ and $\mathbf{TS}_B$ is 0.35 and 0.34 e, respectively, while their dipole moments exceed 9 D. Thus, $\mathbf{TS}_A$ and $\mathbf{TS}_B$ are more polar in the solvent than in the gas phase.

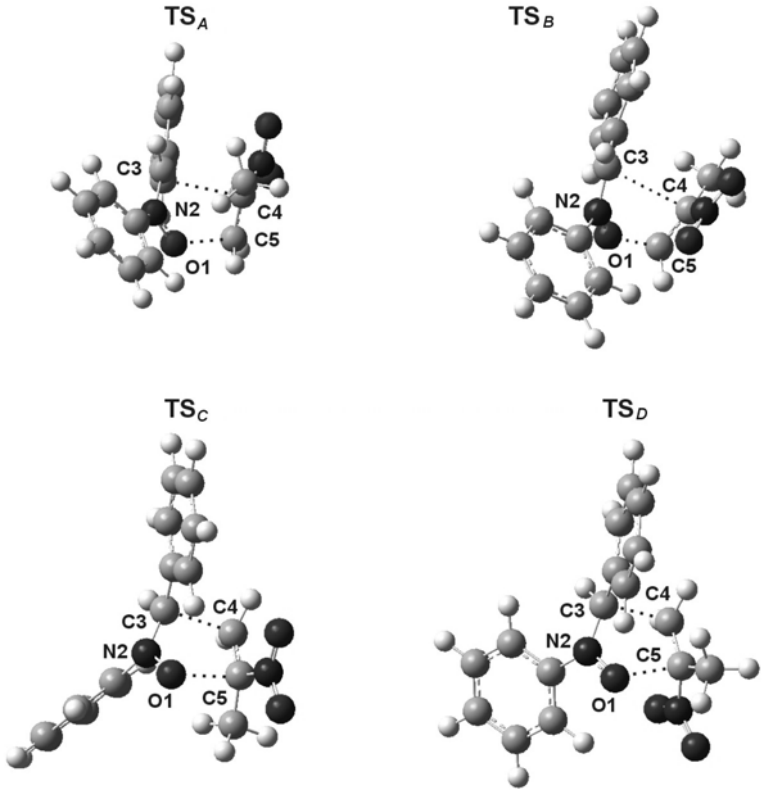

Fig. 2. Transition complexes in the [2+3] cycloaddition of 2-nitro-1-propene to (*Z*)-C,N-diphenylnitrone in the gas phase.

The subsequent critical points on the energy profiles of reactions ***A*** and ***B*** correspond to intermediates $\mathbf{I}_A$ and $\mathbf{I}_B$. The C(5)–O(1) bonds in these structures are almost fully formed with lengths equal to 1.506 and 1.508 Å, respectively. The distances between C(3) and C(4) remain, however, far beyond the limits of values typical for nitroisoxazolidines **3** and **4** (Table 1). The extremely high dipole moments of both intermediates ($\mu > 11$ D) as well as the charge transfer in these species ($t > 0.59$ e) unequivocally indicate their zwitterionic nature.

Transition states $\mathbf{TS'}_A$ and $\mathbf{TS'}_B$ are found upon moving along the coordinates of reactions ***A*** and ***B*** from the valleys of the corresponding intermediates to the valleys of products **3** and **4**. The distances in these transition states between C(3) and C(4) are equal to 2.605 and 2.660 Å, respectively, i.e., much less than in $\mathbf{TS}_A$ and $\mathbf{TS}_B$. The other bonds in the azolidine rings generated differ only slightly. It is interesting to note that charge transfer in $\mathbf{TS'}_A$ and $\mathbf{TS'}_B$ is 1.5 times greater than in $\mathbf{TS}_A$ and $\mathbf{TS}_B$ (Table 1).

Subsequent movement of the system along the reaction coordinates leads directly to minima, corresponding to nitroisoxazolidines **3** and **4**. Thus, The AM1/COSMO calculations indicate that the introduction of toluene into the reaction medium may lead to a change in the reaction mechanism in directions ***A*** and ***B*** from concerted to two-step but does not have a fundamental effect on the profiles of reactions ***C*** and ***D***. As in the gas phase, reaction ***B*** in solution is favored from the viewpoint of kinetics. The activation energy of reaction ***A*** ($\Delta G_A^{\neq}$) is greater than this value for reaction ***B*** ($\Delta G_B^{\neq}$), by 4 kcal/mol. Pathways ***C*** and ***D*** are almost entirely prohibited since $\Delta G_C^{\neq} - \Delta G_B^{\neq} = 12.9$ kcal/mol, while $\Delta G_D^{\neq} - \Delta G_B^{\neq} = 11.3$ kcal/mol.

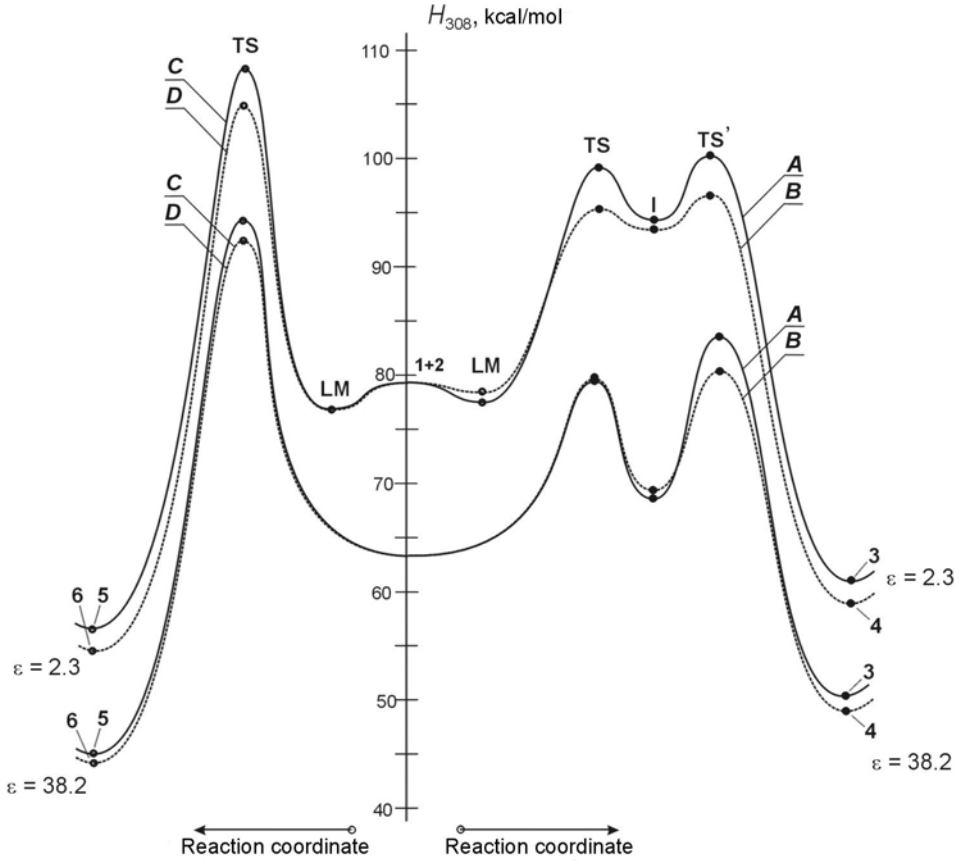

Fig. 3. Energy profiles of the [2+3] cycloaddition of 2-nitro-1-propene to (*Z*)-C,N-diphenylnitrone in the presence of toluene (ε = 2.3) and nitromethane (ε = 38.2).

The use of nitromethane, which is a more polar solvent (ε = 38.2), does not affect the preference for the reaction pathways. Slight changes are found, however, for the energy profiles. In particular, minima for **LM** prereaction complexes do not appear, while the local minima for intermediates $\mathbf{I}_A$ and $\mathbf{I}_B$ are deeper (Fig. 3). Transition states $\mathbf{TS}_C$ and $\mathbf{TS}_D$ also change: they become more asymmetric (Fig. 4) and more polar ($t > 0.34$ e, $\mu > 13$ D) but not so much that the reaction mechanism becomes two-step.

Thus, AM1 and AM1/COSMO calculations of the possible pathways of the [2+3] cycloaddition reactions of 2-nitro-1-propene to (*Z*)-C,N-diphenylnitrone show that the kinetically-preferred product should be 3,4-*trans*-4-methyl-4-nitro-2,3-diphenyl-isoxazolidine **4**. These results are in good accord with our experimental data [19, 20] and also indicate that, in the case of a solvent in the reaction system, the directions leading to the formation of nitroisoxazolidines **3** and **4** may involve a two-step mechanism with a zwitterionic intermediate (Scheme). A detailed study of the reaction kinetics presently underway in our laboratory is necessary to support this hypothesis. These results will be the subject of a separate communication.

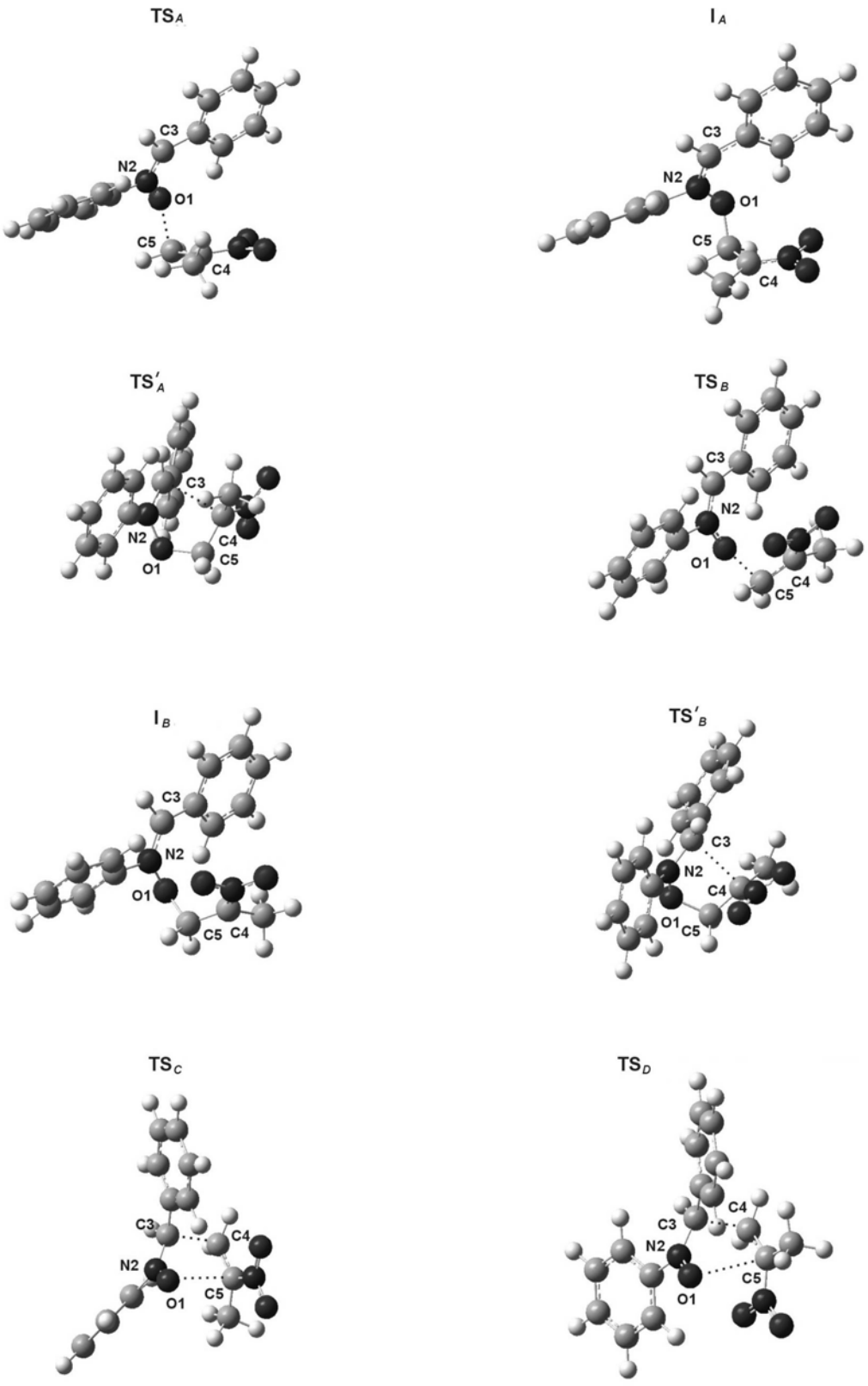

Fig. 4. Selected critical structures in the [2+3] cycloaddition of 2-nitro-1-propene to (*Z*)-C,N-diphenylnitrone in the presence of nitromethane.

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