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Interaction of the Tetramethylammonium Ion with the Cycles of Aromatic Amino Acids beyond the SCF Ab Initio Level

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The last few years have witnessed the development of an increasing interest in the interaction of organic cations with aromatic molecules, due to the gradual recognition of the importance of this phenomenon in the chemistry of host−guest compounds[1,2] and in the structure of proteins and peptides.[3] The possible biological role of the aromatic rings of phenylalanine, tyrosine, and tryptophan interacting with onium ions was suggested early[44] on the basis of the crystal structure[5] of the phosphocholine-binding immunoglobulin FabMcPC603 and of various observations on the site of binding of acetylcholine on the surface of its receptor.[6]

The recent determination of the crystal structure of acetylcholinesterase[7] has revived the interest in this proposal by revealing the fact that 14 such aromatic residues lined the inner walls of a narrow gorge leading to the binding site of the substrate, thereby suggesting that a succession of favorable interactions with its methylammonium head could help acetylcholine to reach its site. Molecular mechanics computations[8] of a flexible acetylcholine molecule progressing in a model of the aromatic gorge built with the crystal coordinates indicated that, indeed, the molecule encountered a number of local minimums of increasing interaction from top to bottom of the gorge, in which appeared the role of two tryptophans, four tyrosines, and one phenylalanine, their relative importance following apparently the order of their affinities for the tetramethylammonium ion (TMA) calculated by two different force fields.[9,10]

A number of ab initio computations have been performed recently on ion−aromatic interactions to obtain a better understanding of their physicochemical nature, but most of the 56 references quoted in ref 3 regarding indole and phenol concern their binding to alkali ions, ammonium or monosubstituted ammonium, with very few concerning TMA itself.[11,12]

Table 1. Characteristics of TMA−Aromatic Interactions[a]

	SCF[b]	MP2[b]	correl[c]	μ[e]	Q[f]	α[g]
benzene	5.59	8.10[d]	2.51	0	34.20	53.41
phenol	7.42	9.46	2.04	1.51	39.17	56.83
pyrrole	7.12	9.67	2.55	1.92	27.75	39.87
indole	8.48	12.12	3.65	2.11	48.57	79.13

[a] Energies in kilocalories per mole. [b] Binding energy corrected for BSSE. [c] Difference MP2-SCF. [d] The utilization of the polarization-optimized basis set 6-31G$^{\alpha\alpha}$ of ref 13, which reproduces accurately the measured enthalpy (9.4 kcal/mol[18] and the polarizability (69.7 au[19] of benzene) being beyond our computing facilities for indole, we use here our 6-31G^{oo} basis set which was seen[13] to reproduce qualitatively the energy and structure results. The moments and the polarizabilities were computed at the SCF level on each molecule MP2-optimized with the same basis set. [e] Dipole moment (Debye units). [f] One-third of the trace of the molecular quadrupole tensor (D·Å). [g] One-third of the trace of the polarizability tensor (atomic units).

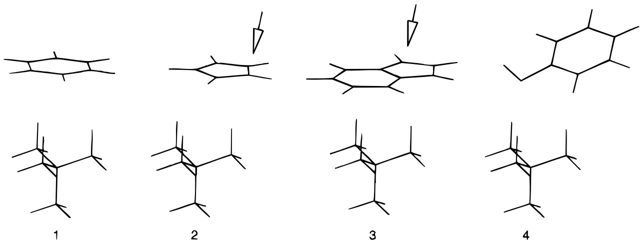

Figure 1. The most favorable complexes of benzene (**1**) pyrrole (**2**) indole (**3**) and phenol (**4**) with TMA. The arrows in pyrrole and indole indicate the position of the nitrogen.

Having observed the difficulty in extrapolating from one ion to another, we have extended to phenol and indole our previous ab initio studies including correlation on benzene and other system of six π electron[13] and we present here the essential observations which result from a comparison of the results with those obtained for pyrrole and benzene computed at the same level of accuracy. The energy results and the structures of the optimized complexes are summarized in Table 1 and Figure 1, respectively. Also given in Table 1 are the computed values of the dipole and quadrupole moments as well as those of the averaged polarizabilities of the ligands.

These observations are as follows:

(a) At the MP2 level, the intrinsic affinities for TMA increase in the sequence benzene (**1**) < phenol (**4**) < pyrrole (**2**) < indole (**3**).

(b) The nature of the interaction revealed by the structures is the same for indole, pyrrole, and benzene, namely, a disposition of the ligand essentially parallel to the plane of three hydrogens of TMA, with a slight distortion from parallelism and a closer approach to TMA for pyrrole, still closer for indole.

(c) In the case of phenol, the pure "cation−π" interaction, which commands the parallelism of the planes, combines with a hydrogen bond-type attraction which makes the aromatic plane deviate from parallelism to the hydrogen plane. Phenol leans toward one hydrogen of TMA while the OH bond rotates out of the molecular plane in order to orient the oxygen lone pair at best (the O···H distance is 2.35 Å and the OH rotation is 32°). This, albeit imperfect, "hydrogen bond-like" interaction clearly gives rise to the increment in stability observed with respect to benzene−TMA, in spite of a loss in the pure ion−π interaction due to the loss in orbital overlap that accompanies the inclination of the plane. Similar, although less pronounced, structural tendencies are seen in the molecular mechanics results quoted

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above and also in the SCF early results.[11] Whether tyrosine in proteins will use this imperfect H-bond tendency or form a direct H-bond to another group as suggested in ref 14 depends of course on its surroundings.

(d) The strong affinity of indole for TMA comprises a large value of MP2 correlation energy. Since correlation corresponds essentially to the effect of dispersion forces[15] which can be expressed by a sum of Lennard-Jones-type terms over the couples of interacting atoms,[16] this large value of E_{corr} for indole—a 10-membered cycle—is easily understood in comparison to the smaller, nearly equal, values obtained for the six-π-electron systems of benzene and pyrrole. In the case of phenol, the large distortion from the parallel disposition disfavors correlation. Note that the large value of the correlation in indole does not imply a dominance of this term in the total energy, as seen in the fact that the percent increase of the indole binding energy with respect to that of benzene is practically the same at the SCF and MP2 levels (52 and 50%, respectively).

(e) The order benzene < pyrrole < indole in binding to TMA is already contained at the SCF level, although the differences are less pronounced than at the correlated level (Table 1). This observation, compared to the results found for Na^+ binding,[14] where dispersion is negligible, indicates clearly the elements involved: the pure electrostatic effect which increases from benzene to pyrrole, then to indole, is enhanced in the largest cycle by the larger polarization, both effects being present at the SCF level. The inclusion of correlation discriminates further. The rationalization of the evolutions observed at the SCF and MP2 levels can be done easily on the basis of the values of the calculated dipole and quadrupole moments and of the polarizabilities given in Table 1.

Finally, even though correlation is not the dominant term in the binding, its introduction has been found necessary to reproduce satisfactorily the measured values of the enthalpies of binding (e.g., benzene−TMA).[13,17] It is clear that, for complexes of the same nature, predictions of relative order and spacing must also include correlation at the same level of theory. Our SCFMP2 calculations satisfy this criterion. As concerns the numerical values of the energies, the present results should be scaled upwards appropriately for the reasons given in footnote *d* of Table 1. As a final remark concerning the correlation term, let us point out that, in the kind of complexes considered, involving a disposition in parallel planes, it appears important (as was done here) to use polarization orbitals on both the "heavy" atoms and the hydrogens in order to ensure the best possible ion−π overlap.

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