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The supermolecule method, as applied to studies of liquid-phase reaction mechanisms taking cyclocarbonate aminolysis in dioxane as an example: specific features

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The supermolecule method was used to describe the mechanism of liquid-phase processes taking the reaction of ethylene carbonate with methylamine as an example. Specific features of the approach are considered. The problem of choosing the reference point for calculating the relative energies of individual reaction steps was solved by introducing the idea of the structure of noninteracting solvated reactants. In this case, no basis set superposition error (BSSE) correction is required because the solvated reactants, the pre-reaction complex, and the transition state have the same atomic composition and are calculated in the same basis set. To calculate the title reaction in dioxane by the supermolecule method with acceptable accuracy, it is sufficient to consider one solvent molecule.

Key words: supermolecule method, solvation, activation energy, complexation energy, pre-reaction complex, aminolysis, cyclocarbonate, density functional theory (DFT), reaction mechanism, basis set superposition error (BSSE), entropy.

Theoretical studies on the mechanisms of chemical reactions in solutions are most often carried out using quantum chemical calculations with continuum models,[1,2] the supermolecule approximation,[1—3] and the molecular dynamics and Monte-Carlo methods.[1,2] The main drawback of the continuum models, the molecular dynamics, and the Monte-Carlo methods consists in the impossibility to account for specific intermolecular interactions between reactants and the solvent.

Specific interactions influence the energy barriers to particular steps of chemical reactions, thus reflecting the effects of the medium. In the supermolecule method, reactant molecules are surrounded by solvent molecules and all specific intermolecular interactions emerge, persist, or change upon any transformations of the reactants inside the supermolecule.

Although the supermolecule method was proposed more than three decades ago,[3] its methodology is far from being well developed, mainly because of high computational cost. In this work, we will consider the following key problems in the method:

1. High computational cost. Calculations of supermolecules require high-performance multiprocessor systems with high storage capacity.

2. Complex shape of the potential energy surface (PES), namely, numerous local minima corresponding to different configurations of the solvent molecules surrounding reactant molecules. The search for all possible configurations requires even more powerful computational facilities.

3. The choice of the reference point for calculating the relative energies. This problem is important for quantum chemical calculations of all reactions, being of crucial importance for investigations of supermolecular systems. In accordance with the classical theory of activated complex it is commonly accepted (especially, in handbooks) that the energies are calculated relative to the sum of the energies of infinitely separated initial reactants.[4,5]

This simplified scheme does not include the pre-reaction complex (**RC**) that exists owing to intermolecular interaction between reactants. In the case of strong intermolecular interaction, the stabilization energy of **RC** can be so high that the energy of the transition state (**TS**) of the subsequent reaction step may be lower than the sum of the energies of infinitely separated initial reactants and the activation energy thus appears to be negative (Fig. 1). Usually, the problem is solved by calculating the activation energy relative to the **RC** energy or by going to the free energy surface. Both approaches have disadvantages. For instance, theory dictates to calculate the energies relative to the sum of the energies of infinitely separated noninteracting reactants, whereas reactants in the **RC** interact with each other and the energy of this interaction should be subtracted from the activation energy.

Yet another problem consists in that for a multichannel reaction, each **RC** corresponds to a particular **TS** on

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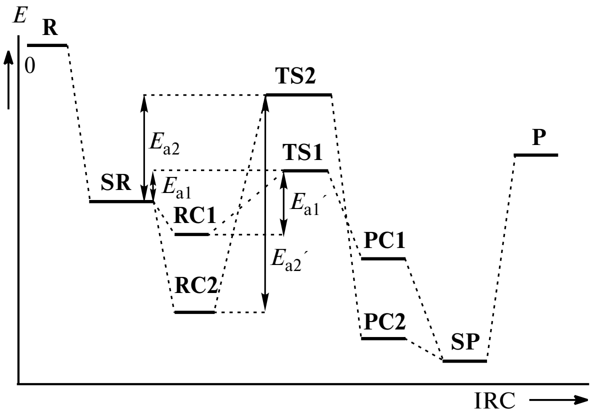


Fig. 1. Energy diagram showing positions of solvated reactants (**SR**), pre-reaction complexes (**RC**), transition states (**TS**), complexed products (**PC**), and solvated products (**SP**) along the **R** → **P** coordinate of the liquid-phase reaction proceeding *via* two concurrent channels with the activation energies E_{a1} and E_{a2}. From this point on **R** denotes infinitely separated initial reactants.

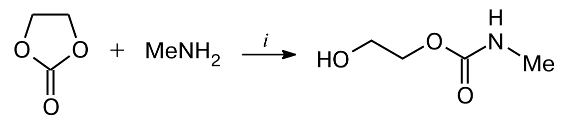
the reaction coordinate (see **RC1** and **RC2** in Fig. 1). The energy barriers to different reaction pathways must be compared using the same reference point for the relative energies and activation energies (we believe that calculations of E_{a1}' and E_{a2}' relative to the energies of **RC**s are incorrect). In this work, we introduce a new reference point on the PES for calculating the relative energies and propose a method for the determination of this point. This reference point corresponds to noninteracting solvated reactants (**SR**, see Fig. 1).

4. The basis set superposition error (BSSE). A supermolecule can consist of a large number of fragments. Therefore, calculations of the energy of formation of the supermolecule from individual molecules require a correct inclusion of the BSSE.

5. Taking account of entropy effects. In some sense, one can take it that the **RC** is formed as the system goes from the gas phase to solution.[6,7] Since the process is essentially a disorder—order transition, it is entropically unfavorable. The formation of an ordered structure does not contradict the concept of a liquid as a system with short-range order.[8] Taking account of entropy and going to the free energy surface causes the energy scale to be shifted in such a manner that the energies calculated relative to the sum of the energies of infinitely separated initial reactants be positive. However, this does not allow one to choose the reference point on the PES because the free energies of activation are also calculated relative to the **RC** energies.

In this work, the problems mentioned above are considered taking methylamine addition to ethylene carbonate in dioxane (Scheme 1) as an example.

Scheme 1



i. Dioxane.

The mechanism of this reaction is of interest in connection with the search for alternative, environmentally safe methods for the synthesis of polyurethanes using no toxic isocyanates. The process has been well-studied experimentally and theoretically.[9—12] All compounds facilitating proton transfer between reactants in the course of nucleophilic addition to carbonyl group, *e.g.*, proton-donating solvents, such as alcohols, can serve as catalysts.[12] The reaction also proceeds smoothly in the catalyst-free regime and its kinetics can be studied experimentally.

The dependence of the apparent rate constant for the reaction in dioxane on the concentration of *n*-butylamine is given by the expression[11,12]

$$k_{\mathrm{app}} = k_1[\mathrm{BuNH_2}] + k_2[\mathrm{BuNH_2}]^2.$$

It follows that there are two main reaction pathways, with participation of one and two amine molecules. The kinetic data agree with the results of quantum chemical calculations, namely, the reaction can proceed through two paths, one involving one and the other involving two amine molecules, each path being consisted of several additional pathways corresponding to single- and multistep reaction mechanisms.[9,10]

In the text below we will consider only some simplest reaction pathways assuming that the energies of other pathways are somewhat lower or higher (in accordance with our previous calculations). The lowest energy barriers to the channels with participation of one and two amine molecules calculated for the gas phase are 33 and 22 kcal mol^{-1}, respectively.[9,10] These theoretical barriers are much higher than the experimental activation energies for the reaction in dioxane; namely, the effective activation energies are 14.0±0.3 (for k_1) and 3.7±0.2 (for k_2) kcal mol^{-1}.[12]

Calculation Procedure

Quantum chemical calculations were carried out within the framework of the density functional theory (DFT) using (i) the nonempirically generalized gradient approximation, the PBE functional,[13,14] and the TZ2P basis set by the PRIRODA program[15,16] and (ii) the B3LYP functional[17] and the 6-311G(d,2p) basis set by the Gamess Firefly v.8.0.0 program[18] based on the Gamess (US) program.[19] Geometry optimization was performed for all starting reactants, stable intermediates, and transition states. The characters of the stationary points found (minima and saddle point on the PES) were determined by calculating the eigenvalues of the matrix of the second energy derivatives with respect to the nuclear coordinates. Correspondence between a particular **TS** and a transformation under study was established by calculating the intrinsic reaction coordinate (IRC).

The BSSE corrections were calculated using the counterpoise method taking into account the changes in the geometries of the components in the complexes.[20,21] Since no methods for BSSE calculations are implemented in the PRIRODA program, the BSSE corrections were calculated only using the GAMESS program.

Results and Discussion

BSSE corrections for calculations of the complexation energies and activation energies. The BSSE concept has long been known and described in detail in the literature.[20,21] However, the applicability of the BSSE correction, methods of calculation, and the correctness of the results obtained upon applying the BSSE correction still remains a moot question.[22—32] Overestimation of the complexation energy originates from the overlap of AOs of the atoms located in the contact area as fragments approach one another. This leads to their interaction and, as a result, atoms of one fragment can use the basis set functions of another fragment and *vice versa*, although individual constituents of the complex were calculated in the corresponding own basis sets only. Thus, formally, the constituents of the complex and the complex *per se* are considered in different basis sets.

We studied how the BSSE influences the complexation energy taking a number of two- and four-component complexes with strong (**S1**—**S5**) and weak (**W1**—**W4**) intermolecular interaction (Fig. 2). The weak intermolecular interaction involves van der Waals forces and weak hydrogen bonds between amine molecules and esters. Complexes with strong intermolecular interaction are characterized by stronger hydrogen and ionic bonds. Strong intermolecular interaction occurs between the amine and carboxylic acid molecules. The components were chosen in such a manner that the atomic composition of the complexes be the same and allow one to compare systems with strong and weak intermolecular interaction calculated using the same common basis set. The exception was complex **S5** whose atomic composition is different from that of the other complexes.

The complexation energies calculated by the PBE/TZ2P and B3LYP/6-311G(d,2p) methods with and without inclusion of BSSE, as well as the BSSE values are listed in Table 1. Figure 2 shows the shortest distances

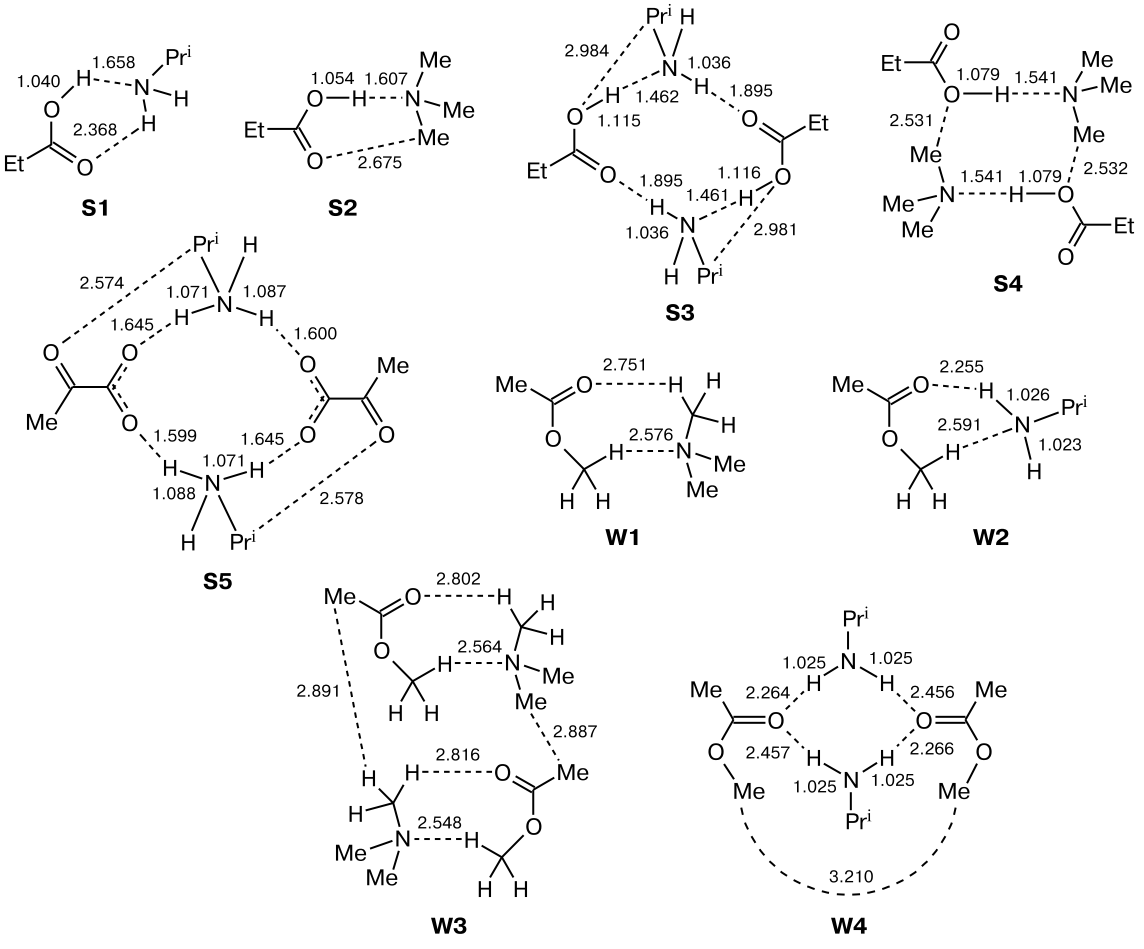


Fig. 2. Structures of complexes with strong (**S1**—**S5**) and weak (**W1**—**W4**) intermolecular interactions. Here and in Fig. 3, shown are the bond length (in Å).

Table 1. Complexation energies (E_c/kcal mol^{-1}) calculated without and with inclusion of BSSE and the BSSE values for complexes **S1**—**S5** and **W1**—**W4**

Complex	N^a	$E_c{}^b$	$E_c{}^c$	E_c + BSSE^c	BSSE^c
S1	2	−12.8	−13.4	−9.6	3.8
S2	2	−12.6	−13.0	−9.4	3.6
S3	4	−36.0	−37.2	−27.1	10.1
S4	4	−28.5	−29.7	−20.4	9.3
S5	4	−54.9	−54.0	−41.1	12.9
W1	2	−2.6	−3.6	−1.3	2.3
W2	2	−3.7	−5.0	−2.3	2.7
W3	4	−6.6	−9.0	−2.4	6.6
W4	4	−11.7	−14.9	−7.4	7.5

[a] Number of fragments.

[b] Calculated by the PBE/TZ2P method.

[c] Calculated by the B3LYP/6-311G(2d,p) method.

between the interacting atomic groups and the lengths of bonds with participation of hydrogen atoms calculated in PBE/TZ2P approximation.

The complexation energies calculated by the two methods are by and large in good agreement. The energy difference is at most 1.2 kcal mol^{-1} for complexes **S1**—**S5**, being higher (to 3.2 kcal mol^{-1}) for systems **W1**—**W4**. It is noteworthy that, irrespective of the strength of intermolecular interaction, the BSSE values calculated for the complexes of the same composition (**S1**, **S2**, **W1**, **W2** and **S3**, **S4**, **W3**, **W4**) in the same common basis sets are of the same order of magnitude. The BSSE values depend on the distances between the atoms through which fragmentation of the complexes occurs and increase as intermolecular interaction strengthens. Also, it is obvious that the BSSE is not too large compared to the complexation energy even provided strong intermolecular interaction (see Table 1); in other words, the problem of negative activation energies persists upon taking into account the BSSE (see Fig. 1).

Besides, complexation can be accompanied by migration of certain atoms from one fragment to another, as in the case of complex **S5**, where NH_2 groups of the initial isopropylamine molecules undergo transformation to ammonium ions through the addition of protons from carboxylic acid components. Then, formal fragmentation of complexes occurs along strong N—H bonds, because the components of the complex differ from the starting reactants. As a consequence, the BSSE is overestimated.

The inclusion of BSSE in the studies of chemical reactions, *i.e.*, the case where one should calculate not only the complexation energies, but also the activation energies, deserves particular attention. Again, one should choose how the activation energies will be calculated, *viz.*, relative to the sum of the energies of infinitely separated original reactants or relative to the **RC** energy. In the former case, the BSSE should be included for the **TS**, which can be formally treated as a "complex" formed by the reactants. In the latter case, it is appropriate to include the BSSE for **RC**. It should also be noted that intermolecular interactions in **RC** and in **TS** are differ appreciably and, hence, the BSSE values will be different.

These assumptions were tested using two **TS** taken from the literature[9—11] as examples (Fig. 3). The **TS1** state is a transition state of the simplest one-step, catalyst-free aminolysis reaction. It is preceded by a weakly bound **RC1** with a formation energy of −4.5 kcal mol^{-1}. The **TS2** state corresponds to the first step of a multistep reaction involving two amine molecules and a catalyst (acetic acid). This transition state is preceded by a sufficiently stable **RC2** with strong intermolecular interaction and a complexation energy of −29.4 kcal mol^{-1}.

The calculated energies of formation of **RC**s and the activation energies are shown in Fig. 3 (PBE/TZ2P) and listed in Table 2 (B3LYP/6-311G(d,2p)). A comparison shows good agreement between the complexation energies calculated using two methods, whereas the activation energies calculated relative to the sum of the energies of infinitely separated initial reactants differ considerably. It should be noted that in both cases, the calculated activation energies are higher than the experimental effective ones. Nevertheless, the results obtained confirm the assumption that the BSSE values for **RC**s and **TS**s differ appreciably because intermolecular interactions in **TS**s are stronger than in **RC**s. In the case of **TS2**, the problem of negative activation energies remains unsolved despite the inclusion of BSSE because the correction is much smaller than the complexation energy value.

Thus, the data in Table 2 do not allow one to choose a suitable method for calculating the activation energies. The inclusion of BSSE is ambiguous because the BSSE correction depends on the intermolecular interaction force. In the text below we present yet another, more versatile, method for calculating the relative energies; it requires the introduction of a new type of structures, namely, **SR**s, and excludes calculations of the BSSE.

Table 2. Energies of formation of structures **RC1** and **RC2** (E_c), activation energies (E_a, E'_a) of structures **TS1** and **TS2**, and the BSSE values obtained from B3LYP/6-311G(d,2p) calculations

Structure	BSSE	E_c	$E_a{}^a$	$E_a{}'^b$
	kcal mol^{-1}			
RC1	3.0	−5.6	—	—
RC2	9.5	−30.4	—	—
TS1	5.9	—	35.9	41.6
TS2	12.0	—	−14.0	16.4

[a] Calculated relative to **R**.

[b] Calculated relative to **RC**.

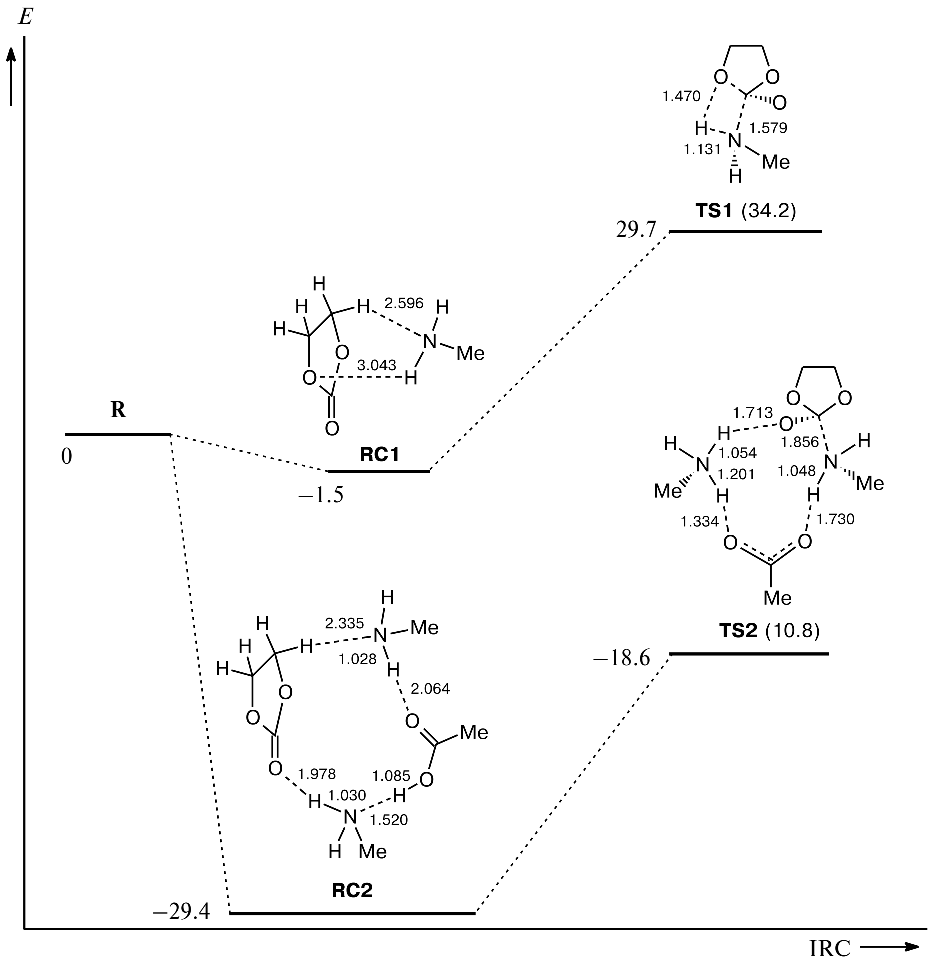


Fig. 3. Energy diagram showing positions of weakly (**RC1**) and strongly (**RC2**) bound pre-reaction complexes and transition states (**TS1** and **TS2**). The activation energies (in kcal mol^{-1}) calculated relative to the corresponding **RC** energies by the PBE/TZ2P method are given in parentheses.

Energy calculations for solvated reactants and how to choose the configuration of the solvation shell in the supermolecule. A severe problem in the supermolecule method consists in high computational cost of calculations. It can be minimized by reducing the number of solvent molecules in the supermolecule model. Earlier, quantum chemical modeling of chemical reactions showed that the mechanism of a reaction in solution can be correctly described taking into account a few (one or two) solvent molecules[33,34] because additional molecules do not affect the mechanism.

Main criteria for choosing the necessary number of solvent molecules may include the occurrence of specific interactions between the reactants or **TS** and the solvent as well as the possibility of embedding solvent molecules into the **TS** of, *e.g.*, a proton transfer cycle. Specific interactions should persist in the reduced supermolecule model. In the absence of specific interactions it is sufficient to include in the model one or two solvent molecules required to form the structure of **SR** (see below).

Choosing a unified reference point for calculating the relative energies of structures is one of the most important problems in the supermolecule method. As mentioned above, these energies can be calculated relative to the **SR** energy (see Fig. 1). The **SR** structure can be obtained by embedding one or more solvent molecules between reactant molecules in such a manner that the reactant molecules be at sufficiently long distances from one another in order to neglect the interaction between them.

It is important to assess how correct is to compare the results of the supermolecule calculations carried out using different number of explicitly considered solvent molecules. Actually, models including different number of solvent molecules represent fragments of the same global supermolecule, namely, the solution *per se*. The size of the fragment chosen influences only the degree of approximation to the real reaction in bulk solution, *viz.*, the larger the fragment the better the approximation. If all specific interactions between the reactants and the solvent are taken into account, intermolecular interactions of the super-

Table 3. Complexation energies (E_c/kcal mol^{-1}) and activation energies (E_a/kcal mol^{-1}) calculated relative to the sum of the energies of infinitely separated reactants (I), the **RC** energies (II), the sum of the energies of separately solvated reactants minus the energy of the solvation shell (III), and the **SR** energies (IV) for the reaction involving one (**3**) and twenty (**4a—e**) dioxane molecules

Structure	E_c (**RC**)			E_a (**TS**)				E_c (**PC**)			
	I	III	IV	I	II	III	IV	I	II	III	IV
3	−8.8	−1.9	−2.7	21.6	30.4	28.4	27.7	−5.9	2.9	0.9	0.2
4a	−72.6	−3.2	−2.2	−43.9	28.6	25.5	26.4	−69.0	3.5	0.4	1.3
4b	−71.1	−1.7	−0.8	−43.4	27.7	26.0	26.9	−69.0	2.0	0.4	1.3
4c	−72.5	−3.1	−2.2	−44.1	28.4	25.3	26.3	−68.7	3.9	0.7	1.7
4d	−72.2	−2.8	−1.9	−42.8	29.4	26.6	27.5	−68.1	3.0	1.3	2.3
4e	−71.4	−2.0	−1.1	−42.4	29.1	27.0	28.0	−67.4	4.0	2.0	2.9

molecule with the rest of the solution can be ignored because these interactions are by and large identical and their energies are subtracted in calculations of the relative energies of **SR**, **RC**, and **TS**. Since the **SR**, **RC**, and **TS** structures have the same atomic composition, their energies are calculated using the same common basis set and there is no need to calculate the BSSE.

Taking account of the aforesaid, the reaction of methylamine with ethylene carbonate in dioxane was studied. We assumed that the effects of the medium can be considered using only one dioxane molecule involved in the one and only possible specific interaction, namely, the formation of a hydrogen bond between a dioxane O atom and an amino proton of methylamine. For comparison, the reaction in the supermolecule containing twenty dioxane molecules was calculated.

Table 3 lists the complexation energies of **RC** and **PC** and the activation energies of **TS**; the most important of these structures are shown in Fig. 4. Calculations of the energies relative to the sum of the energies of infinitely separated initial reactants (variant I) are commonly accepted; however, the activation energies thus obtained are negative which is unacceptable for comparison with experimental values.

Type-II calculations can also be found in the literature. In this case, the main disadvantage consists in that the **RC** energy includes the energy of interaction between reactants which can be different for different **RC** isomers formed in different reaction pathways. This difference increases as intermolecular interactions strengthen.

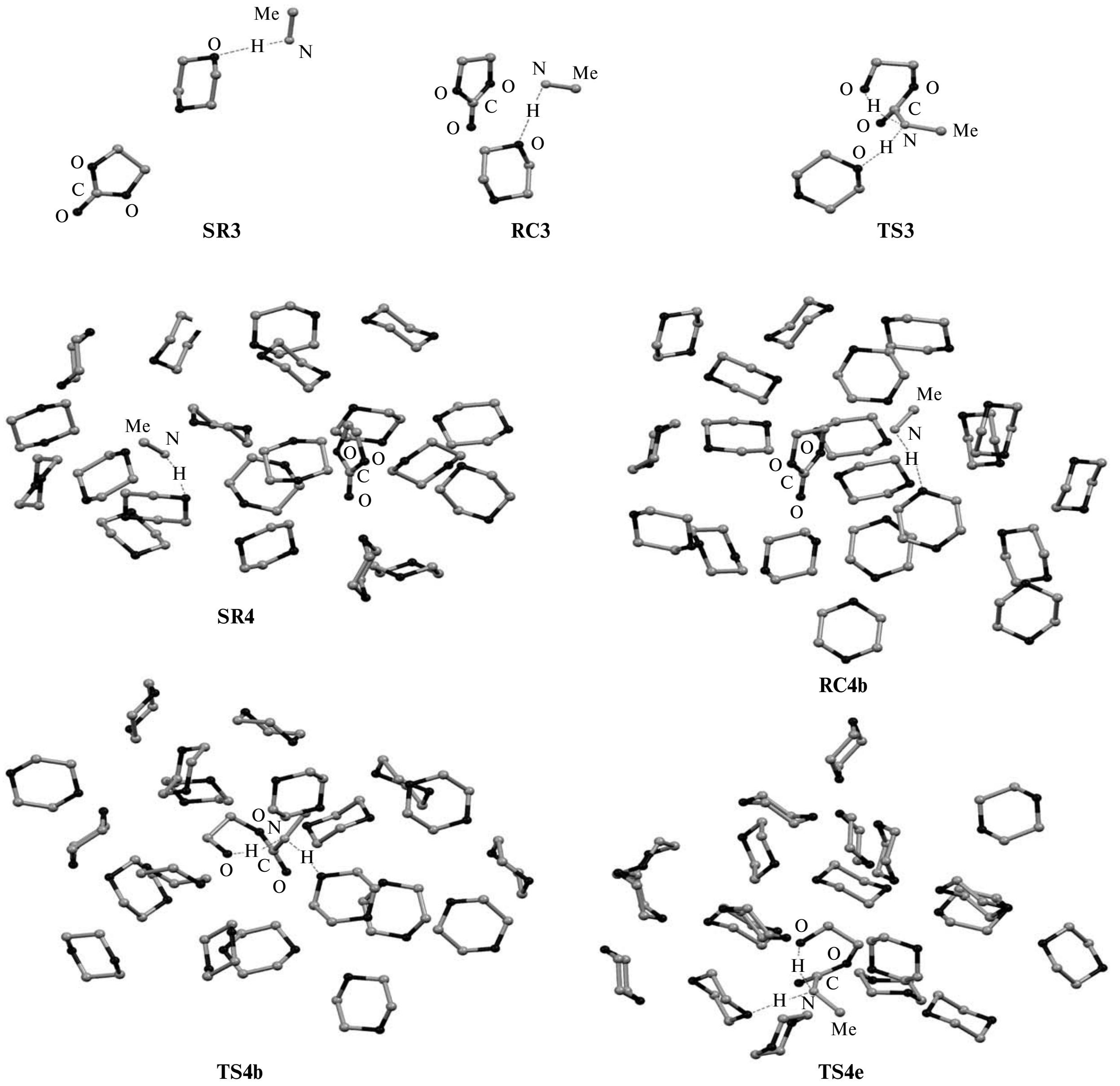
Type-III calculations are reduced to the following: calculations of each reactant surrounded by solvent molecules, summation of these energies (in the case in point, two reactants), and subtraction of the doubled energy of the solvated shell, namely, the dioxane molecule or the supermolecule comprising twenty dioxane molecules. It seems that this approach is less precise because the reactants, **RC**, and **TS** are calculated in different basis sets. When calculating large supermolecules, differences in the basis sets introduce only a small error, but this error increases for calculations with one dioxane molecule (see Table 3).

In Type-IV calculations the energies are computed relative to the **SR** energies**.** The advantage of this approach consists in that the **SR**, **RC**, and **TS** structures are calculated in the same approximation using the same common basis set. We believe this is the best method.

Let us consider how to choose the configuration of solvent molecules surrounding reactants. For the reaction with a single dioxane molecule there is one and only configuration of this molecule that includes a specific interaction with methylamine. As the number of dioxane molecules in the supermolecule increases, the number of possible configurations also increases. We considered five configurations of the solvent molecules around the reactants. In structures **4a—d** (**RC4a—d** and **TS4a—d**), reactants are completely surrounded by the solvent molecules, while in structures **4e** (**RC4e** and **TS4e**), reactants are located on the periphery of the supermolecule. Geometry optimization revealed one specific interaction between the reactants and the medium, *viz.*, a hydrogen bond between a dioxane O atom and a H atom of the amino group for each configuration.

It was found that the configuration of the solvent molecules has little effect on the energy of the supermolecule and, consequently, on the complexation energy and activation energy (see Table. 3). This is due to the fact that the loose solvation shell adapts to the reactants during geometry optimization of the supermolecule. Thus, the energy characteristics of the reaction depend slightly on the configuration of the solvent molecules surrounding the reactants provided that all specific interactions are taken into account. It should be noted that the complexation energies and activation energies obtained for the model with one solvent molecule are in good agreement with those calculated for the model with twenty dioxane molecules (see Table 3).

It follows that calculations of reactions in the supermolecule approximation do not require the search for all possible configurations of solvent molecules. For each pos-



SR3 RC3 TS3

SR4 RC4b

TS4b TS4e

Fig. 4. Key types of structures containing one (**3**) and twenty (**4**) dioxane molecules. In most cases, H atoms are omitted.

sible reaction pathway it is sufficient to consider a single configuration with a minimum number of solvent molecules. Any structure characterized by specific interaction between the reactant and the solvent can be chosen as the **SR** structure and serve as common reference point for calculating all relative energies.

Entropy effect for reactions in supermolecule. The theory of liquid-phase reactions assumes that the process occurs in the kinetic regime, *i.e.*, reactants rapidly diffuse to the solvent cage and the diffusion step does not influence the reaction rate. Therefore, the emphasis is placed on studies of the interaction between (i) reactants and solvation shell and (ii) reactant molecules inside the cage. Since the cage configuration is non-rigid and exists due to the presence of a large number of weak interactions, numerous configurations of solvent molecules corresponding to numerous local minima on the PES are possible. Rapid interconfigurational transitions with low activation barriers (of the order of kT) are also assumed and there is no reason to choose a particular configuration as the main one.[2]

Since all local minima should be considered to be equivalent, an averaged description of the influence of solvation shell on the reactants is required. Formally, this can be done by going from the PES to the free energy surface and, hence, by taking into account the entropy changes.[2] In this case, the activation barrier corresponds to the free energy surface and its relation to the experimental effective activation energy becomes less clear.

Calculations of entropy changes are only necessary to determine the pre-exponential factor which governs the probability for the reaction to occur. Entropy has no effect on the activation barrier to the reaction. As was confirmed above, the energy spread of different solvent cage configurations is small. Within the accuracy of calculations, the average energy can not differ significantly from the energies of individual configurations. Therefore, the averaged description taking account of all configurations does not offer any advantages.

It is a rare case that attention is paid to the fact that a bimolecular reaction in solution proceeds through a monomolecular transformation of the **RC** inside the solvent cage rather than a collision of two isolated molecules. In this case, the whole supermolecule should be considered as one large molecule whose components are bonded through weak interactions. For monomolecular reactions, the entropy changes including the changes in the activation entropy approach zero[5,35] and, consequently, the change in the free energy can not be appreciably different from the change in the potential energy.

We calculated the free energy surface of the reaction between ethylene carbonate and methylamine with participation of one and twenty dioxane molecules (Table 4). From the data in Table 4 it follows that the main changes in entropy correspond to transformation of infinitely separated initial reactants **R** to **SR**. Transitions **SR** → **RC** → **TS** → → **PC** are characterized by much smaller entropy changes that should approach zero in the limiting case. Owing to minor entropy change, the Gibbs energies ΔG^{298} calculated relative to the **SR** energy are only 3.4—5.0 kcal mol^{-1} higher than the energies calculated conventionally. Therefore, going from the PES to the free energy surface provides no additional information for understanding the mechanism of liquid-phase reaction and is thus impractical. Moreover, the activation barriers obtained for the free energy surface can hardly be compared with the experimental values due to the presence of various channels and to the multistep character of the reaction for each channel in solution.

Table 4. Changes in enthalpy (ΔH), entropy contribution ($T\Delta S$), and Gibbs energy (ΔG) in different reaction steps calculated for 298 K

Transition	ΔH^{298}	$T\Delta S^{298}$	ΔG^{298}
		kcal mol^{-1}	
R → **SR3**	−4.7	−15.8	11.1
R → **SR4**	−46.2	−189.9	143.7
SR3 → **RC3**	−1.3	1.4	−2.7
SR4 → **RC4a—e**	−1.3—0.3	−1.8—2.8	−3.2—1.0
RC3 → **TS3**	26.3	−6.7	33.0
RC4a—e → **TS4a—e**	25.4—28.3	−(6.1—1.2)	29.5—31.5
TS3 → **PC3**	1.5	−3.5	5.0
TS4a—e → **PC4a—e**	2.3—4.0	−2.3—1.7	2.3—4.6

Summing up, our study of methylamine addition to ethylene carbonate in dioxane in the supermolecule approximation showed that in some cases there is no need to carry out quantum chemical calculations using a large number of solvent molecules. It is appropriate to determine the optimum number of solvent molecules for each particular reaction (the accuracy of calculations should remain almost the same in this case). It may appear that one solvent molecule is sufficient. It is not always necessary to search for all local minima on the PES, corresponding to different configurations of the solvation shell around the reactants, since the energy differences between these configurations after geometry optimization will be small. Since the **SR**, **RC**, and **TS** structures have the same atomic composition, their energies are calculated using the same basis set and there is no need to calculate the BSSE. We propose to use the energy of **SR**, where the reactants are separated by at least one solvent molecule, as a common reference point for calculating the relative energies. Since the liquid-phase reaction proceeds in the solvent cage by the mechanism of monomolecular transformation of the solvated **RC**, the change in entropy can be ignored.

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