Probability of Reaction Pathways of Amine With Epoxides in the Reagent Ratio of 1:1 and 1:2

Iryna O. Borysenko
Oles Honchar Dnipro National University: Dniprovs'kij nacional'nij universitet imeni Olesa Goncara
Sergiy I. Okovytyy (sokovyty@icnanotox.org)
Oles Honchar Dnipro National University: Dniprovs'kij nacional'nij universitet imeni Olesa Goncara
https://orcid.org/0000-0003-4367-1309
Jerzy Leszczynski
Jackson State University

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Abstract

The algorithm for generating and estimating the probability of possible reaction pathways for multichannel bimolecular interactions was used to predict the reaction products in the reagent ratio of 1:1 and 1:2. Here we have considered the possible reaction pathways of the reaction of amine ((1S,2S,4S)-bicyclo[2.2.1]hept-5-en-2-ylmethanamine (1) with epoxides (2-((cyclohexyloxy)methyl)oxirane (2), 2-(phenoxymethyl)oxirane (3), (N-(oxiran-2-ylmethyl)-N-phenylbenzenesulfonamide 8) in order to explain experimental observed data, which indicate differences in the reactivity of glycidyl ethers and glycidylsulfonamide with framework amines. Based on the proposed algorithm [39], we have investigated the reaction in the reagent ratio of 1:1 and 1: 2. Calculated values of activation barriers indicate a low probability of formation of interaction products of amine (1) with epoxide (8) with a (1:2) reagent ratio due to steric hindrances in the reaction center.

Introduction

Mono- and diepoxide compounds have gained wide popularity due to the broad range of their applications as building blocks for the construction of biologically active systems [1–5], monomers for highly biocompatible and biodegradable polymers [6–11], bases for adhesives [12], and modifiers of polymer compositions [13]. Epoxy cycle opening reactions can be considered as model in the study of complex processes of crosslinking of epoxy monomers with hardeners or their polymerization. In this regard, the study of the mechanisms of opening of the epoxy cycle is undoubtedly an important and urgent task of modern chemistry.

Experimental studies [14, 15] have shown that the interaction of amine ((1S,2S,4S)-bicyclo[2.2.1]hept-5-en-2-ylmethanamine (**1**) with epoxides (2-((cyclohexyloxy)methyl)oxirane (**2**), 2-(phenoxymethyl)oxirane (**3**) forms a mixture of products that correspond to reactions with a ratio of reagents 1:1 and 1:2 (amino alcohols **4, 5** and **6, 7**, respectively, Scheme 1). While in the case of epoxide (N-(oxiran-2-ylmethyl)-N-phenylbenzenesulfonamide **8**) the reaction ends with the formation of product (**9**), that corresponds to a reagent ratio 1:1.

For such compounds, the study of mechanism and the dependence of the ratio of products on the ratio of the initial reagents was already published [15]. The aim of this work was to study the possible reaction pathways of the aminolysis of epoxides (**2, 3, 8**) considering the conformational lability of the reagents in order to explain the experimentally observed formation of products (**6, 7**) and the absence of product (**10**).

Over the last decades several computer assisted automatic methods for systematic searching reaction pathway and determining reaction mechanisms have been proposed. Among these methods the following should be noted: anharmonic downward distortion following (ADDF) method [16–19]; artificial force-induced reaction (AFIR) method [20–24]; transition state search using chemical dynamics simulations (TSSCDS) method [25–28]; the ZStruct2 method developed by Zimmerman's research group

[29–31]; and molecular dynamics and coordinate driving (MD/CD) method proposed by Li and coworkers [32]. Since each method for searching reaction pathway aims to provide a balance between high accuracy, comprehensive potential energy surface search and low computational costs, the development of new, efficient algorithms for studying reaction paths remains an urgent issue for computational chemistry.

Computational Details

The program PCModel v 9.2 [33] was used to perform conformational analysis at the MMX force field level [34]. Conformational search calculations were carried out using the GMMX technique.

Semi-empirical calculations by PM7 [35] method were carried out using MOPAC2016 [36] program, DFT calculations at the M062X/6-31G(d) [37] level of theory were performed using the Gaussian 16 program [38]. Barrier heights evaluated at semi-empirical level were calculated using PM7-TS method as single point calculations based on PM7 geometry. Vibrational frequencies were calculated for all stationary points to confirm whether the optimized geometry corresponds to a minimum or a TS. The solvent effect, where mentioned, was taken into account by consideration of a solute molecule surrounded by several solvent molecules.

Results And Discussion

In order to study the features of aminolysis of epoxides (**2, 3, 8**) we applied the algorithm for generation and assessment of probability of possible reaction pathways for multiple channel bimolecular interactions proposed in our previous study [39], which was devoted to the interaction of epoxide (**2**) with amine (**1**) to obtain glycidyl ether (**4**).

This algorithm includes conformational search for reaction intermediate using Molecular Mechanics (MMX) approach, based on the obtained conformation construction of structures of transition states and pre-reaction complexes, and calculation of activation energies to further determine the probable reaction pathways.

In this work, initially, we studied the reaction of amine (**1**) with epoxides (**3, 8**) in the ratio of reactants 1:1. Then the investigation of the reaction in the ratio of reagents 1:2 was carried out according to the analogous procedure.

The reaction we have considered proceeds through S_N2-like mechanism forming bipolar ion (**5i,9i**) as an intermediate on the rate-limiting endorgonic stage (Scheme 2).

Located conformations of bipolar ions (**5i, 9i**) could be straightforward applied for construction of starting geometry for optimization of transition states of the corresponding reactions. This statement follows from Hammond’s postulate which states that in the case of endorgonic stage the geometry of the intermediate should be close to the geometry of the transition state.

The proposed strategy consists of the following steps:

(I) Conformational analysis of intermediates (**5i, 9i**) using Molecular Mechanics (MMX) approach.

(II) Construction of starting geometries for TS localization based on the most stable conformations of the intermediates (**5i, 9i**) by setting up C-O and C-N bond lengths close to model aminolysis reaction [39].

(III) Locating TSs and pre-reaction complexes at semi-empirical (PM7) level followed by calculations of activation barriers using PM7-TS method. In the case when the optimization of TSs yielded the structures already existing in the set, they were excluded from the sample.

(IV) Locating TSs, pre-reaction complexes at M062X/6-31G(d) level of theory. As starting geometries, we have used TS geometries that had been obtained in the step (III). Similarly, to step (III), the repeating structures were excluded from the sample.

(V) The reaction paths obtained by M062X/6-31G(d), whose contributions to the overall rate constant were the largest, have been selected for calculation of reaction paths considering the influence of the solvent.

Let us now apply the strategy described in the steps I-V in more details for reaction of amine (**1**) with epoxides (**3, 8**). The assumed ratio of reactants is 1:1.

Conformational analysis

Calculations were carried out using MMX force field within GMMX technique as implemented in PCModel v 9.2 program.

Since the conformational transitions in the intermediates (**5i,9i**) are associated with rotation around the bonds, in order to generate the initial structures by the GMMX method the algorithm that randomly selects a subset of the bonds intended for rotation was chosen. The N-C-C-O torsion angle value was fixed at 180° because this angle value corresponds to the trans-opening state of the epoxy ring. All other torsion angles were used to create conformations by the GMMX method. Based on the previous study [39] for GMMX calculation the value of energy window equal to 40 kJ/mol was chosen.

Of all the found conformations we were interested in the most stable conformer with the highest population. The total number of conformations selected for further localization of transition states for possible pathways was equal to 15 in case of intermediate (**5i**) and 11 in case of intermediate (**9i**).

Locating of TSs and pre-reaction complexes at semi-empirical (PM7) level

Geometry of conformations from previous step has been modified by setting up length of forming N-C and breaking O-C bonds lengths equal to 1.782 Å and 1.999 Å, respectively. This corresponds to the transition state geometry parameters of model reaction (interaction of methylamine with oxirane) (see [39]).

After localization of TS structures and exclusion of repeating ones the pre-reaction complexes and energy barriers were calculated. Table 1 shows obtained activation barrier values for the first step of aminolysis reaction and contributions of each routes to the total reaction rate constant. The overall contributions to the total reaction rate constant (k_i) were calculated using equation (1).

$$k_i = \frac{\exp(-\Delta G_i / RT)}{\sum_i \exp(-\Delta G_i / RT)} \qquad (1)$$

According to PM7 method the largest contribution of 66.9% to the total reaction rate is made by TS that corresponds to the reaction path number 4 in the case of intermediate (**5i**). For intermediate (**9i**) the largest contributions to the total reaction rate equal to 45.0 and 43.0 % are made by TSs that correspond to the reaction paths 6 and 7.

For all these transition states, the presence of a hydrogen bond (NH•••O) is observed, which leads to the stabilization of the structure (Figure 1).

Table 1. The values of PM7 heat of formation (kJ/mol), the activation energy (kJ/mol) calculated at PM7-TS and M062X/6-31G(d) levels of theory. Conformers of intermediate (**5i, 9i**) for possible reaction channels and the contribution of located pathways to overall rate constant of the reaction of amine (**1**) with epoxide (**3, 8**) are included.

Intermediate	Pathway	PM7		M062X/6-31G(d)	
		$\Delta H^{\neq}$ PM7-TS, kJ/mol	k_i,%	$\Delta E^{\neq}$zpc, kJ/mol	k_i,%
5i	1	156.4	0.0	149.3	0.8
	2	139.2	9.3	-	-
	3	149.1	0.2	-	-
	4	134.3	**66.9**	142.3	14.4
	5	148.8	0.2	141.9	16.9
	6	151.0	0.1	151.4	0.4
	7	140.7	5.0	149.5	0.8
	8	137.5	18.0	138.5	**66.7**
	9	147.4	0.3	145.2	4.4
9i	1	136.9	3.7	147.0	0.0
	2	135.0	8.0	129.2	19.2
	3	159.0	0.0	136.0	1.3
	4	149.1	0.0	131.7	7.3
	5	143.7	0.2	141.4	0.1
	6	130.7	**45.0**	137.2	0.8
	7	130.8	**43.1**	127.8	**33.7**
	8	157.0	0.0	127.6	**37.6**
	9	191.4	0.0	147.0	0.0

Study of reaction in vacuo at M062X/6-31G(d) level of theory

The starting geometries for the localization of transition states were structures obtained by the PM7 method.

All of 18 possible reaction paths obtained for intermediates (**5i, 9i**) by the PM7 method were studied at the M062X/6-31G(d) level of theory. After excluding TSs with the same geometries, 7 TS conformations were obtained for intermediate (**5i**) and 9 for intermediate (**9i**).

Starting geometry for optimization of pre-reaction complexes was generated by displacement of atoms in the TS structures along imaginary normal vibrational mode. The activation barriers were calculated for each reaction channel (Table 1).

The largest contribution of 66.7% to the total reaction rate is made by TS of intermediate (**5i**) that corresponds to path 8. In accordance with the results for intermediate (**9i**) the largest contributions to the reaction rate (33.7 and 37.6%) are from the TS conformations that correspond to paths 7 and 8 respectively. The structures of these TS conformations are shown in Figure 2.

The most energetically favorable reaction paths were also examined considering solvent effects.

Study of reaction with 1:2 reagent ratio in vacuo

The procedure for studying the aminolysis reaction with 1:2 reagent ratio was similar to that described above for 1:1 reagent ratio. Let us discuss the obtained results.

At the first step we carried out conformation search for intermediates (**6i,7i,10i**) (Scheme 3). For these intermediate **6i, 7i, 10i** the number of unique conformations was 41, 7, and 8, respectively.

At the second step of the study, the transition states and pre-reaction complexes for each found conformer of all three intermediates were localized at PM7 and M062X/6-31G(d) levels of theory. Subsequently, the activation barriers of possible reaction channels and the contribution of each TS to the total reaction rate were calculated. As can be seen from Table 2 the results of the semi-empirical and the DFT methods are slightly different. The largest contribution to the overall reaction rate for intermediate **6i** is from the TSs number 22 (80.4%) obtained by PM7 method. However, at the M062X/6-31G(d) level the TS 24 has the largest input of 21.8%. For intermediate **7i** at the PM7 level the largest contribution to the overall reaction rate (94.9%) is from the TS number 4. Interestingly, M062X/6-31G(d) method predicts TS number 1 to have the highest contribution. In case of intermediate **10i** the largest contributions to the overall reaction rate equal to 25.7 and 54.3% are from TSs number 6 and 7 as obtained by PM7 method. M062X/6-31G(d) method showed that TSs number 1 and 7 have the greatest contribution to the rate of reaction equal to 59.1 and 40.0%, respectively. The structures of these TS conformations are shown in Figure 3.

Study of reaction with explicit consideration of solvent at M062X/6-31G(d) level of theory

Since the experimental reaction was carried out in the presence of the protic solvent 2-propanol [15], the specific solvation with solvent was modelled in this study by adding two molecules of alcohol to the investigated molecular system. The initial position of solvent molecules in the transition state can be characterized by the formation of hydrogen bonds between alcohol and epoxide, alcohol and alcohol, alcohol and amine molecules. The structures of the transition states of the formation of aminoalcohols in the presence of the solvent (**5,6,7,9,10**) are given in Figure 4, and their cartesian coordinates are included in the Supporting Information.

The participation of two alcohol molecules leads to the relay transfer of a proton from the nitrogen atom of amine to oxygen atom of epoxide along the chain of solvent molecule. Thus, simultaneous activation of epoxide and amine by two solvent molecules occurs and leads to lower activation barrier of the reaction by 23.2 – 64.8 kJ/mol (Table 3).

All reactions with a reagent ratio of 1:1 are characterized by barriers from 127.6 to 139.0 kJ/mol *in vacuo*, and from 66.6 to 91.5 kJ/mol within explicit consideration of solvent molecules. For reactions with a reagent ratio of 1:2 the values of $\Delta E^{\neq}$ are also close to those predicted for the 1:1 ratio and range from 117.5 to 128.5 kJ/mol *in vacuo* and 78.1 to 94.3 kJ/mol within explicit consideration of solvent molecules.

In the case of the interaction of epoxide (**8**) with amine (**1**), the value of the activation energy at the reagent ratio 1:2 is higher by 11.6 – 27.7 kJ/mol than the corresponding values predicted for the ratio of 1:1. The obtained results are consistent with the experimental data, according to which in this case only the product of the interaction with the 1:1 reagent ratio is formed. The plausible reason for the observed increase in the energy barrier is the large steric hindrance for the interaction of bulk reagents in a process characterized by 1:2 reagent ratio. The obtained activation barriers are consistent with experimental data, which indicate differences in the reactivity of glycidyl ethers and glycidylsulfonamide with framework amines.

Table 2. The values of PM7 heat of formation (kJ/mol), the activation energy (kJ/mol) calculated at PM7-TS and M062X/6-31G(d) levels of theory. Conformers of intermediate (**6i, 7i, 10i**) for possible reaction channels and the contribution of located pathways to overall rate constant of the reactions of glycidyl ethers (**4,5)** with epoxide (**2,3**) and glycidylsulfonamide (**9**) with epoxide (**8**) are included.

Intermediate	Pathway	PM7		M062X/6-31G(d)	
		$\Delta H^{\neq}$ PM7-TS, kJ/mol	k_i,%	$\Delta E^{\neq}zpc$, kJ/mol	k_i,%
6i	1	160.2	0.0	131.9	5.6
	2	146.2	9.9	132.8	4.0
	3	187.5	0.0	139.7	0.2
	4	181.2	0.0	143.7	0.1
	5	150.1	2.1	150.7	0.0
	6	173.4	0.0	147.1	0.0
	7	152.1	0.9	132.6	4.2
	8	149.8	2.4	131.9	5.5
	9	160.4	0.0	129.7	13.5
	10	159.1	0.1	132.6	4.2
	11	160.8	0.0	143.1	0.1
	12	154.4	0.4	132.8	3.9
	13	172.1	0.0	138.3	0.4
	14	162.3	0.0	130.7	9.1
	15	176.3	0.0	141.5	0.1
	16	165.8	0.0	142.3	0.1
	17	164.8	0.0	133.8	2.6
	18	185.1	0.0	148.5	0.0
	19	166.9	0.0	143.1	0.1
	20	177.4	0.0	172.8	0.0
	21	201.0	0.0	146.6	0.0
	22	141.0	**80.4**	132.9	3.8
	23	155.0	0.3	145.5	0.0
	24	167.7	0.0	128.5	**21.8**
	25	199.3	0.0	141.7	0.1
	26	190.7	0.0	164.1	0.0

	27	163.3	0.0	142.6	0.1
	28	161.3	0.0	148.9	0.0
	29	160.3	0.0	132.5	4.4
	30	149.2	2.9	148.5	0.0
	31	210.5	0.0	132.1	5.2
	32	162.7	0.0	139.4	0.3
	33	211.2	0.0	146.2	0.0
	34	182.3	0.0	139.8	0.2
	35	165.3	0.0	156.9	0.0
	36	161.3	0.0	138.2	0.4
	37	155.1	0.3	130.5	9.9
	38	155.5	0.2	146.3	0.0
	39	224.8	0.0	149.9	0.0
	40	160.1	0.0	155.0	0.0
	41	245.0	0.0	158.7	0.0
7i	1	163.6	3.3	123.4	**99.5**
	2	207.7	0.0	139.8	0.1
	3	185.9	0.0	139.5	0.2
	4	155.3	**94.9**	143.6	0.0
	5	165.2	1.7	148.9	0.0
	6	183.9	0.0	138.6	0.2
	7	242.0	0.0	162.3	0.0
10i	1	233.1	0.0	117.5	**59.1**
	2	179.1	0.0	155.4	0.0
	3	153.3	16.8	134.1	0.1
	4	157.5	3.1	128.2	0.8
	5	235.0	0.0	137.2	0.0
	6	152.3	**25.7**	151.7	0.0
	7	150.4	**54.3**	118.5	**40.0**

	8	200.5	0.0	142.6	0.0

Table 3. Calculated values of activation energy for the most favorable pathways of aminolysis reactions with a reagent ratio of 1:1 and 1:2 calculated by M062X/6-31G(d)

Structure of epoxides	Intermediate	Pathway	reagent ratio	*in vacuo* for rate-limiting stage	Explicit consideration of two 2-propanol molecules
				$\Delta E^{\neq}$kJ/mol	$\Delta E^{\neq}$kJ/mol
2	-	-	1:1	139.0*	74.2
	6i	24	1:2	128.5	80.1
3	5i	8	1:1	138.5	84.0
	7i	1	1:2	123.4	72.0
8	9i	8	1:1	127.6	66.6
		7	1:1	127.8	91.5
	10i	1	1:2	117.5	94.3
		7	1:2	118.5	78.1

*Data from [39]

Conclusions

Conformational analysis of primary products of reactions could be considered as general procedure for generation of transition state structures in the case of multiple channel reactions. Method of generation of transition state structures for multiple channel reactions that considers the high conformational mobility of the reactants and the possibility of varying their orientation during the reaction was tested in this study. Conformational analysis of investigated epoxy esters derivatives, conducted using method of molecular mechanics MMX, revealed structures with the lowest energies – the most stable conformers of primary products of epoxy compounds aminolysis. Transition state structures for the reaction of aminolysis of glycidyl ethers and glycidylsulfonamides with frame amines were localized using quantum-chemical methods PM7 and M062X/6-31G(d). Formation of 1:1 and 1:2 products of glycidyl eters aminolysis are determines by steric effect and formation of N-H•••O hydrogen bond in transition state. Calculated values of activation barriers indicate a low probability of formation of interaction products of amine with epoxyglycidylsulfonamides with a 1:2 reagent ratio, which is consistent with and explains experimental data.

Declarations

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Conflicts of interest/Competing interests

The authors declare that they have no conflict of interest.

Availability of data and material

Additional data (Cartesian Coordinates and Gibbs free energies of TS conformations from the M062X/6-31G(d) calculation) are available as Supplementary Information.

Code availability

Not applicable.

Authors' contributions

All authors contributed to the study conception and design. Material preparation, data collection, computer simulation were performed by Iryna O. Borysenko. Analysis of the obtained data was performed by Iryna O. Borysenko, Sergiy I. Okovytyy and Jerzy Leszczynski. The first draft of the manuscript was written by Iryna O. Borysenko and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Scheme

Please see the Supplementary Files for the Scheme 1, 2 and 3.

Figures

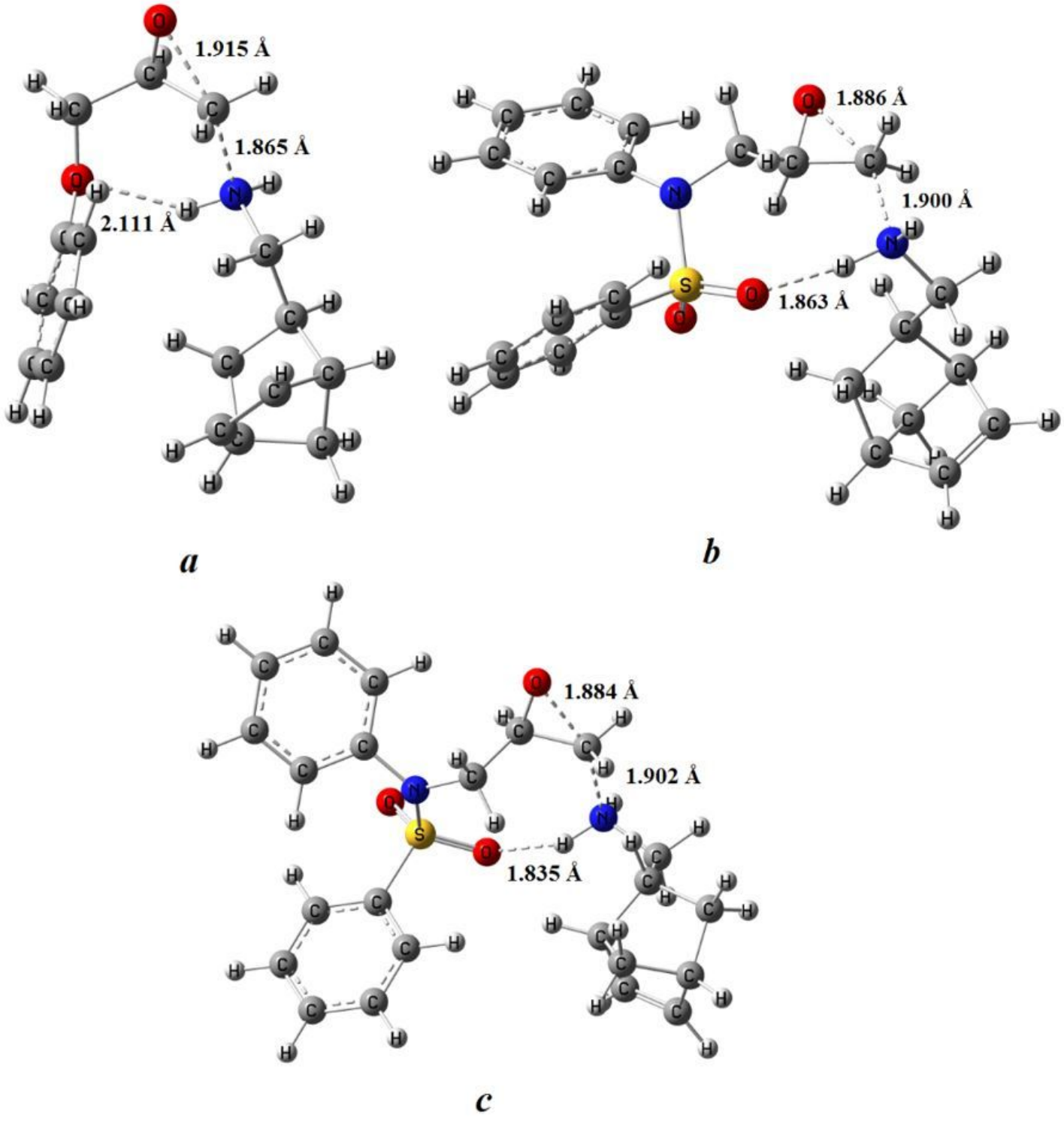

Figure 1

TS structures that correspond to the most energetically favorable reaction paths for aminolysis of epoxides (**3,8**) with 1:1 reagent ratio in vacuo calculated by the PM7 method: *a* – intermediate **5i** path 4; *b* – intermediate **9i** path 6; *c* – intermediate **9i** path 7.

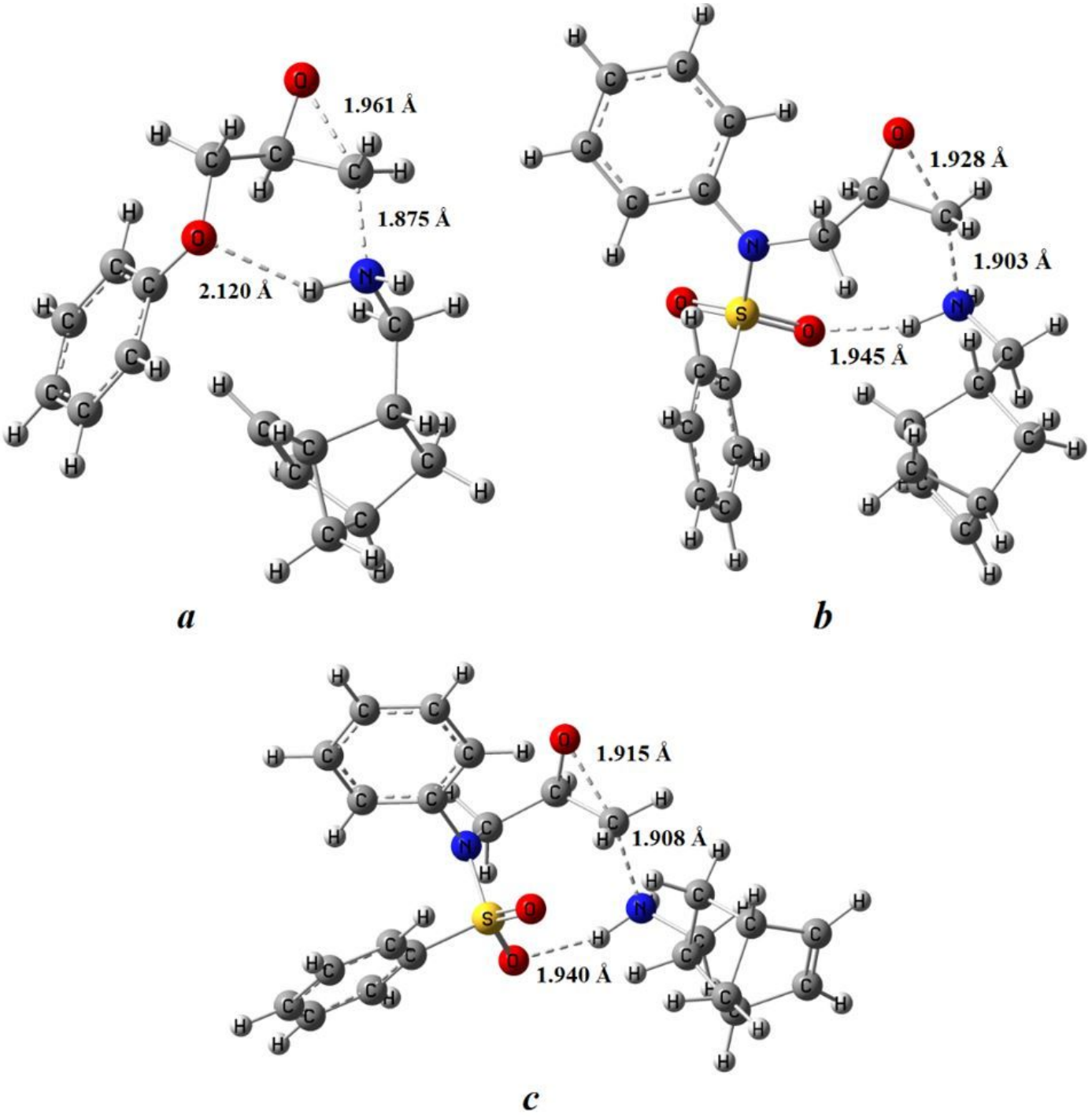

Figure 2

TS structures corresponding to the most energetically favorable reaction paths for aminolysis of epoxides (**3**,**8**) with 1:1 reagent ratio in vacuo calculated by M062X/6-31G(d) method: *a* – intermediate **5i** path 8; *b* – intermediate **9i** path 7; *c* – intermediate **9i** path 8.

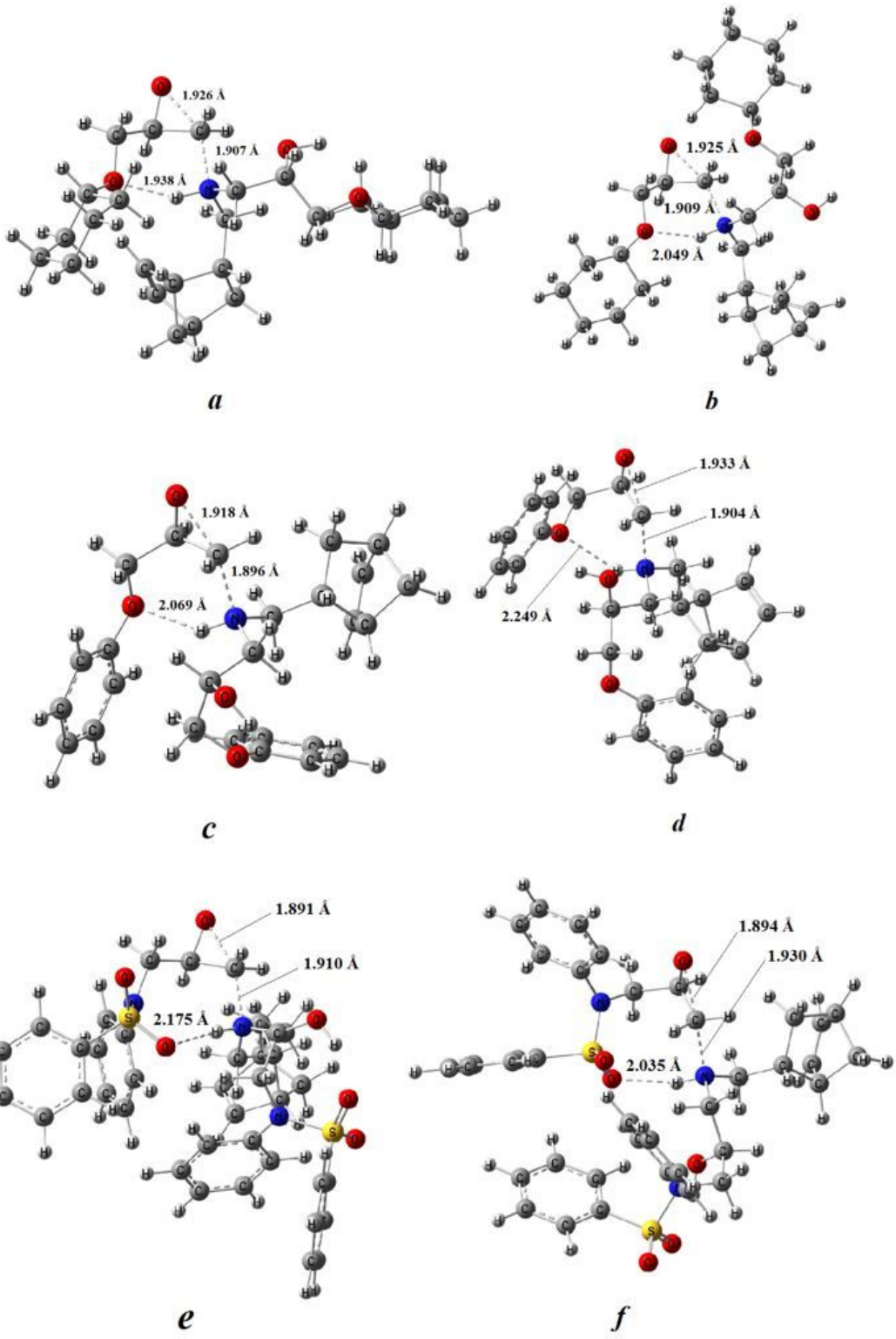

Figure 3

TS structures that correspond to the most energetically favorable reaction paths for aminolysis of epoxides (**3,8**) with 1:2 reagent ratio in vacuo calculated by PM7 and M062X/6-31G(d) method:

a – intermediate **6i** path 22 (PM7); *b* – intermediate **6i** path 24 (M062X/6-31G(d)); *c* – intermediate **7i** path 4 (PM7); *d* – intermediate **7i** path 1 (M062X/6-31G(d)); *e* – intermediate **10i** path 7 (PM7); *f* –

intermediate **10i** path 1 (M062X/6-31G(d)).

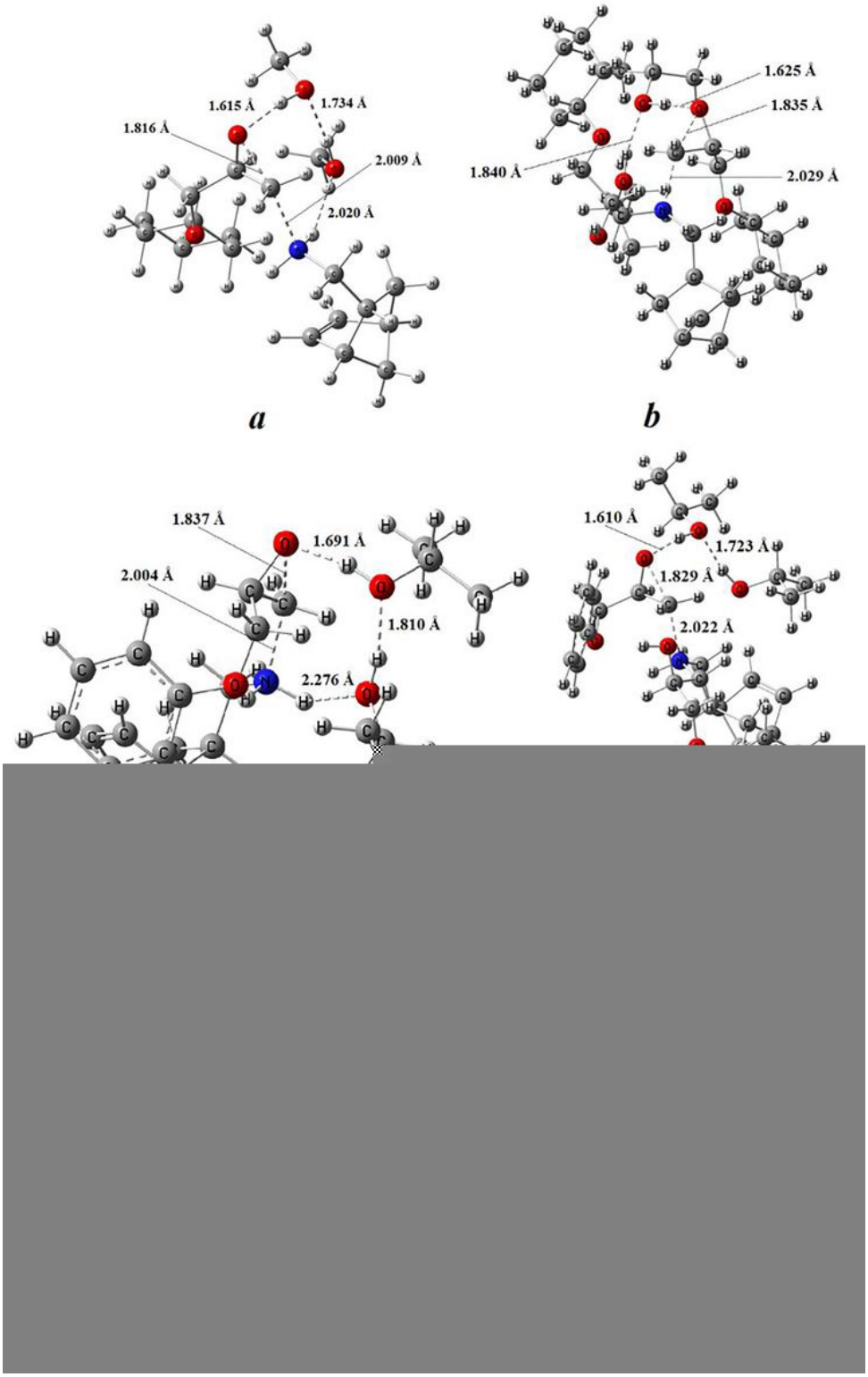

Figure 4

TS structures that correspond to the most energetically favorable reaction paths for aminolysis of epoxides (**2,3,8**) with a 1:1 and 1:2 reagent ratio with explicit consideration of solvent calculated by M062X/6-31G(d) method: *a* – epoxide **2**, 1:1 reagent ratio [39]; *b* – epoxide **2**, 1:2 reagent ratio; *c* – epoxide **3**, 1:1 reagent ratio; *d* – epoxide **3**, 1:2 reagent ratio; *e* – epoxide **8**, 1:1 reagent ratio; *f* – epoxide **8**, 1:2 reagent ratio.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- scheme1.jpg
- scheme2.jpg
- scheme3.jpg
- Supplementary.docx