

Modeling of Dimers of Chiral Trifluoroacetylated Aminoalcohols

D. V. Zlenko^{a,*}, M. G. Mikhaleva^b, and S. V. Stovbun^b

^aMoscow State University, Moscow, Russia

^bSemenov Institute of Chemical Physics, Russian Academy of Sciences, Moscow, Russia

*e-mail: dzlenko@gmail.com

Received July 29, 2015

Abstract—The formation of nanodroplets in solutions of gelating trifluoroacetylated amino alcohols (TFAAA), constituting one of the fractions of the dispersed phase, is simulated by the molecular dynamics method. It is shown that the main contribution to the energy of formation of nanodroplets comes from dispersion forces (~ 14 kJ/mol), which constitutes 3/4 of the total energy of interaction of a pair of molecules. The dipole–dipole component of the interaction energy for the molecules with anticollinear dipole moments is $\sim kT$. It is shown that there are differences in the topology of pairs of bound homochiral TFAAA molecules, associated with their nonhomeomorphicity. In the first case, the chiral tetrahedrons of the molecules are nested into each other. During condensation, due to the formation of stacks, such pairs are capable of anisotropic growth. In the second case, the tetrahedrons join via their bases, creating isometric nuclei for isotropic condensation.

Keywords: chirality, dipole moment, anisometry, supramolecular structures, molecular modeling

DOI: 10.1134/S1990793116030131

INTRODUCTION

The phenomenon of threshold formation of solitary, extremely anisometric supramolecular structures (strings) in dilute solutions of low–molecular–weight homochiral N-trifluoroacetylated α -aminoalcohols (TFAAA) was studied in [1]. It was experimentally found that, at subthreshold TFAAA concentrations, the solution contains dispersed–phase particles [2]. In the range of optical transparency, accessible for dynamic light scattering measurements, the disperse isometric phase of the solution is represented by two TFAAA fractions: nanodroplets with sizes of no more than 5–10 nm and mesophase particles ~ 20 –40 nm in diameter [3]. We have previously shown that these nanodroplets have a high internal molecular mobility and are extremely heterogeneous; i.e., they have little or no internal volume. The surface of the droplets is characterized by a fractal dimension of ~ 1.6 , topologically corresponding to a one–dimensional beam of diverging rays [3]. In terms of dynamics, such objects can be thought of as stochastically born, branching, and then disappearing molecular-thin rays diverging from a central location. That the disperse phases coexist in the solution at quasi-equilibrium for $\sim 10^5$ s or more suggests that the local curvatures of the surfaces of the nanodroplets and mesophase microparticles are similar and that the mesophase itself is apparently formed during the condensation of nanodroplets as they diffuse in the volume of the vessel [3, 4].

Since TFAAA nanodroplets have a high internal molecular mobility, the electrostatic energy binding of the molecules in them was estimated using the Keesom approximation [3]. The energy of the dipole–dipole interaction for a pair of molecules was estimated to be $\sim (1/3)kT$, a value not contradicting the idea of the intense movement of molecules relative to each other and of the variability of the nanodroplet shape [3].

The aim of the present work was to study the topology of the spatial structure of pairs of aggregated TFAAA molecules formed in the solution and the relationship of this structure to the pattern of the resulting condensed phases. This was accomplished by studying pair interactions between molecules in nanodroplets by the full-atomic molecular dynamics (MD).

METHODS

Molecular dynamics calculations were performed using the GROMACS-4.5.5 software package [5] in combination with the OPLS-AA force field [6]. The integration step for all calculations was 0.5 fs. The characteristics of the long-range electrostatic interactions were calculated by the PME method [7] with a standard set of parameters (interpolation polynomial order, 4; computational grid spacing, 1.2 Å). The cut-off radii of the short-range electrostatic and dispersion interactions and of the list of neighboring atoms were

1.25 nm. All the calculations were performed with periodic boundary conditions at 300 K and a constant isotropic pressure of 1 atm. The process of constructing the models of TFAAA and solvent molecules and of the modeling scenes was described in [3].

Since the formation of strings occurs during the cooling of TFAAA solutions, a superheated solution with a temperature of 300 K was chosen as the initial state. The solution was thought of as a system in which TFAAA molecules in random orientations occupied sites of a cubic lattice at 2-nm steps [3]. The interstitial space between the TFAAA molecules was filled with solvent molecules pre-relaxed for 100 ns.

The final modeling scenes contained 125 TFAAA molecules in a 1000 m³ volume, which corresponds to a concentration of 0.2 M. This concentration is well below the percolation threshold of formation of a classical gel, corresponding to the experimentally established range of formation of low-molecular-weight chiral gels and strings in dilute solutions [1, 8]. For each scene, molecular dynamics calculations were performed for 100 ns. In analysis, the second halves of the MD trajectories were used, which obviously satisfy the condition of diffusion equilibrium [3].

RESULTS AND ITS DISCUSSION

Within the framework of the molecular mechanics method, two terms of interactions, describing the nonvalence interactions of pairs of atoms, are normally considered: electrostatic and dispersion forces. In addition to the total electrostatic energy of a pair of TFAAA molecules, we also calculated the dipole interaction energy of the molecules, approximating them by point dipoles. The values of the energy of interaction between TFAAA molecules per pair of molecules are listed in the table.

On average, the calculated energy of interaction of a pair of TFAAA molecules in the point dipole approximation is ~ 1.1 kJ/mol, i.e., $\sim 0.4kT$, which is very close to the estimate by the Keesom formula, $\sim (1/3)kT$ [3]. At the same time, TFAAA molecules in nanodroplets are brought very closely together. On average, the distance between them is within the first coordination layer, $r \sim 7$ Å, as indicated by the radial distribution functions [3]. A comparison of the intermolecular distance r with the van der Waals radii of the molecules [9] shows that the interacting dipole moments of the molecules cannot be considered pointlike. It is more clearly seen in constructing the local dipole moments created by individual polar functional groups (excluding the total uncompensated charge of the group). For example, Fig. 1 displays a model of the TFAAA-5 molecule [10], with the indicated partial atomic charges, local dipole moments, and overall dipole moment of the molecule. The figure also clearly shows the chiral tetrahedron formed by two carbon atoms and a nitrogen atom (at the base)

and the hydrogen atom at the chiral carbon atom (at the vertex). The dipole moment of the molecule forms a small angle with the plane of the chiral tetrahedron base (Fig. 1). Given the multidirectionality of the local dipole moments, it is easy to see that a simple dipole approximation for a pair of tightly adjacent molecules can give a substantially incorrect assessment of the energy of their interaction. Indeed, this is directly confirmed by MD calculations, according to which the average energy of electrostatic interaction of TFAAA molecules (table) is ~ 4.2 kJ/mol ($\sim 1.7kT$). It should be noted that this energy in heptane is ~ 1.0 – 1.5 kJ/mol higher. This is apparently due to the local polarization of the medium, which leads to a relative increase in the size of the nanodroplets in heptane (table).

The total energy of electrostatic interaction of a pair of molecules in a droplet for molecules with collinear dipoles is higher by kT than the formally obtained dipole–dipole interaction energy. The dependence of the dipole–dipole interaction energy on the angle φ between the dipole moments (Fig. 2a) more or less accurately reproduces the behavior of the similar dependence for the full energy of electrostatic interaction (Fig. 2b); it has one minimum corresponding to the stable state with antiparallel orientation of the dipole moments. A characteristic feature of the curves is an almost complete absence of any dependence of the electrostatic or dipole energy on the angle φ between the dipoles in the range of sharp angles. This fact can be explained by the local interaction of the partial charges of the atoms and by the deformation of the molecule, factors that significantly compensate the energy loss associated with the repulsion of collinear dipoles. Dependences similar to those obtained for TFAAA-5 in cyclohexane (Fig. 2b) were observed for all the investigated solutions of chiral TFAAA.

The most significant contribution to the interaction of TFAAA molecules comes from dispersion forces, which, on average, provide an intermolecular bonding energy of ~ 14 kJ/mol ($\sim 5.6kT$), i.e., almost threefold higher than the electrostatic contribution (table). This result generally reflects the linear dependence of the dispersion interaction energy on the surface area of the intermolecular contact and, therefore, is consistent with the relationship between the dispersion interaction energy of a pair of TFAAA molecules with the solvent ((63.6 ± 5.7) kJ/mol or $\sim 25kT$, table), which are present in the nanodroplets in a proportion of $\sim 4 : 1$, since 75–80% of the nanodroplet volume is occupied by the solvent [3]. Note that, for the TFAAA-4 and TFAAA-8 molecules, the sizes of which are similar, as are those of their side groups, the interaction energy of TFAAA-4, a doubly chiral molecule, is significantly greater than that of singly chiral TFAAA-8.

The dispersion interactions energy of a pair of molecules also depends on the angle φ (Fig. 3), with the effect being observed in different solvents for all chiral

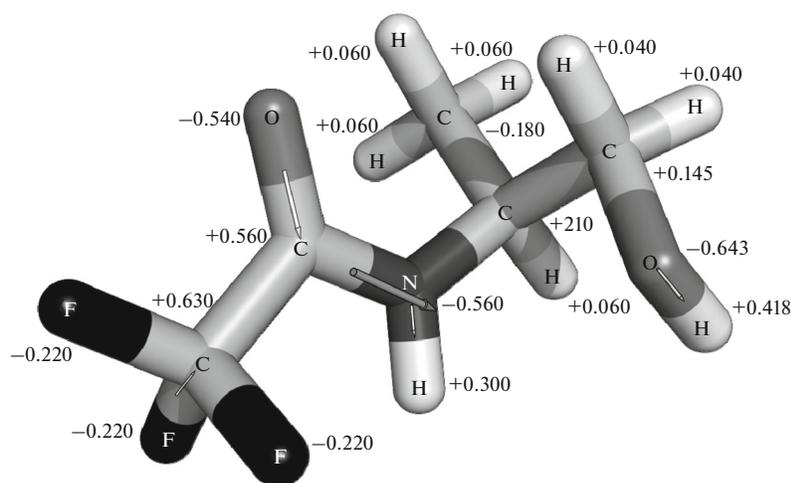


Fig. 1. Electrostatic parameters of the TFAAA-5 molecule [10]. The atoms are indicated by the symbols of the elements; numerals indicate the partial charges; light arrows represent the local dipole moments of the polar groups. The dark arrow represents the total dipole moment vector. The length of the arrows is proportional to the dipole moment magnitude.

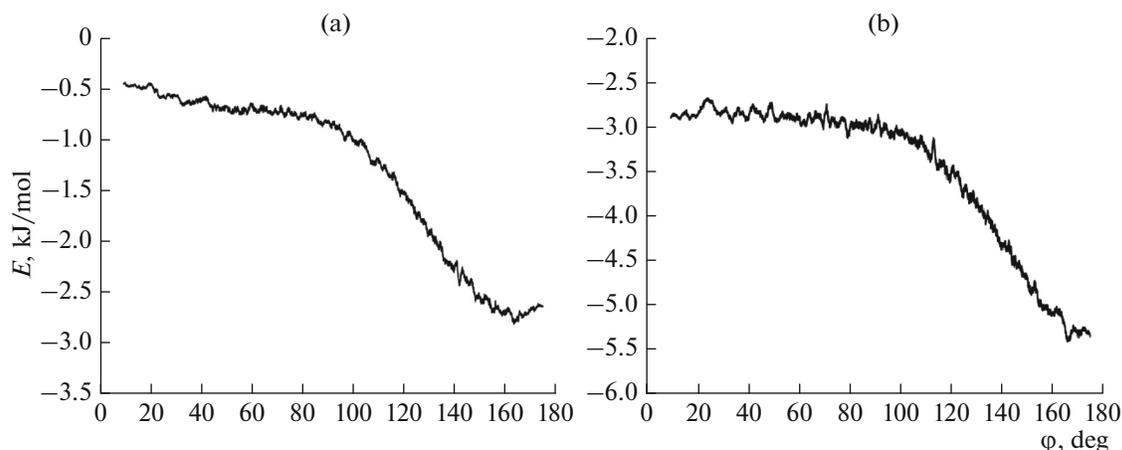


Fig. 2. Dependence of the energy of the electrostatic interaction between the TFAAA-5 molecules in a nanodroplet consisting of 9.6 ± 2.3 molecules and existing for 5.2 ns in cyclohexane on the angle φ between the dipole moments of the molecules: (a) the dipole–dipole interaction energy in the point dipole approximation; (b) the electrostatic interaction energy of the molecules determined using the molecular mechanics method.

TFAAA, in both heptane and cyclohexane (Fig. 3), but not observed for achiral TFAAA-2. Note that, to high accuracy, the short-range dispersion interaction energy of molecules is the sum of the energies of pair dispersion interactions of the atoms that constitute these molecules, and, obviously, with this value of r , it is not related anyhow to the total dipole moment of the molecule. The observed minimum in the dispersion interaction energy at the anticollinear orientation of the dipoles clearly demonstrates a good spatial correspondence between the surfaces of TFAAA molecules or their complementarity namely in this orientation. Indeed, since the interatomic force of attraction is proportional to the sixth power of the distance (the energy of mutually induced dipoles), even a slight

increase of the distance in a pair of atoms will lead to a significant reduction in the dispersion energy of the bond. On the other hand, whether this complementary arises depends on the angle between the dipole moments (Fig. 3).

Given that the dispersion interaction energy is much greater than the dipole–dipole interaction energy means that the dipole moments of the molecules adjust themselves in part to the complementary conformation caused by dispersion forces. For homochiral pairs of TFAAA molecules, all other (non-complementary) mutual arrangements of the molecules yield a dispersion interaction energy lower by $\sim 1.5kT$ (Fig. 3).

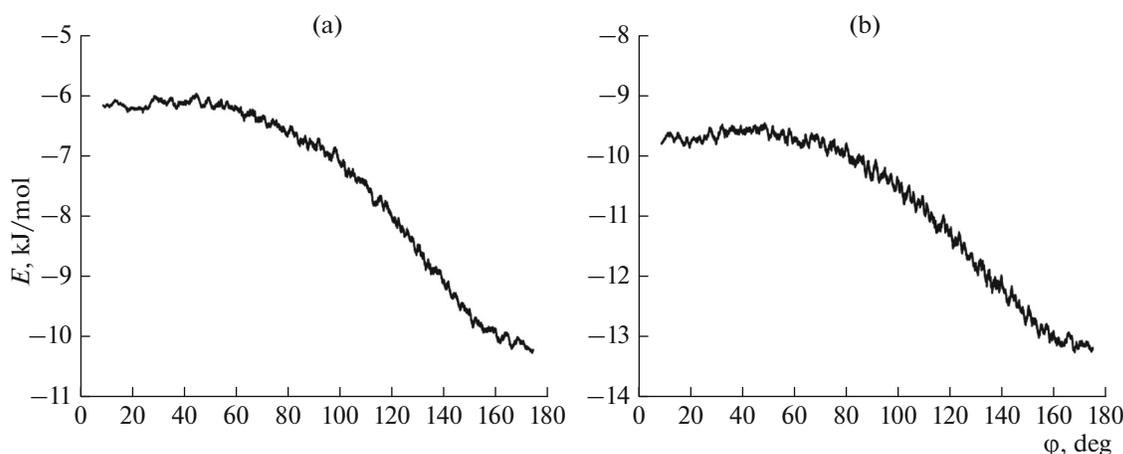


Fig. 3. Dependence of the dispersion interaction energy of pairs of molecules in TF AAA nanodroplets on the angle φ between the dipole moments of the (a) TF AAA-5 and (b) TF AAA-8 molecules in heptane. The dispersion interaction energy for chiral TF AAA molecules depends on the angle between the dipoles, with the minimum of the dispersion energy corresponding to the anticollinear orientation of the dipoles.

Let us estimate the fraction (n) of pairs of TF AAA molecules in a nanodroplet the dipoles of which are collinear by using a two-level model:

$$n = \exp\left(-\frac{E_{\max} - E_{\min}}{kT}\right) \sim 0.1,$$

where E_{\max} and E_{\min} are the total energies corresponding, respectively, to the anticollinear and collinear orientations of the dipoles obtained from calculations ($\sim 2.5kT$). The formation of complementary pairs with anticollinear dipole moments is quite consistent with the previously detected abnormally large value of the self-diffusion coefficient of the TF AAA molecules in the nanodroplet, $\sim 8 \times 10^{-5} \text{ cm}^2/\text{s}$ [3], which is much larger than the values typical of liquids. This is indicative of a strongly correlated motion of molecules in nanodroplets [3].

The energy of dispersion interaction in a pair of chiral TF AAA molecules depends on the specific features of their chemical structure. For example, for the TF AAA-8 molecule, which contains a bulky butyl group [10], the depth of the minimum corresponding to the anticollinear orientation of the dipoles is $(1.0\text{--}1.5)kT$ lower (Fig. 3b) than that for the TF AAA-5 molecule, which contains a small methyl group (Fig. 3a). Apparently, the relatively large total surface of the side groups and, hence, a high energy of pair dispersion interaction gives rise to alternative low-energy orientations of the molecules.

The formation of complementary pairs can be directly detected by analyzing the relative arrangement of the molecules in the droplet. Let us consider the dependence of the total potential energy of interaction of pairs of molecules on the angle between arbitrary chosen directions in the structure of the molecules. Since the TF AAA molecules have no natural long, or conversely, short specific axes and their shape, as

shown above, may undergo noticeable distortions, the molecular vector describing the spatial position of the chiral tetrahedron was selected as the characteristic direction. The molecular vector is meant to be a vector the start and end of which are associated with the centers of some selected atoms. We chose the vector directed from the chiral carbon atom to the hydrogen atom bonded to it, known as the normal vector to the chiral tetrahedron base. In this case, the nonhomeomorphicity of the bodies formed by nested tetrahedrons and tetrahedrons with common bases will make it possible to define differences in the topology of pairs of TF AAA molecules.

The dependence of the total potential energy of binding of a pair of TF AAA molecules on the angle ψ between the normal vectors to the base of the tetrahedron upon averaging over all the mutual orientation of the dipole moments is shown in Fig. 4. For structurally different chiral TF AAA-5 and TF AAA-8, such a dependence is nonmonotonic and has two minima, corresponding to the collinear and anticollinear orientations of the vectors (Fig. 4). For TF AAA-5, with a small side group, the depth of the collinear well differs little from the depths of the anticollinear well, being $\sim 0.6kT$ (Fig. 4a). For TF AAA-8, with a large butyl group, the wells are deeper: with the collinear and anticollinear well depth being $\sim kT$ (3 kJ/mol) and $\sim 2kT$ (5 kJ/mol), respectively. Note that this result is valid with allowance for averaging over all possible mutual orientations of the dipole moments at a fixed value of the angle ψ (Fig. 4). Since the dipole moments themselves virtually lie in the plane of the base of the chiral tetrahedron (Fig. 1), one can consider the following options of the nonhomeomorphic mutual orientation of the chiral tetrahedrons in space. In the first case, the tetrahedrons are oriented with the bases facing each other, whereas in the second, the tet-

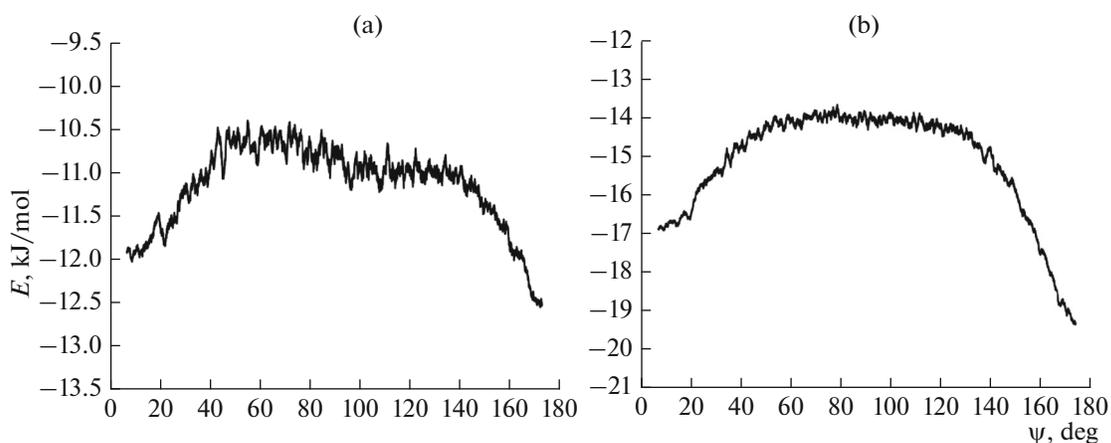


Fig. 4. Dependence of the total potential energy of interaction of a pair of TF AAA molecules in a nanodroplet in heptane on the angle ψ between the normals to the chiral tetrahedron plane: (a) TF AAA-5 and (b) TF AAA-8.

rahedrons are stacked so that the vertex of one tetrahedron faces the base of another. The latter configuration corresponds to the previously described model of a stacked arrangement of molecules [11] and, obviously, provides prerequisites for the formation of anisometric particles via the successive extension of the stack through attachment of additional molecules. In fact, the successive increase in the size of the stack at the expense of new molecules will lead to the formation of a quasi-one-dimensional (molecular thin) aggregates, which can be considered as nuclei of experimentally observed supramolecular strings [1]. At the same time, pairs of molecules in which the tetrahedra are oriented so that the chiral bases face each other can be considered as nuclei of isometric TF AAA condensate particles, which are also consistently observed in experiments [1]. Note that, the configuration in which two chiral tetrahedron are located nearby has not been considered, since it is believed to be unrealistic because of a strong dependence of the dispersion of force on the distance.

For achiral TF AAA-2, the dependence of the total energy on the angle between both the structural vectors and the dipole moments is virtually nonexistent, and therefore, it is not shown. We assume that this is what leads to the formation of isometric precipitates in solutions of achiral TF AAA, in contrast to the quasi-one-dimensional stacking condensation of homochiral TF AAA, resulting in the formation of strings [11]. Solutions of achiral TF AAA-2 in acetone, methanol, dimethyl sulfoxide, carbon tetrachloride, water, liquid ammonia, and butanol were experimentally investigated [11]. It was demonstrated that, in all ranges of concentrations, up to the solubility limit, no strings were formed, despite the large dipole moment of the TF AAA-2 molecule, a factor that, according to the semi-empirical rule [9], is favorable for their formation. Note also that TF AAA-2 solutions produced no nanodroplets [2]. The absence of nanodroplets in

solutions of achiral TF AAA [10] suggests that the complementarity in pairs of molecules imposed by chirality must play an important role in the formation of a nanodispersed phase.

As can be clearly seen from Fig. 5, increases in the interaction energy of a pair of TF AAA molecules at the collinear and anticollinear structural orientations of the structural vectors is observed over the entire range of mutual orientations of the dipole moments. Both these configurations are energetically more favorable than any other mutual orientation of the molecules. Note also that the interaction energy as a function of the mutual arrangement of the molecules (Fig. 5) has no other local minima, which confirms the correctness of the above analysis of the topology of pairs of TF AAA molecules.

The formation complementary pairs in which the molecules are bound to each other more strongly than to the outside molecules should influence the statistically averaged properties of the nanodroplet as a whole. In addition to the anomalously large diffusion coefficient, such an influence can be detected by analyzing the dependence of the point dipole moment of the drops as a whole on its size. In the absence of a correlation in the orientation of the dipole moments, the total dipole moment of the droplet must be proportional to the square root of the number of its constituent molecules. However, as can be seen from Fig. 6, the dependence of the point dipole moment of nanodroplets on their linear dimensions is linear. It was estimated that $\sim 90\%$ of the molecules in the nanodroplet form pairs with zero dipole moment, since their dipole moments are anticollinear. Consequently, the point dipole moment of the nanodroplet is determined by a small fraction of pairs with collinear dipoles. Assuming that the formation of such pairs is a result of a bimolecular reaction, we find that the number of such pairs should be proportional to the square of the number of molecules, whereas the variance of

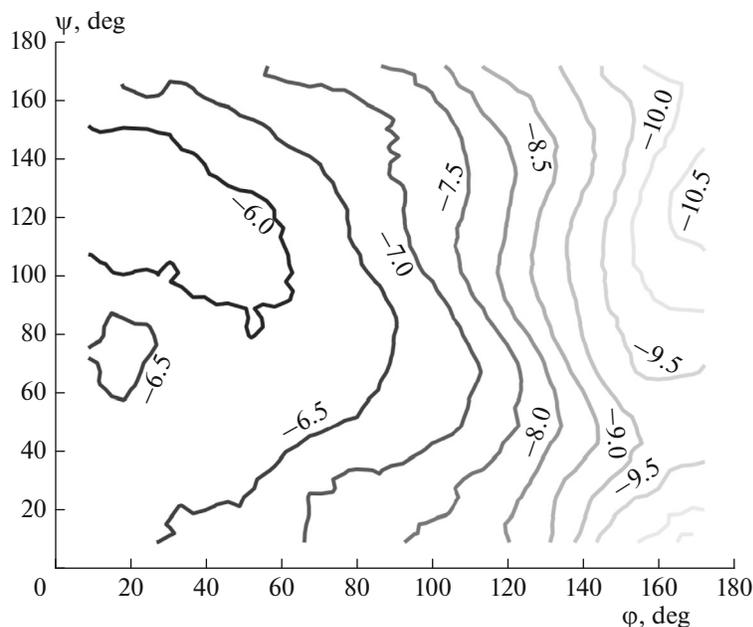


Fig. 5. Dependence of the total potential energy (kJ/mol) on the angles between the dipole moments (φ) and the normals to the planes of the chiral tetrahedron bases (ψ) in pairs of TFAAA-5 molecules in nanodroplets in heptane. Clearly visible are minima corresponding to the open stacks and closed pairs of molecules at the anticollinear orientation of the dipoles.

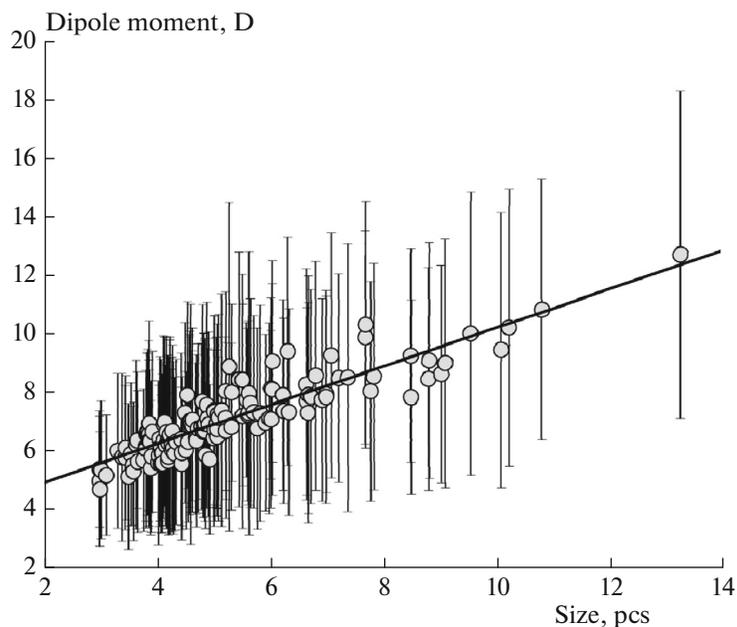


Fig. 6. Dependence of the point dipole moment of TFAAA-5 nanodroplets in heptane on their size. The dependence exhibits a pronounced linear behavior, indicative of the assembling of molecules into stable complementary pairs.

this quantity should be linear in the number of molecules in the droplet. Thus, the linear dependence of the calculated dipole moment of the nanodroplet on the number of particles clearly indicates the formation of complementary pairs of molecules with anticollinear dipole moments.

CONCLUSIONS

Molecular dynamics simulations of the nanodispersed phase observed in dilute solutions of TFAAA enabled to analyze the energies of intermolecular interactions. It was shown that the main contribution to the interaction energy comes from dispersion forces

Energies (kJ/mol) of dipole–dipole (A), electrostatic (B), and dispersion (C) interaction between TFAAA molecules in nanodroplets with each other and with the solvent

System	Number of molecules	TFAAA–TFAAA			TFAAA–solvent	
		A	B	C	A	B
TFAAA-4/cyclohexane	16.1 ± 2.6	−2.68 ± 1.14	−17.7 ± 2.9	−0.98 ± 0.43	−0.35 ± 0.20	−68.7 ± 5.1
TFAAA-4/heptane	21.1 ± 4.1	−6.11 ± 1.19	−19.4 ± 2.4	−1.11 ± 0.47	−0.30 ± 0.19	−60.8 ± 4.1
TFAAA-5/cyclohexane	9.6 ± 2.3	−3.65 ± 1.31	−9.1 ± 2.3	−1.18 ± 0.89	−0.51 ± 0.28	−62.8 ± 3.9
TFAAA-5/heptane	13.3 ± 3.6	−4.38 ± 1.32	−11.6 ± 2.6	−1.15 ± 0.66	−0.45 ± 0.24	−54.8 ± 4.6
TFAAA-8/heptane	12.0 ± 2.2	−4.01 ± 1.15	−14.4 ± 2.3	−1.01 ± 0.65	−0.29 ± 0.22	−70.7 ± 4.6

(~14 kJ/mol), more specifically, 3/4 of the total energy of interaction in a pair of molecules. For the anticollinear orientation of the dipole moments of the TFAAA molecules, their dispersion interaction binding energy is higher by more than kT , indicative of a complementary interaction between the molecules. In this case, the orientation of the dipole moments of the molecules in most of the observed pairs was anticollinear.

It was shown that there are two types of pairs of molecules with nonhomeomorphic structures, i.e., with different topologies. In the first case, the chiral tetrahedrons of the molecules are nested into each other. During condensation, due to the formation of anisometric stacks, such pairs are capable of anisotropic growth and can serve as nuclei of supramolecular strings. In the second case, the tetrahedra join via their bases thereby forming isometric nuclei for an isotropic precipitate.

ACKNOWLEDGMENTS

The MD calculations were carried out on the “Lomonosov” supercomputer at the Moscow University Supercomputer Center.

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Translated by V. Smirnov