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Is the T-Shaped Toluene Dimer a Stable Intermolecular Complex?

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By means of molecular mechanics and *ab initio* calculations, we show that toluene dimer can assume two different minimum energy structures. Both these arrangements are stacked with the methyl groups being parallel and anti-parallel to each other. Although our findings do not agree with the current opinion that one minimum energy structure is T-shaped, they appear to be consistent with available experiments on jet-cooled toluene.

The interaction between aromatic residues plays a key role in many chemical and biological processes. These interactions, usually termed as $\pi-\pi$ interactions,[1] can influence the stereochemistry of organic reactions[2] and the binding affinities in host−guest chemistry.[3] In biological molecular systems, aromatic residues can engage in specific energetically favorable interactions. Base stacking, for example, is certainly important in stabilizing the helical structure of DNA.[4,5] Similarly, the interactions between planar aromatic residues are determinant in stabilizing the tertiary structure of proteins.[6−8]

In the case of the benzene dimer, it has long been known that the T-shaped structure, with the planes of the rings perpendicular to each other, corresponds to the global minimum of the intermolecular potential surface.[9] The T-shaped arrangement is found, in fact, in crystalline benzene.[10] The stacked "sandwich" structures (i.e., with superimposed planes) and the "edge-displaced" (i.e., with the ring planes parallel-displaced), stabilized by dispersive interactions,[9] are also local minima for the benzene dimer. The benzene dimer is often treated as a prototype of aromatic−aromatic interactions,[12,11] but its relevance to the general properties of aromatic residues has been recently questioned by Chipot et al.[11] who proposed the toluene dimer as a better prototype for $\pi-\pi$ interactions in proteins.[13] In this respect, the analysis of protein structures by Burley and Petsko[6] and by Brocchieri and Karlin[14] tends to indicate that stacked conformations are adopted significantly more often in proteins than expected by chance.

Toluene−toluene interactions have been less studied with respect to benzene−benzene interactions. There is widespread agreement in the literature[11,15,16] that for the toluene dimer there exist at least two competing minima that, by analogy with the results obtained on benzene complexes, are often ascribed to one T-shaped and one stacked conformation.[11,17] From the experimental standpoint, spectroscopic investigations of jet-cooled toluene[15] showed that at least two dimers exist, although the experimental technique adopted could not reveal their precise structural nature. Earlier theoretical calculations of the geometry of toluene clusters using empirical force fields predicted a stacked dimer and a stable, albeit at much higher energy, T-shaped dimer that has the methyl moiety of a monomer pointing toward the ring of the partner.[17] Extensive theoretical calculations for the benzene−benzene, benzene−toluene, and toluene−toluene interactions were done by Chipot et al.[11] In this study, the relative stability of T-shaped and stacked conformations were determined by a constrained search in the conformational space, i.e., by varying the centroid−centroid distance while maintaining the relative orientation of the two methyl groups fixed. Each constrained search, for T-shaped or stacked relative orientations, was done by (i) an *ab initio* calculation at the MP2/6-31G+(2d,p) level corrected for the basis set superposition error[18] (BSSE) ,and (ii) an empirical force field. The authors concluded that, in contrast to the case of benzene, the T-shaped complex is not the more stable minimum for the toluene dimer. Manifestly, the authors seem to support the view of two competing minima, the stacked and the T-shaped arrangements, for both benzene−benzene and toluene−toluene dimers, with interchanged binding energy. In this paper we collect strong theoretical indications that there is only one class of stable complexes for the toluene dimers, i.e., the stacked complexes. We also show that this finding is in contrast with current interpretation of theoretical and experimental data but not with the data[11,15] themselves.

TABLE 1: Atomic Charges (in electrons) for the Empirical Potential

atom type[a,b]	charges
CT	-0.330422
HC	0.096465
CA_1	0.143625
CA_2	-0.115342
HA_2	0.109987
CA_3	-0.210331
HA_3	0.139573
CA_4	-0.056016
HA_4	0.105644

[a] Entries in the first column refer to the AMBER atomic types.[22]
[b] The CA_1 carbon atom is bound to the *C*T methyl carbon. CA_2, CA_3, and CA_4 are in ortho, meta, and para positions with respect to *CT*, respectively.

Following a well-established procedure,[19−21] all possible minima for the intermolecular potential energy surface (PES) of the toluene−toluene complex were determined by quenching 4000 structures regularly sampled from a 4 ns molecular dynamics (MD) simulation at 300 K of two toluene molecules in a cubic box of 25 Å sidelength interacting through the AMBER[22] force field. The atomic point charges were obtained

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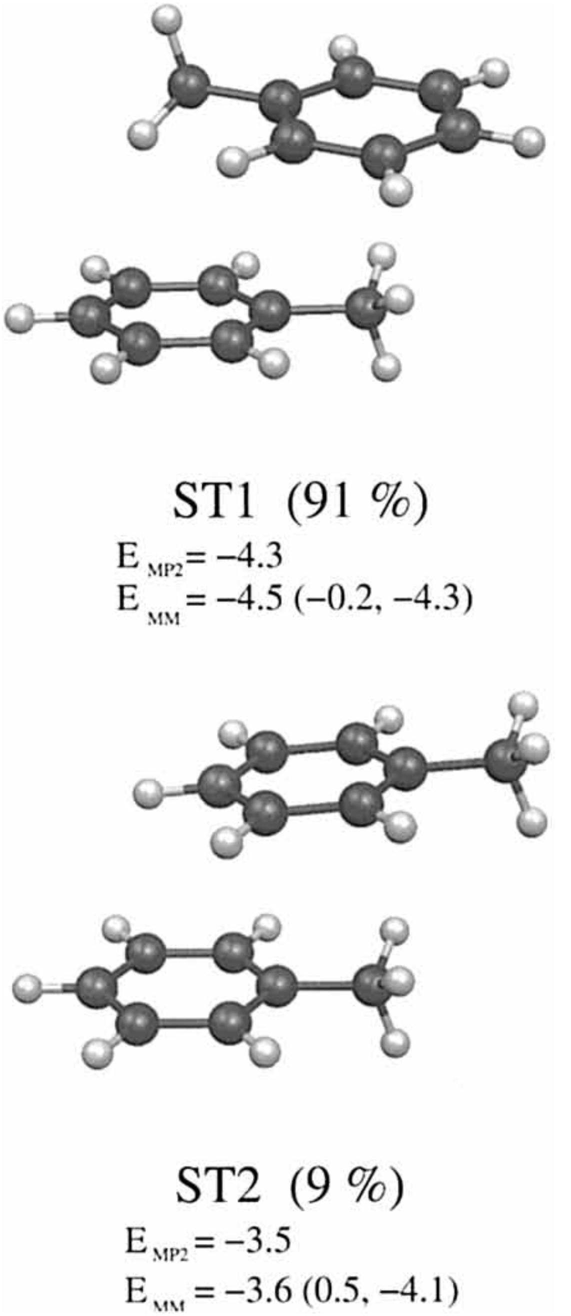

Figure 1. Minimum energy structures for the toluene dimer. In the picture the following data are reported: (i) the population, i.e., the fraction (in percentage) of configurations sampled by a 300 K MD trajectory of two interacting toluene molecules that, after conjugate gradient minimization, yield the corresponding minimum; (ii) the *ab initio* binding energy (E_{MP2}); (iii) the AMBER binding energy (E_{MM}) with, in brackets, the electrostatic and dispersive contributions. Energies are in kcal mol^{-1}.

TABLE 2: PDB Structure of ST1 and ST2

REMARK	1				ST1		
ATOM	1	CB	PHE	1	−11.392	−11.418	0.434
ATOM	2	HB1	PHE	1	−12.348	−11.882	0.670
ATOM	3	HB2	PHE	1	−10.689	−12.181	0.100
ATOM	4	HB3	PHE	1	−11.525	−10.693	−0.368
ATOM	5	CG	PHE	1	−10.851	−10.726	1.667
ATOM	6	CD1	PHE	1	−11.217	−9.397	1.948
ATOM	7	HD1	PHE	1	−11.884	−8.869	1.282
ATOM	8	CE1	PHE	1	−10.716	−8.753	3.095
ATOM	9	HE1	PHE	1	−10.998	−7.732	3.309
ATOM	10	CZ	PHE	1	−9.848	−9.438	3.964
ATOM	11	HZ	PHE	1	−9.464	−8.944	4.845
ATOM	12	CE2	PHE	1	−9.482	−10.767	3.686
ATOM	13	HE2	PHE	1	−8.817	−11.294	4.354
ATOM	14	CD2	PHE	1	−9.985	−11.410	2.540
ATOM	15	HD2	PHE	1	−9.702	−12.431	2.327
ATOM	16	CB	PHE	2	−7.844	−8.650	0.706
ATOM	17	HB1	PHE	2	−7.777	−8.943	1.753
ATOM	18	HB2	PHE	2	−8.712	−8.002	0.583
ATOM	19	HB3	PHE	2	−6.942	−8.111	0.420
ATOM	20	CG	PHE	2	−7.994	−9.879	−0.164
ATOM	21	CD1	PHE	2	−7.461	−11.112	0.256
ATOM	22	HD1	PHE	2	−6.950	−11.182	1.204
ATOM	23	CE1	PHE	2	−7.600	−12.255	−0.553
ATOM	24	HE1	PHE	2	−7.192	−13.201	−0.228
ATOM	25	CZ	PHE	2	−8.268	−12.166	−1.787
ATOM	26	HZ	PHE	2	−8.374	−13.043	−2.410
ATOM	27	CE2	PHE	2	−8.798	−10.934	−2.211
ATOM	28	HE2	PHE	2	−9.310	−10.865	−3.161
ATOM	29	CD2	PHE	2	−8.660	−9.792	−1.401
ATOM	30	HD2	PHE	2	−9.066	−8.847	−1.728
REMARK	1				ST2		
ATOM	1	CB	PHE	1	−9.288	−6.681	−10.579
ATOM	2	HB1	PHE	1	−9.929	−7.040	−9.774
ATOM	3	HB2	PHE	1	−9.827	−5.940	−11.169
ATOM	4	HB3	PHE	1	−8.399	−6.215	−10.154
ATOM	5	CG	PHE	1	−8.889	−7.848	−11.457
ATOM	6	CD1	PHE	1	−9.688	−8.209	−12.558
ATOM	7	HD1	PHE	1	−10.584	−7.650	−12.782
ATOM	8	CE1	PHE	1	−9.325	−9.304	−13.364
ATOM	9	HE1	PHE	1	−9.942	−9.588	−14.205
ATOM	10	CZ	PHE	1	−8.165	−10.040	−13.070
ATOM	11	HZ	PHE	1	−7.894	−10.890	−13.681
ATOM	12	CE2	PHE	1	−7.364	−9.681	−11.971
ATOM	13	HE2	PHE	1	−6.477	−10.254	−11.744
ATOM	14	CD2	PHE	1	−7.727	−8.587	−11.165
ATOM	15	HD2	PHE	1	−7.114	−8.318	−10.317
ATOM	16	CB	PHE	2	−10.601	−10.633	−9.802
ATOM	17	HB1	PHE	2	−9.736	−10.155	−9.342
ATOM	18	HB2	PHE	2	−11.234	−11.065	−9.028
ATOM	19	HB3	PHE	2	−11.163	−9.881	−10.355
ATOM	20	CG	PHE	2	−10.142	−11.725	−10.743
ATOM	21	CD1	PHE	2	−10.910	−12.049	−11.878
ATOM	22	HD1	PHE	2	−11.826	−11.515	−12.079
ATOM	23	CE1	PHE	2	−10.483	−13.064	−12.755
ATOM	24	HE1	PHE	2	−11.072	−13.308	−13.627
ATOM	25	CZ	PHE	2	−9.288	−13.759	−12.498
ATOM	26	HZ	PHE	2	−8.959	−14.538	−13.172
ATOM	27	CE2	PHE	2	−8.522	−13.441	−11.362
ATOM	28	HE2	PHE	2	−7.604	−13.976	−11.164
ATOM	29	CD2	PHE	2	−8.950	−12.427	−10.486
ATOM	30	HD2	PHE	2	−8.359	−12.182	−9.616

by a restrained electrostatic potential fit[23] of *ab initio* (MP2/6-31G*(0.25) level of theory) derived electrostatic potentials (Table 1). The dipole moment deriving from this charge distribution is 0.34 D, in good agreement with that calculated *ab initio* (0.37 D) at the MP2/6-31G*(0.25) level of theory and with the experimental value[24] of 0.37 D. The same calculations were repeated, for comparison, using the empirical potential of Chipot et al.[11] The program ORAC[25] was used in all the MD simulations and energy minimizations. Both empirical potentials after quenching gave the same two minima (see Figure 1) from now on indicated as ST1 and ST2 (the PDB coordinates of these two structures are reported in Table 2). According to “our” force field (Table 1), the binding energy for ST1 and ST2 is −4.5 and −3.6 kcal mol^{-1}, respectively, with ST1 representing 91% of all the minima (with the potential of Chipot et al. the binding energy of ST1 is −4.4 kcal mol^{-1}, which is 1 kcal mol^{-1} lower than that of ST2, and represents 90% of all the minima). These results show that unconstrained scanning of the PES at 300 K for the toluene−toluene intermolecular interactions does not produce, after quenching, any stable T-shaped minimum either with our potential or with the potential adopted by Chipot et

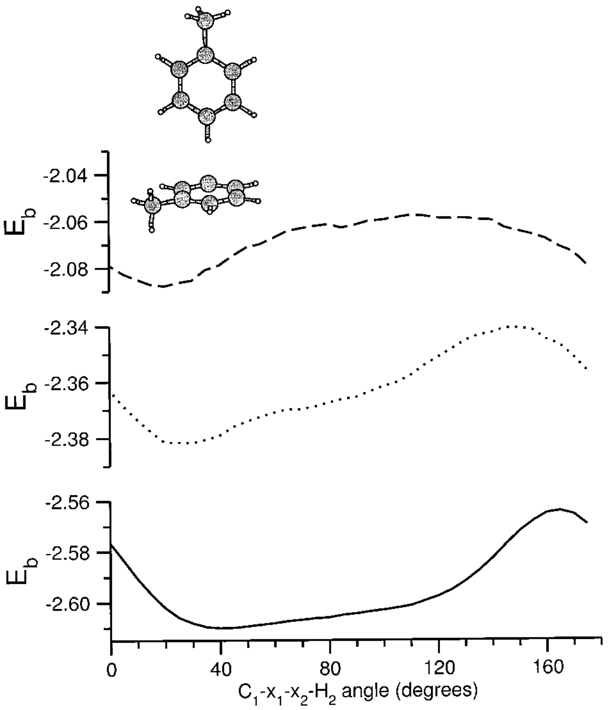

Figure 2. Binding energy (E_b) as a function of the $C_1-x_1-x_2-H_2$ dihedral angle (see text): solid line refers to the MP2-6-31G*(0.25) *ab initio* calculations; dashed and dotted lines refer to our and Chipot et al. molecular mechanics calculations, respectively. Energies are in kcal mol^{-1}. The dimer structure corresponding to the relative minimum energy is represented in the picture.

al.[11] For the structures corresponding to ST1 and ST2, we calculated the BSSE-corrected MP2 binding energy using a 6-31G* basis set, where the exponent of the polarization functions for the carbon atoms is replaced by a more diffuse one ($\alpha(d) = 0.25$). The MP2/6-31G*(0.25) level of theory was shown to give a good agreement with higher level (MP4, coupled cluster) calculations using more extended basis sets in the case of aromatic interactions.[5,9,16,21] All *ab initio* calculations were done using the NWChem package.[26] The *ab initio* binding energies of ST1 and ST2 are in excellent agreement with the molecular mechanics values (see Figure 1).

To show that the T-shaped complex analyzed in ref 11 is not a stationary point of the PES, we repeated the calculations done in ref 11. To this end, two sets of calculations were performed using (i) empirical potentials, and (ii) BSSE-MP2/6-31G*(0.25) *ab initio* method. For the determination of the most favorable constrained T-shaped complex, the two toluene molecules were kept, as done in ref. 11, at a ring centroid distance of 5.0 Å (5.1 Å in the case of the molecular mechanics calculation) with the two methyl moieties perpendicular to each other, while the $C_1-x_1-x_2-H_2$ dihedral angle (with C_1, x_1, x_2, H_2 being the methyl carbon of molecule 1, the centroid of molecule 1, the centroid of molecule 2, and the methyl hydrogen in the ring plane of molecule 2, respectively) was varied from 0° to 360° in steps of 5°. The favored T-shaped geometry according to *ab initio* calculations corresponds to a dihedral angle of about 40°. Both empirical potentials, in remarkable agreement with *ab initio* data, gave similar results (see Figure 2). The Chipot et al. energies for the T-shaped minimum using the potential of Table 1 of ref 11 were perfectly reproduced.[27]

Starting from the constrained most favorable T-shaped minimum (see Figure 2), a conjugate gradient minimization[28] was performed using the empirical potential of Table 1. The optimization ended up in a stacked complex, i.e., ST2. Along the minimization path 17 snapshots were taken; at each snapshot the *ab initio* BSSE-corrected binding energy was calculated. Results are collected in Figure 3. The *ab initio* binding energy decreases almost monotonically, along the path determined using the empirical potential, reaching its lowest value at the ST2 structure, with virtually no barrier between T-shaped and stacked complexes.[29]

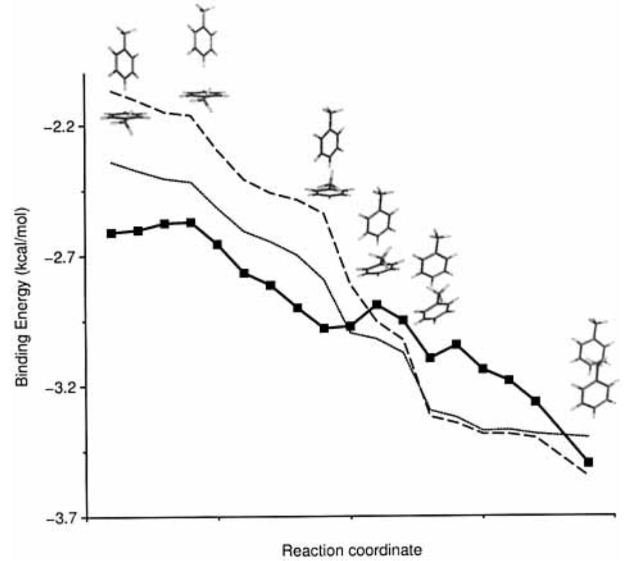

Figure 3. Binding energy of the toluene dimer along the conjugate gradient trajectory connecting the most stable constrained T-shaped structure and a stacked structure as determined using the empirical potential of the Table 1. Solid line refers to the BSSE-MP2/6-31G*-(0.25) binding energy. The dashed line refers to molecular mechanics binding energy using the potential of Table 1. The dotted line refers to the Chipot et al. empirical potential.[11]

Why does the toluene dimer, in contrast to benzene, not form stable T-shaped structures? Unlike benzene, toluene has a small permanent dipole moment and, while the quadrupole−quadrupole interaction in benzene tends to favor a T-shaped conformation, the dipole−dipole interaction in toluene favors an antiparallel stacked structure. The presence of the methyl moiety in toluene also makes a significant contribution in the dispersive interactions: if in our empirical force field of Table 1 we turned off the atomic charges, starting from any T-shaped conformation we get a single stacked minimum conformation, with aligned methyl groups (ST2). Not surprisingly, the only way to get a stable T-shaped conformation is to turn off, along with the charges, also the dispersive interactions on the methyl group: in this case a benzene-like T-shaped minimum is recovered.

In conclusion, the toluene dimer has two minimum conformations and both (ST1 and ST2) are stacked. ST1 is stabilized by electrostatic interactions as well as dispersive interactions and is 1 kcal mol^{-1} more stable than ST2; ST2 is stabilized mainly by dispersive interactions while electrostatics is destabilizing (see Figure 1).

Our results offer an alternative interpretation of hole burning spectroscopy measurements of supersonic jet gaseous toluene.[15] As suggested in ref 15, the broadness and red shift in the hole burning electronic transition can be due to the interactions of the antiparallel dipole moments in the first excited singlet state. This hypothesis is consistent with the arrangement of the ST1 structure where toluene monomers are antiparallel. Therefore the more stable ST1 complex could be the dimer giving rise to the broad signal at the monitoring frequency of 37385 cm^{-1}, while the virtually unshifted and sharp peak at monitoring frequency of 37454 cm^{-1} could be due to the ST2 stacked dimer.

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