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A Novel Tyrosine Derivative to Study Non-Covalent Assembly Involving C–H···O Hydrogen Bonding

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A novel tyrosine derivative, 3-*N*-tosyl-4-*p*-tosyloxybenzyl oxazolidin-4-one (TTBO), $C_{24}H_{23}NO_7S_2$, was synthesized. It shows high affinity to chloroform in a ratio of 1:1 as evidenced by spectroscopic studies. Ab initio 3-21G*//PM3 calculations indicate that the C–H···O hydrogen bond with a strength of up to 5.9 kcal/mol may be responsible for the non-covalent assembly.

Weak directional interactions of the type C–H···O are currently one of the main topics of hydrogen-bond research[1–3] in both experimental and theoretical fields. The strengths of the C–H···O hydrogen bonds, as judged from spectroscopic and geometric data, cover a wide range which overlaps with "normal" O/N–H···O hydrogen bonds for more acidic C–H donor types [such as C≡C–H, $CHCl_3$, $CH(NO_2)_3$],[4] and which merge with van der Waals interactions for the weakest C–H donors.[5] We discuss here the interaction between chloroform and 3-*N*-tosyl-4-*p*-tosyloxybenzyl oxazolidin-4-one (TTBO) based on ab initio calculations with the 3-21G*//PM3 basis set at the PM3 optimized geometries.

TTBO was synthesized and characterized by ^{1}H NMR (300 MHz), ^{13}C NMR, and FT-IR spectroscopies. The details will be published elswhere. The structure of TTBO is shown in Fig. 1. TTBO forms a 1:1 complex with chloroform, as evidenced by the continuous variation method[6] (job plot), i.e., solutions of different mole fractions were prepared and their absorbances were measured. It was found that the absorbance is maximum at a mole fraction of 0.5, indicating the TTBO–$CHCl_3$ stoichiometry to be 1:1 (Fig. 2); the association constant[7] was found to be 2.6×10^4 M^{-1}. The experimental findings of this study were complemented by quantum chemical semiempirical and ab initio computations on the substrate and adduct species. To understand the nature of the bonding in the 1:1 complex, we examined the molecular and electronic structures theoretically by quantum chemical computations, the results of which reflect the gas-phase situation. The molecules were initially subjected to complete structural optimization at the Hartree–Fock level. Due to the large size of TTBO and its adduct, structural

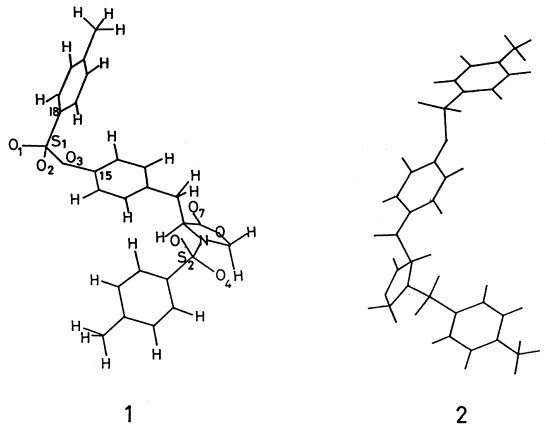

Fig. 1. PM3 optimized geometries of TTBO. The dihedral angles C_{18} $S_1O_3C_{15}$ are 68.7 ° and 175.9 ° in **1** and **2** respectively.

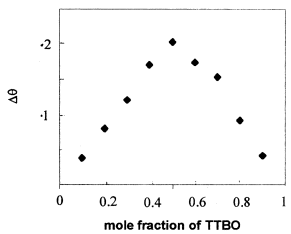

Fig. 2. Titration of 1 mM of TTBO with 1 mM $CHCl_3$ in methanol in the formation of 1:1 adduct (Job plot) at 20 °C ($\Delta\theta$ is the difference in circular dichroic absorbance).

optimization was carried out by the semiempirical PM3 method.[8] At PM3 optimized geometries, single-point ab initio MO calculations were performed with the 3-21G* basis set. The bonding in these species was examined by a natural bond orbital (NBO) analysis,[9] and the natural charges on the different atomic centers and the covalent bond orders were obtained. The computations were performed using the GAUSSIAN 94[10] suite of programs in a DIGITAL CELEBRIS XL590 Computer upgraded with 192 MB RAM.

We characterized different conformers of TTBO by complete structural optimization using the PM3 method. Single-point ab initio calculations with the 3-21G* basis set at PM3 optimized geometries reveal that the energy difference between these conformers is small and lies within 1.5 kcal/mol. We examined the hydrogen bonding with two geometrical arrangements, **1** and **2** (Fig. 1). The calculations predict that **2** is lower in energy than **1** by 0.7 kcal/mol. We characterized the structures of A1, B1, and C1 with hydrogen bonding involving oxygen bonded to S1, S2, and the carbonyl oxygen, respectively. The structures are shown in Fig. 3a. The adduct geometries of A2, B2, and C2, obtained from structure **2** of TTBO, are shown in Fig. 3b. The hydrogen-bond distance is close to 1.80 Å in A1 and B1, while in the remaining structures it is longer in the range of 2.48 to 2.52 Å. These lengths are shorter than the sum of the van der Waals radii of O and H (2.6 Å), and are typical for hydrogen-bond lengths involving a C-H donor and an oxygen acceptor. These values are close to the intermolecu-

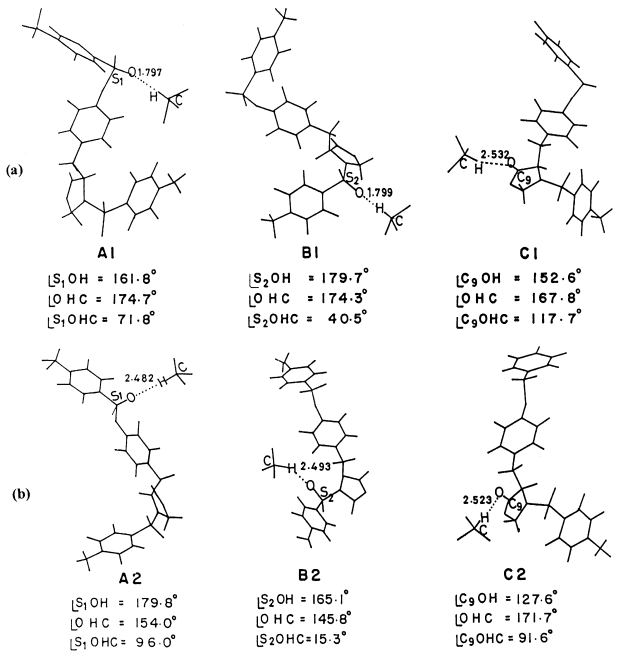

Fig. 3. PM3 optimized geometries of 1:1 complex formed from TTBO, (a) **1** and (b) **2**.

Table 1. NPA Charge on the Hydrogen Bonding Sites, Hartree–Fock 3-21G*//PM3 Energies (for Chloroform the NPA Charge on Hydrogen and Total Energy Are 0.31 and −1410.40643)

TTBO Type	Atomic Center	NPA Charge	Total energy atomic units	Binding energy kcal/mol
1	O_1	−0.95		
	O_4	−0.97	−2283.60072	
	O_7	−0.57		
2	O_1	−0.96		
	O_4	−0.96	−2283.60190	
	O_7	−0.57		
A1	O	−1.00	−3694.01374	4.1
	H	0.36		
B1	O	−1.00	−3694.01616	5.7
	H	0.36		
C1	O	−0.60	−3694.01577	5.4
	H	0.34		
A2	O	−0.98	−3964.01596	4.8
	H	0.34		
B2	O	−0.99	−3694.01050	1.4
	H	0.34		
C2	O	−0.59	−3694.01771	5.9
	H	0.34		

lar C–H···O–C lengths of 2.34 to 2.45 Å observed in benzoquinone crystal.[11] The shorter H-bond lengths in A1 and B1 lead us to infer the possibility of stronger hydrogen bonding interactions in them.

The Hartree-Fock 3-21 G*//PM3 energies of the 1:1 complex is found to be lower when TTBO has geometry **2**, as compared to that of **1**. The stabilization energy with reference to the component species, which corresponds to the strength of the hydrogen bond formed, is also found to be more pronounced when the amino acid derivative possesses geometry **2**. Complexes C1 and C2, which involve the carbonyl oxygen as the hydrogen-bond acceptor, have significant binding energies of 5.4 and 5.9 kcal/mol, respectively. B2 has a lower stabilization energy of 1.4 kcal/mol, probably due to repulsive interactions between the chloroform hydrogen and the proximal hydrogens in TTBO. The binding energies in A1 and A2 are moderate, the values being 4.1 and 4.8 kcal/mole, respectively. The PM3 method also gives evidence for hydrogen-bonding stabilization, though the magnitude is small.

The net charges on the atomic centers obtained by a Natural Population Analysis (NPA) and the total energy (in atomic units) are listed in Table 1. Wiberg's covalent bond order[12] of the hydrogen bond is very small (∼0.01 to 0.05), indicating a negligible covalent character to the hydrogen bond. Significant net atomic charges on the hydrogen bonding centers suggest the role of dipolar interactions between the two units in the adduct. It is noted that the chloroform H is slightly more electropositive in the 1:1 complex compared to the free chloroform. Similarly, the acceptor oxygen center exhibits more negative charge in the adduct than in TTBO.

The present theoretical analysis reveals the existence of competing hydrogen-bonding interactions between chloroform and the different acceptor oxygen centers of TTBO in the gas phase. The energy gain achieved through hydrogen bonding is in the range of 4.1 to 5.9 kcal/mol, except in conformation B2, which has a low binding energy of 1.4 kcal/mol. A NBO analysis led to the conclusion that the C–H···O bond has a negligible covalent character, and that dipolar interactions may play a significant role in hydrogen-bond formation. The ΔG obtained from K (2.6×10^4 M^{-1}, 5.91 kcal/mol) agrees with gas-phase calculations, indicating that the dipolar interaction drives complex formation. The hydrogen-bonding distances of 2.48 to 2.52 Å, the nearly linear X–O···H directional property and the magnitude of binding energies in most of the conformation that we studied clearly provide support for hydrogen binding between TTBO and $CHCl_3$ in the gas phase.

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