The Magnitude of [C−H···O] Hydrogen Bonding in Molecular and Supramolecular Assemblies

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Abstract: Ab initio calculations at the MP2/6-311++G** level on model systems (*N*-methylpyridinium complexes of dimethyl ether and dimethyl phosphate anion) provide quantitative measures of the large stabilization energies that arise from [C−H···O] contacts in charged systems. These attractive interactions control (i) the self-assembly of bipyridinium-based catenanes and rotaxanes in solution, (ii) the self-organization of left-handed Z-DNA with alternating [dC−dG] sequences in the solid state, and (iii) the binding of pyridinium derivatives with single- and double-stranded DNA. Slightly attractive interactions occur between the donor ether and phosphate moieties and a neutral pyridine molecule in the gas phase. Electrostatic potential and solvation calculations demonstrate that [C−H···O] interactions which involve a cationic [C−H] donor are dominated by electrostatic terms.

Introduction

The architectures of interlocked molecules and molecular complexes are determined by various types of noncovalent interactions. Figure 1 shows pictorially three different systems—a crown ether-based catenane (Figure 1a), a DNA−porphyrin complex (Figure 1b), and a complex of two double-stranded DNA helices. While structurally diverse and seemingly unrelated, these systems have, in common, strong intermolecular [C−H···O] hydrogen bonds.

A wealth of structural information has been obtained[1] for catenanes and rotaxanes formed from interlocked π-electron-deficient bipyridinium-based cyclophanes and π-electron-rich dioxyarene-based macrocyclic polyethers. In molecules such as the [2]catenane shown in Figure 1a, both [$\pi\cdots\pi$] stacking interactions between the π-electron-rich and π-electron-deficient aromatic units and [C−H···O] hydrogen bonds have been identified[2] as important bonding interactions.

Porphyrin derivatives, bearing appended pyridinium rings, bind single- and double-stranded DNA (Figure 1b).[3] Qualitative molecular modeling studies indicate close contacts between the pyridinium rings and the phosphate groups, but the energies associated with these interactions are not known.[4] [C−H···O] hydrogen bonds between the acidic pyridinium hydrogen atoms and the negatively charged phosphate oxygen atoms might play a primary role in these molecular recognition processes. Indeed, in crystals of left-handed Z-DNA with alternating [dC−dG] sequences, close [C−H···O] contacts between adjacent nucleic acid molecules are observed[5] systematically (Figure 1c). These interactions involve the phosphate oxygen atoms and the [C−H] groups of guanine heterocycles.

Recently, Dixon et al.[6] proposed that [C−H···O] hydrogen bonding can be an important factor in amide conformations and dimerizations as well as protein folding. High-level theoretical studies have provided computational support for interactions of 2−3 kcal mol^{-1} between α-CH bonds and peptide carbonyl oxygens in such neutral systems.[6b]

We have undertaken a quantum mechanical investigation of the interactions between charged and uncharged systems, in which the main nonbonded contacts involve [C−H] bonds on

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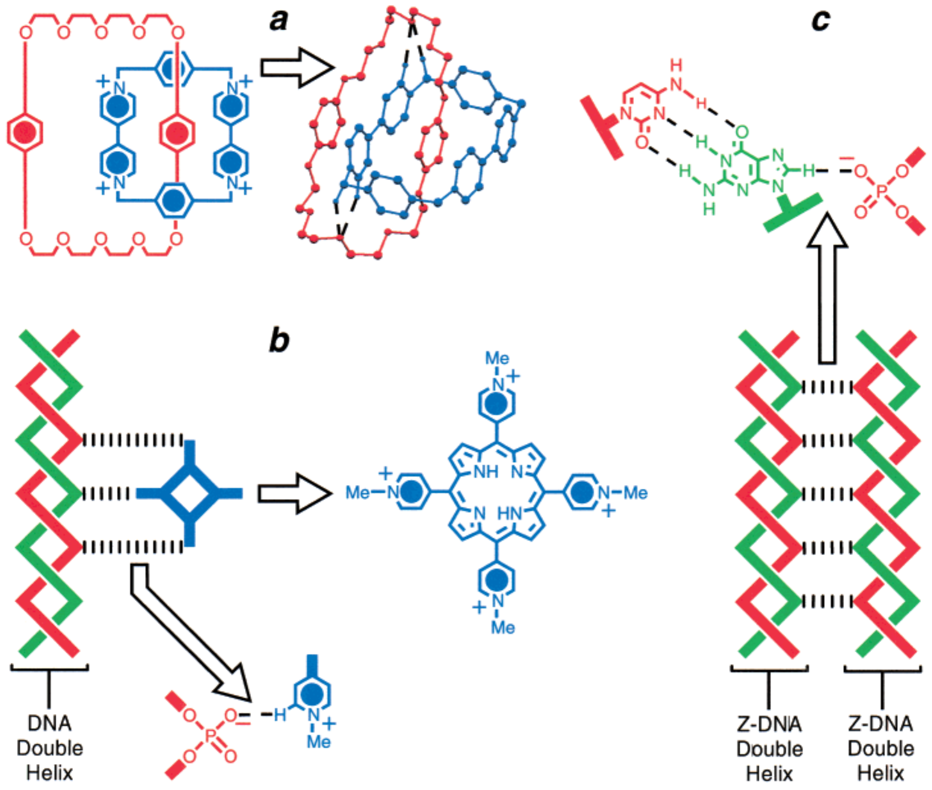

Figure 1. (a) Geometry adopted by a bipyridinium-containing [2]catenane in the solid state and the associated intracatenane $[C-H\cdots O]$ interactions. (b) Schematic representation of a supramolecular assembly composed of a DNA double helix and a pyridinium-containing derivative and the intercomponent $[C-H\cdots O]$ interactions. (c) Schematic representation of the geometry adopted by two adjacent left-handed Z-DNA double helices with alternating [dC−dG] sequences in the crystal and the associated interhelix $[C-H\cdots O]$ interactions.

electron-deficient species and oxygen atoms on electron-rich species. We describe these attractive interactions as $[C-H\cdots O]$ interactions or $[C-H\cdots O]$ hydrogen bonds, consistent with the conclusions of previous investigations.[6,7] We have selected the *N*-methylpyridinium cation[8] ($MePy^+$), dimethyl ether (Me_2O), and the dimethyl phosphate anion $[(MeO)_2PO_2^-]$ as the components of model $[C-H\cdots O]$ complexes. Here, we report the computational analysis of the geometries and interaction energies of the $[C-H\cdots O]$ hydrogen bonds existing in $[MePy{\cdot}Me_2O]^+$ and $[MePy{\cdot}(MeO)_2PO_2]$ dimeric complexes.

Computational Methods

Geometries of complexes involving the aromatic protons of $MePy^+$ with Me_2O and $(MeO)_2PO_2^-$ were first optimized at the restricted Hartree−Fock (RHF) level and characterized as minimums by harmonic frequency analysis. Further geometry optimization of the RHF structures was then carried at the correlated second-order Møller−Plesset (MP2) level. The 6-311++G** basis set was utilized throughout, which includes polarization and diffuse functions on all hydrogen atoms in order to account for electronic anisotropy of protons involved in hydrogen bonding. Zero-point energy corrections utilized in the determination of binding energies are based on the RHF vibrational frequencies and were scaled by a factor of 0.89.

Constrained optimizations of pyridine (Py) complexes (resulting from removal of the methyl group from $MePy^+$) were performed subject to geometric constraints described in the Results and Discussion section (vide infra). Key bond lengths and angles were held fixed with values equal to those in the analogous $MePy^+$ complexes, with all other geometric parameters optimized on the MP2/6-311++G** surface.

The effect of basis set superposition error (BSSE) on the MP2 binding energies was determined through the counterpoise method of Boys and Bernardi.[9] Solvation calculations utilized the polarizable continuum model (PCM) of Tomasi et al.[10] with dielectric constants of 80.1 (H_2O) and 4.81 ($CHCl_3$) using RHF wave functions. All calculations were performed with the Gaussian 98 program system.[11]

Results and Discussion

Early investigations of the physical properties of organic compounds suggested[12,13] that [C−H] groups might be involved in attractive hydrogen-bonding interactions. However, conclusive evidence for the existence of $[C-H\cdots O]$ hydrogen bonds was provided[14] by crystallographic studies. A wealth of structural[13,15] and spectroscopic[16,17] data revealed that these interactions occur systematically with certain distances ($[H\cdots O] = 2.0-3.0$ Å, $[C\cdots O] = 3.0-4.0$ Å) and angles ($[C-H\cdots O] = 90-180°$). It is now well recognized that $[C-H\cdots O]$ hydrogen bonds play a fundamental role in determining the packing of organic molecules in the solid state.[13,15,18] They assist and often control molecular recognition events in biological[4−6,19] and artificial[1,8,20] systems. They are of primary importance in crystal

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engineering,[18,21] in template-directed synthesis,[1] in receptor–substrate interactions,[1,8,20] and in determining the tertiary structures of biomolecules.[5,6] The need to understand the fundamental properties of [C–H···O] hydrogen bonds has stimulated[7] systematic and thorough computational analyses, and recently, a definitive study of [C–H···O] hydrogen bonds in neutral complexes has been reported.[6,7f]

Model complexes of $MePy^+$ and Me_2O, with the ether oxygen atom at an initial distance of 2.0 Å from the ortho, meta, and para pyridinium hydrogen atoms were constructed and preoptimized at the RHF/6-311++G** level of theory. A structure similar to **A** (Figure 2) was obtained when the acceptor was next to either the ortho or the meta pyridinium hydrogen atom in the initial orientation. Geometry **B** was obtained when the acceptor was next to the para pyridinium hydrogen atom in the initial orientation. These resultant complexes were then optimized at the correlated MP2/6-311++G** level, giving rise to the geometric parameters provided in Figure 2. PCM solvation energies for **A** and **B** were calculated for $CHCl_3$ and H_2O solvent.

Optimized structures were generated in a similar fashion for the $MePy^+$ complex of $(MeO)_2PO_2^-$. Bifurcated structure **C** (Figure 2) was obtained when the acceptor was next to either the ortho or the meta pyridinium hydrogen atom in the initial orientation, and geometry **D** was obtained when the acceptor was next to the para pyridinium hydrogen atom.

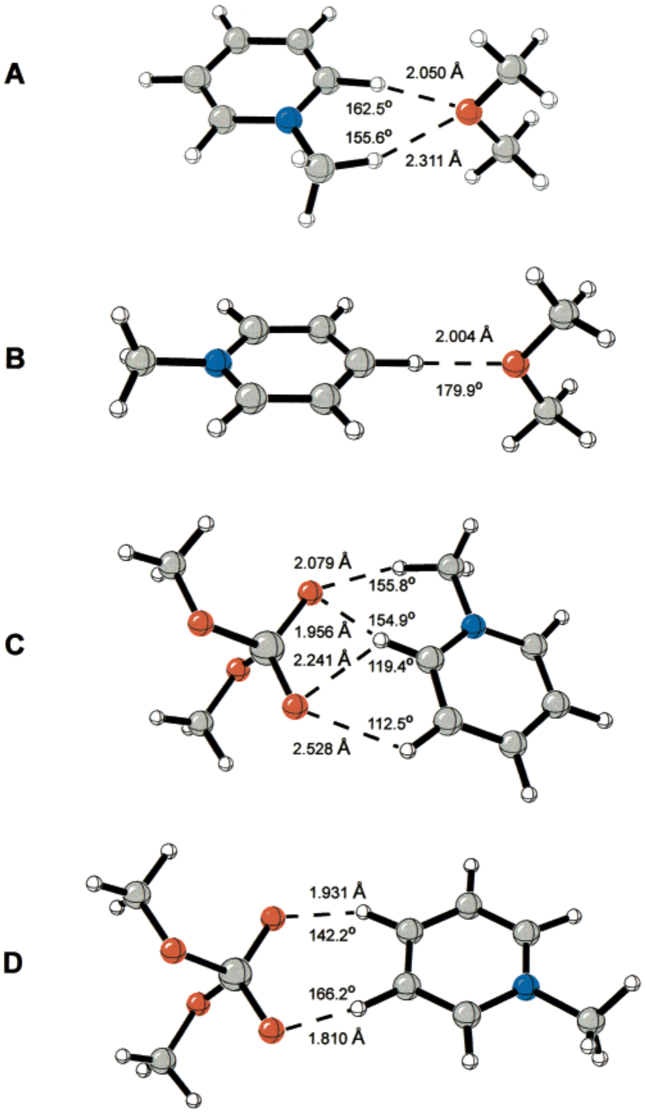

Figure 2. MP2/6-311++G** optimized geometries **A** and **B** of the complex $[MePy{\cdot}Me_2O]^+$ and **C** and **D** of the complex $[MePy{\cdot}(MeO)_2PO_2]$ and associated [C–H···O] distances and angles.

To determine the effect of the charge of the cationic pyridinium nitrogen atom on the binding energies, analogous Me_2O and $(MeO)_2PO_2^-$ complexes of the neutral Py were optimized at the MP2/6-311++G** level. The [C–H···O] lengths and angles were held to be the same as those in the $MePy^+$ complexes. The Py ring and the Me_2O and $(MeO)_2PO_2^-$ skeletons were allowed to optimize with respect to these constraints.

In **A** (Figure 2), the oxygen atom of Me_2O interacts simultaneously with the pyridinium hydrogen atom in the ortho position and with one of the hydrogen atoms of the methyl group. These bifurcated [C–H···O] interactions have indeed been observed[2] experimentally in the solid state (Figure 1a) for catenanes and rotaxanes incorporating 4,4′-bipyridinium units and polyether chains. The [C–H···O] distances and angles are remarkably similar to those determined[2c] experimentally (2.2–2.6 Å and 140–160°) by single-crystal X-ray analysis for catenanes and rotaxanes incorporating 4,4′-bipyridinium units and polyether chains. In **B** (Figure 2), the oxygen atom of the acceptor interacts with the pyridinium hydrogen atom in the para position. The oxygen atom of the acceptor and the pyridinium ring of the donor are also coplanar in **B**.

The BSSE-corrected, gas-phase MP2/6-311++G** interaction energy is -10.0 kcal mol^{-1} in **A** and -7.5 kcal mol^{-1} in **B** (Table 1). This difference is a result of the fact that two [C–H···O] interactions are present in **A**, while only one is

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Table 1. MP2/6-311++G** Interaction Energies for the *N*-Methylpyridinium ($MePy^+$) and Pyridine (Py) Complexes **A**−**D**

	ΔE (kcal mol^{-1})			
geometry	gas phase[a]	gas phase[b]	$CHCl_3$[c]	H_2O[d]
A	−12.2 [−10.0]	−1.9 [−0.2]	−2.2	+4.5
B	−9.2 [−7.5]	−2.9 [−1.3]	+0.2	+6.1
C	−93.1 [−88.1]	−4.7 [−1.4]	−19.7	+4.2
D	−84.2 [−79.6]	−11.5 [−7.2]	−16.0	+6.1

[a] The interaction energies (ΔE) were calculated by subtracting the energies of the separately optimized and zero-point-corrected donor and acceptor molecules from the energy of the optimized and zero-point-corrected complex [MP2/6-311++G** + ZPE(RHF)]. The values in brackets correspond to the basis set superposition error (BSSE)-corrected interaction energies. [b] The values in parentheses refer to the complexes derived from **A**−**D** by removing the methyl group and the positive charge of the donor $MePy^+$, followed by constrained optimization (MP2/6-311++G**). The values in brackets correspond to the BSSE-corrected interaction energies. [c] BSSE-corrected interaction energies for **A**−**D** including solvation energies calculated using the PCM for $CHCl_3$ ($\epsilon = 4.81$). [d] BSSE-corrected binding energies for **A**−**D** including solvation energies calculated using the PCM for H_2O ($\epsilon = 80.10$).

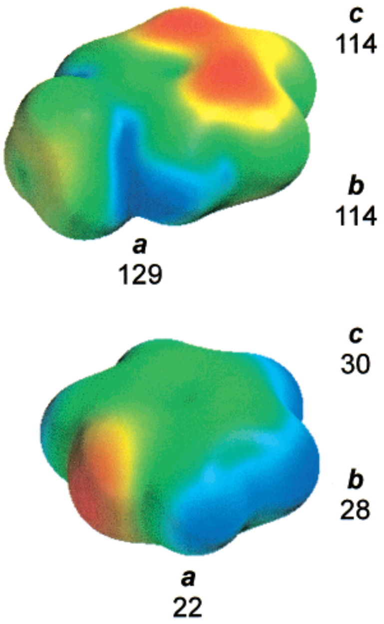

Figure 3. RHF/6-311+G** electrostatic potential (kcal mol^{-1}) mapped on the van der Waals surfaces of (left: red = 92, blue = 133) $MePy^+$ and (right: red = −46, blue = 30) Py and the values calculated on their hydrogen atoms in the (a) ortho, (b) meta, and (c) para positions.

associated with **B**. The RHF/6-311+G** electrostatic potential was mapped on the van der Waals surface of $MePy^+$ (left side of Figure 3) by employing the geometry adopted by this H-bond donor as depicted in **A**. The favorable electrostatic potential at position a favors complex **A**. The interaction energy is reduced to only −2.2 kcal mol^{-1} in $CHCl_3$ and becomes positive in H_2O. The depressive effect of the dielectric constant of the solvent on the [C−H···O] interactions suggests that these interactions are dominated by electrostatic terms. In **B**, the attractive [C−H···O] interactions are suppressed by the solvent and the interaction energy in $CHCl_3$ or H_2O is positive.

The interaction energies for the neutral Py complexes derived from **A** and **B** are significantly smaller than for the charged systems (Table 1). The electrostatic potential map of Py (right side of Figure 3) shows no electron-deficient “pocket” next to the nitrogen atom, in contrast to that observed for $MePy^+$. The electrostatic potential near the para Py hydrogen atom is larger than that of the ortho hydrogen; accordingly, the complex derived from **B** is more stable than that derived from **A**. The reversed trend in interaction energies for the Py complexes is also a result of a more favorable arrangement for dipole−dipole interactions in **B**. In the $MePy^+$ complexes, instead, charge-dipole interactions are facilitated in **A**.

In **C** (Figure 2), two phosphate oxygen atoms interact simultaneously with three pyridinium hydrogen atoms. In **D** (Figure 2), the same two phosphate oxygen atoms interact simultaneously with two pyridinium hydrogen atoms. The associated interaction energies are −88.1 kcal mol^{-1} for **C** and −79.6 kcal mol^{-1} for **D** (Table 1). These observations suggest that these [C−H···O] interactions might well be the noncovalent forces responsible for the binding of pyridinium-containing cations with single- and double-stranded DNA. The interaction energies for the Py complexes derived from **C** and **D** are significantly smaller (Table 1), and the complex derived from **D** is more stable than the one derived from **C**. The interaction energies for **C** and **D** are considerably weaker in the presence of a solvent. They drop to −19.7 and −16.0 kcal mol^{-1}, respectively, in $CHCl_3$ and become positive in H_2O (Table 1). The magnitudes of the [C−H···O] interactions associated with these complexes decrease as the dielectric constant of the solvent increases, consistent with the electrostatic nature of these interactions.

Conclusions

Large interaction energies (−10.0 and −7.5 kcal mol^{-1}) accompany the [C−H···O] contacts between the *N*-methylpyridinium cation and the neutral dimethyl ether in the gas phase. The energies of interaction are ∼1 order of magnitude weaker in similar complexes of the neutral pyridine donor. The noncovalent, ionic bonds are much stronger (−88.1 and −79.6 kcal mol^{-1}) in the *N*-methylpyridinium complex of the dimethyl phosphate anion.

With one exception, the attractive [C−H···O] forces are maintained in $CHCl_3$ but are no longer significant in H_2O. The influence of the solvent dielectric constant on the strength of these noncovalent bonds, together with electrostatic potential calculations on the donor, indicates that [C−H···O] forces are dominated by electrostatic terms.

Our calculations demonstrate that the association between pyridinium cations and ethers or phosphates is remarkably strong and involves supramolecular contacts between [C−H] bonds of the cationic component and oxygen atoms on the electron-rich species. The role of these electrostatic interactions in supramolecular processes such as those shown in Figure 1 is established. These results can lead to the development of new supramolecular receptors with recognition properties dominated by [C−H···O] interactions. In particular, the design of substrates able to interact specifically with phosphate groups can be envisaged. Considering the ubiquity and role of phosphate groups in biomolecules (e.g., DNA, RNA, and phosphorylated metabolites), these investigations might well have fundamental implications in biological processes as well.

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