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Dimethyl sulfoxide–monoethanolamine clusters: prevailing coordination motifs

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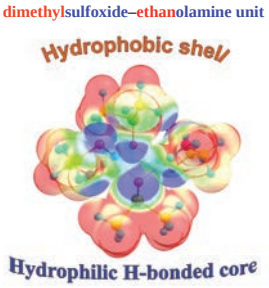
Nonempirical simulations at the MP2/6-31++G(d,p) level revealed favorable building blocks in the dimethyl sulfoxide (DMSO)–monoethanolamine (MEA) binary system. The analysis of diverse coordination motifs of MEA and DMSO molecules showed that energetically preferable configurations are those composed of equal numbers of DMSO and *gauche* MEA molecules, where OH, NH_2, and SO groups of all molecules are conglomerated in a hydrophilic core surrounded with a hydrophobic methyl–methylene shell, and amino groups act as bridges between the two parts.



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Liquid mixtures based on dimethyl sulfoxide (DMSO) or monoethanolamine (MEA) are widely used in cryobiology[1,2] due to their ability to be overcooled and preserve living organisms in an original state.[3,4] In an aqueous DMSO solution, the most substantial overcooling is attained[5] at a DMSO concentration of 33 mol% (–76 °C), while it occurs[6] at a concentration of 23 mol% (–55 °C) in an aqueous MEA solution. Therefore, the DMSO–MEA binary system is of particular interest. The phase diagram of this system exhibits an ordinary eutectics at a component ratio of 1 : 1; and the corresponding overcooling is –32 °C.[7] What are the structure–energetic reasons for the inherent features of the equimolar composition? Are they related to the peculiarities of hydrogen bonding in the system? These questions are important since H-bonds are responsible for the solvation of bioorganic species.

To shed light on the problem at the microscopic level, we carried out nonempirical simulations of $(MEA)_k(DMSO)_m$ clusters with the use of the Moeller–Plesset second-order (MP2) perturbation theory and a Gaussian basis set of double-zeta quality extended with diffuse and polarization functions on all nuclei [6-31++G(d,p)]. On the one hand, this basis set is sufficiently flexible to reproduce the electron density redistribution that accompanies the H-bond formation and, at the same time, relatively compact to avoid the linear dependence in the case of medium-sized clusters. The absolute stability of clusters was confirmed by the normal coordinate analysis carried out for each optimized structure. Relative stability against dissociation into constituent molecular fragments was estimated taking into account the counterpoise correction for the basis set superposition error (BSSE). Both vertical (DE_{vert}) and adiabatic (DE_{ad}) dissociation energies were estimated as follows:

$$DE_{vert} = \sum_{i}^{k} E'[DMSO^{(i)}] + \sum_{j}^{l} E'[MEA^{(j)}] - E(MEA_lDMSO_k) + BSSE'$$

$$DE_{ad} = \sum_{i}^{k} E[DMSO^{(i)}] + \sum_{j}^{l} E[MEA^{(j)}] - E(MEA_lDMSO_k) + BSSE,$$

where $DMSO^{(i)}$ and $MEA^{(j)}$ denote *i*-th DMSO and *j*-th MEA molecules in a MEA_lDMSO_k cluster; *E′* is the energy of a molecular fragment at its configuration within the cluster, and *E* is the energy of the whole cluster or a molecular fragment at their optimum configurations; BSSE and BSSE′ stand for 50% BSSE corrections taking into account or neglecting the structure relaxation of fragments, respectively. The 50% correction is a good compromise in the case of H-bonded systems,[8] which enables one to obtain a reliable estimate of the bonding energy in a situation when the basis set superposition error is partly counterbalanced by the basis set incompleteness error. Adiabatic energies reflect the overall stability of the system under presumable thermodynamic equilibrium between clusters and their individual constituents, while the vertical energies give tentative upper estimates of the activation energy of the process. Thermal corrections were introduced based on the data of conventional statistical thermodynamic calculations (at 298 K and 1 bar) when only vibrational-rotational contributions were taken into account, while translational ones were excluded because the clusters are model representatives of liquid-phase fragments where mobility is substantially hampered by the surrounding molecular layers, and it can be neglected at a picosecond timescale. All calculations were carried out with the use of the Firefly 8.2 program package,[9] and the results were visualized with the Chemcraft software.[10]

The DMSO molecule has one stable configuration[11] with *r*(S–O) = 1.49 Å, *r*(S–C) = 1.80 Å, *φ*(O–S–C) = 106.4°, and *φ*(C–S–C) = 96.5°. The MEA molecule has 14 different conformers, 13 of which have mirror structures, and almost all of them occur or temporarily appear in one or another phase state;[12–21] *gauche* conformers are predominant in a gas and a liquid, while *trans* (or *anti*) conformers, in a solid. Individual *gauche* conformers are stabilized by intramolecular –O–H···N (energetically favorable in stationary approximation) or –N–H···O (with a longer total lifetime under dynamic conditions) hydrogen bonds.[21] When searching

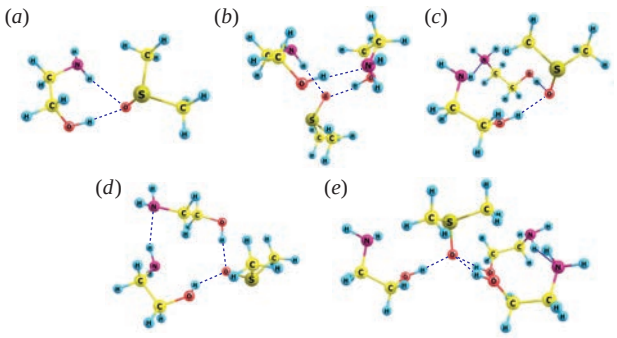

Figure 1 Structures of MEA_kDMSO clusters at (*a*) $k = 1$, (*b*)–(*d*) $k = 2$, and (*e*) $k = 3$.

for the possible structures of mixed clusters, various initial configurations were generated by arbitrarily rotating various MEA isomers around a DMSO molecule with a sole restriction, namely, the relative closeness of OH or NH_2 groups of MEA molecules to the SO fragments of DMSO. Upon the optimization of all the systems at the MP2/6-31G(d,p) level, typical total electronic energy ranges were distinguished, and those structures, which fall in the lowest energy range, were selected for a further thorough analysis.

In the DMSO–MEA system, the DMSO molecule can be only an H-bond proton acceptor, while the hydroxyl and amino groups of MEA are both proton donors and acceptors depending on the neighborhood. This is well illustrated by the stable configuration of a MEA_1DMSO_1 cluster [Figure 1(*a*)], in which both functional groups of MEA are hydrogen-bonded to the SO group of DMSO. Note that the O–H···O(DMSO) bond is substantially shorter than N–H···O(DMSO) (1.839 *vs.* 2.393 Å), and the amino group resides closely to a methyl group of DMSO (at an N···C distance of about 3.42 Å). The vertical dissociation energy (DE_{vert}) of the cluster (Table 1) is nearly by half higher than the adiabatic one (DE_{ad}) and almost twice as high as the Gibbs energy under normal conditions (ΔG^0_{298}). The values show that a mean H-bond energy [*E(*H-bond), which is the total adiabatic binding energy of the cluster normalized to the number of H-bonds], is about 4.4 or 3.4 kcal mol^{-1} at 0 or 298 K, respectively.

The *trans* MEA conformer can form only one hydrogen bond with DMSO, either OH···O(DMSO) or NH···O(DMSO), which makes such structures less stable. Taking into account that *gauche* conformers prevail in both individual gas and liquid MEA phases, one may expect that mixing with DMSO should not drastically alter the structural preferences. Furthermore, as follows from the modeling of medium-sized $(MEA)_n$ clusters, intramolecular hydrogen bonds in MEA molecules cannot survive when several molecules unite: intermolecular bonds are energetically favorable compared to intramolecular ones.[22] Then, the insertion of a DMSO molecule in a relatively weak intramolecular hydrogen bond in a MEA molecule, which results in the formation of two H-bonds, one of which is strong, is a highly probable process. However, already two *gauche* MEA molecules can scarcely be arranged closely to an SO group in such a way that four H-bonds stabilize the system because of steric hindrances. This is well illustrated by the structure-energetic characteristics of $(MEA)_lDMSO$ clusters with $l = 2$ and 3.

Table 1 Energetic characteristics of MEA_lDMSO_k clusters: vertical (DE_{vert}) and adiabatic (DE_{ad}) dissociation energies at 0 K and the apparent Gibbs energy of process under normal conditions (ΔG^0_{298}).

l	*k*	Structure image	DE_{vert}/kcal mol^{-1}	DE_{ad}/kcal mol^{-1}	ΔG^0_{298}/kcal mol^{-1}
1	1	Figure 1(*a*)	12.7	8.8	6.8
2	1	Figure 1(*b*)	26.9	20.7	15.2
2	1	Figure 1(*c*)	24.4	18.8	13.8
2	1	Figure 1(*d*)	22.8	20.8	15.1
3	1	Figure 1(*e*)	36.5	27.5	18.3
2	2	Figure 2(*a*)	40.7	33.7	23.8
2	2	Figure 2(*b*)	33.8	31.3	17.4

At a MEA to DMSO molar ratio of 2 : 1, the most stable local configuration is that where an intermolecular H-bond between MEA molecules is O–H···N [Figure 1(*b*)]. Either MEA molecule forms only one H-bond with DMSO, one O–H···O(S) and the other N–H···O(S). Only in this case, all H-bonds are nearly linear [with the smallest O–H···O(S) and largest N–H···O(S) angles of 167° and 179°, respectively] and relatively short [$r_{(S)O\cdots H(O)}$ = = 1.90 Å, $r_{(S)O\cdots H(N)}$ = 2.10 Å, and $r_{(O)H\cdots N}$ = 1.84 Å]. The C, N, and O atoms of two MEA molecules and the O atom of DMSO form a boat with methylene boards and a dimethyl keel; the amino group, which acts as a proton acceptor, is not far from a methyl group of DMSO. The complex system is quite stable: judging from the DE and Gibbs dissociation energies (Table 1), H-bonds are noticeably stronger than in a MEA_1DMSO_1 cluster, namely, E_0(H-bond) = 6.9 kcal mol^{-1} and E_{298}(H-bond) = 5.1 kcal mol^{-1}.

Less stable (the total electronic energy of the cluster is higher by 2.4 kcal mol^{-1}) is the structure [Figure 1(*c*)] in which two *gauche* MEA molecules form O–H···O(S) hydrogen bonds, being bound to each other *via* a weak N–H···N contact [$r_{(N)H\cdots N}$ = 2.35 Å and $\varphi_{N-H\cdots N}$ = 151°]. Note that this kind of bond between MEA molecules is the weakest in the case of individual MEA clusters.[22] In the mixed system, both amino groups are arranged closely to a DMSO methyl group (N···C distances are 3.41 and 3.95 Å). As a result, there are two visible contact triangles, namely, the (conditionally) lower O(MEA)···O(S)···O(MEA) and upper N(MEA)···C(Me)···N(MEA) ones. Dissociation energies of the system (see Table 1) enable us to estimate the mean hydrogen-bond strengths as E_0(H-bond) = 6.3 kcal mol^{-1} and E_{298}(H-bond) = = 4.6 kcal mol^{-1}, which are about 0.5 kcal mol^{-1} smaller than those in the above structure.

The situation is improved when at least one MEA molecule has a *trans* conformation [Figure 1(*d*)] despite the fact that the total electronic energy of the system is higher by 1.9 kcal mol^{-1}. Even the strongest hydrogen bond O–H···O(S) is characterized by an (O)H···O distance of 1.77 Å and an O–H···O angle of 168°; and at a visually less hindered contact between the MEA molecules, the corresponding N–H···N bond is again long and strained (2.29 Å and 140°), so that E_0(H-bond) = 6.9 kcal mol^{-1}. Upon thermal correction, we obtain E_{298}(H-bond) = 5.0 kcal mol^{-1}, which is consistent with the fact that a more extended skeleton of *trans* MEA conformer provides more space for the adjustment of MEA molecules around DMSO, and their internal distortions are smaller. At the same time, the structure is spatially looser, which is not favorable in view of the building blocks of condensed-phase specimens.

At a larger number of MEA molecules in the close vicinity of DMSO, they steadily prefer to form O–H···O(S) hydrogen bonds with the latter. This is well illustrated by the structure of $(MEA)_3DMSO$ [Figure 1(*e*)]. It comprises almost all the favorable features of smaller systems and resembles a three-horn chandelier, where *gauche* MEA molecules can be considered as horns. This conformation seems preferable as providing the closeness of the amino groups of MEA to the methyl groups of a DMSO hook. In a weak N–H···N bond between two MEA horns, the proton-donating amino group is close to a methyl group. A separately coordinated MEA molecule resides closely to the other methyl group. The structure armoring O–H···O(S) hydrogen bonds are all slightly distorted with O···H distances of 1.83 to 1.85 Å and O–H···O angles of 163–171°. For this system (see Table 1), E_0(H-bond) and E_{298}(H-bond) are about 6.9 and 4.6 kcal mol^{-1}, respectively. The latter value is similar to that of the least stable (of the aforementioned) MEA_2DMSO cluster stabilized by three

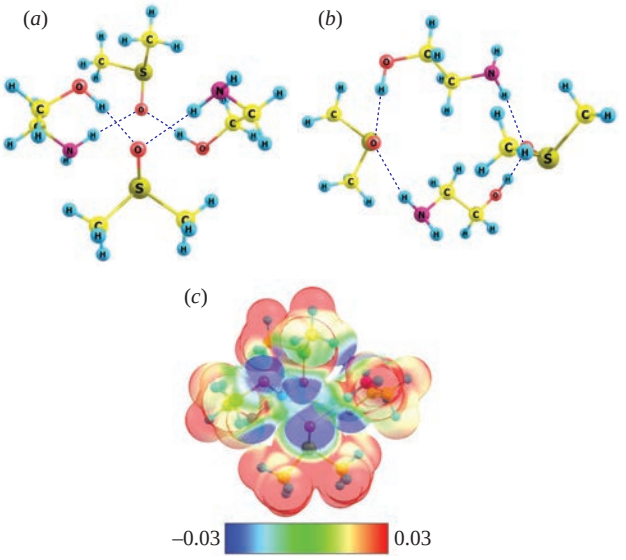

Figure 2 Structures of MEA_2DMSO_2 cluster that involves (*a*) *gauche* and (*b*) *trans* MEA molecules; and (*c*) electrostatic potential map of structure (*a*).

H-bonds. In the MEA_3DMSO system, three strong (O)H···O(S) bonds are supplemented with a weak (N)H···N bond, which means that the coordination of MEA molecules to DMSO is strong, while they can be easily reoriented. The flexibility of such a cluster unit reflected by difference between the H-bond energies at 0 and 298 K does not enable us to consider it as a structure-determining one. Absolutely the same can be said about the MEA_4DMSO four-horn chandelier.

The most promising building blocks in systems composed of a large number of MEA and DMSO molecules should be those where MEA molecules act as bidentate bridges rather than side branches around a DMSO hook. Among the above small clusters, only those with a 1 : 1 ratio between DMSO and MEA meet the requirement. In these systems, the superiority of *gauche* MEA conformers is especially pronounced.

The most energetically favorable conformation of the MEA_2DMSO_2 cluster is shown in Figure 2(*a*). Both of the MEA molecules form H-bonds with each DMSO molecule in such a way that the O and N atoms of all four particles are arranged in vertices of a twisted hexagon, one DMSO molecule residing above, while the other under the mean hexagon plane. All methylene groups of MEA and methyl groups of DMSO form a coating of the hexagon. This is due to the compactness of *gauche* MEA conformers, which enables the hydrophilic groups of all molecules to be gathered within a relatively small spatial domain. Amino groups are a sort of bridges between the hydrophilic core and hydrophobic shell of the cluster system. The dissociation energy of thus organized system is very high (see Table 1): E_0(H-bond) = = 8.4 kcal mol^{-1} and E_{298}(H-bond) = 6.0 kcal mol^{-1}. Hence, eacH-bond itself is very strong; taking into account the fact that any reorganization of the cluster needs a substantial distortion of at least two bonds simultaneously, one can see that this configuration is a good candidate as a stable structural unit.

When both MEA molecules are *trans* conformers, the resulting MEA_2DMSO_2 cluster is generally similar at first glance [Figure 2(*b*)]. However, a closer look at it reveals a drastic difference: this structure is much less compact. Although all six O and N atoms are again arranged in vertices of a twisted hexagon, the edges of the latter are much longer because they include the hydrophobic parts of MEA molecules. This spatial alteration of hydrophilic and hydrophobic groups results in an overall increase in the electronic energy of the system by 11.8 kcal mol^{-1} relative to the system with core–shell separation of the hydrophilic and hydrophobic molecular segments. The H-bond strengths deduced from the data in Table 1 are E_0(H-bond) = 7.8 kcal mol^{-1} and E_{298}(H-bond) is about only 4.4 kcal mol^{-1}, the latter value being nearly by a third smaller than that of the cluster that involves *gauche* MEA conformers. The decrease in the mean H-bond strength is observed despite nearly the same geometrical parameters of hydrogen bonds, when (O)H···O(S) distances are 1.87 and 1.88 Å, and (N)H···O(S) distances are 2.13 and 2.16 Å.

Thus, the most favorable mutual arrangement of MEA and DMSO molecules is attained at an equimolar ratio between the constituents. Promising building blocks of such compositions are tetramolecular ones based on *gauche* MEA molecules, which form H-bonds with both neighboring DMSO molecules, so that any O(S) group of the latter is involved in both (S)O···H(O) and (S)O···H(N) bonds. The resulting compact arrangement of all six OH, NH_2, and SO molecular parts forms a hydrophilic core surrounded with a hydrophobic methylene–methyl shell. Such blocks are sufficiently rigid due to the closed sequence of strong hydrogen bonds, and they should not be noticeably distorted by the neighbors, the interaction with which can be either weak H-bonding (*via* amino groups) or dispersion coordination (*via* methyl and methylene groups). Insofar as amino groups act as bridges between hydrophilic and hydrophobic parts even inside the tetramolecular units, the shells of the neighboring units can be complementary. This is illustrated by the electrostatic potential map of the cluster [Figure 2(*c*)] on overlapping scaled (by 1.2) van der Waals atomic spheres where positive-sign red-orange segments correspond to the hydrophobic shell, while negative-sign blue ones, to the hydrophilic core.

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