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Cation π interaction between acetylcholine and the benzene ring

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Abstract. Ab initio self-consistent-field second-order Møller–Plesset perturbation theory computations including basis set superposition error and zero-point vibrational energy corrections have been performed on the complexation of benzene with the polar head of acetylcholine (ACh). The ACh–benzene complex is about 0.5 kcal/mol less stable than the corresponding tetramethylammonium (TMA)–benzene complex, with a structure a little distorted with respect to the latter. The electronic structure of ACh is little modified by the ligand. Overall, the replacement of one methyl group of TMA by the acetyl tail of ACh does not affect strongly the complexation to benzene, as far as the main interaction is concerned.

Key words: Acetylcholine-benzene – Ab initio self-consistent-field second-order Møller-Plesset – Complexation energy – Structure

1 Introduction

Acetylcholine (ACh) is a rather simple molecule of formula $(CH_3)_3N^+(CH_2)_2OC{=}OCH_3$ whose biological importance is connected with its role as a neurotransmitter between neurones and at other neurocellular junctions. For instance, at the synaptic cleft separating a nerve cell from a muscle cell, the arrival of a nerve impulse at the tip of the nerve axon causes the release of ACh molecules which, by binding to protein receptors (AChR) in the postsynaptic membrane, trigger the opening of sodium channels [1–3], hence depolarization, then muscle contraction. For the process to function properly, the channel openings must be rapidly terminated: this is accomplished in the synapse itself by the enzyme acetylcholinesterase (AChE), which hydrolyzes the ACh molecules into choline and acetic acid [4].

The two processes involve interactions of ACh with the proteins AChR and AChE. Concerning the enzyme, the resolution of its crystal structure has revealed the presence of a "gorge" leading to the active site and which is lined up with 14 aromatic amino acid residues, suggesting that the substrate could be helped down its path by a succession of favorable sites of "cation π" interactions with the ammonium head [5]. Concerning the receptor, no detailed crystal structure is available, but a reasonably probable model of the channel part of the protein emerges from a large number of experimental [6] and theoretical [7] investigations. Furthermore, the appreciable number of aromatic residues detected in the region of the binding site of the neurotransmitter suggests their participation in the interaction [8]. These structural findings and an increasing number of other chemical and biochemical observations tend to confirm the early hypothesis [9] that the interactions and specificity of ACh involve quite generally this particular kind of cation–aromatic interaction.

Pioneer computations on such interactions were performed using empirical potential functions [10] with tetramethylammonium (TMA) and monomethylammonium (MMA) as models. More recently, a similar technique was used to consider the interactions of ACh in the "gorge" leading to the active site of its hydrolytic enzyme [11, 12]. On the other hand, ab initio computations of various accuracies have been conducted on cation π interactions, using as models small cationic entities from alkaline ions to ammonium and its monomethyl and tetramethyl derivatives (MMA and TMA) and reducing the ligand to the aromatic part of the amino acid considered: benzene for phenylalanine, phenol for tyrosine, indole for tryptophan, etc. [13–19]. References [14–19] introduce correlation at the self-consistent-field (SCF) second-order Møller–Plesset (MP2) level of theory, a necessity in order to reasonably reproduce by calculations the values of the enthalpies of binding measured in the gas phase [14, 17]. Differences in numerical values occur according to the basis set utilized and to the definitions used for the basis set superposition error (BSSE) and correlation corrections: Kim et al. [14] used a 6-311 + G** basis, with conveniently averaged BSSE and MP2 correlation corrections; Caldwell and Kollman [15] used standard MP2 corrections with a

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6-31G* basis set and concentrated rather on the comparison with an additive molecular mechanics model including an ad hoc approximation of the ab initio polarization term. Basch and Stevens [16] also utilized 6-31G* with or without core potentials but, with their "reduced variable space method", they defined a considerably reduced SCF BSSE and neglected it completely at the MP2 level. Our own studies [17, 18] used standard BSSE and MP2 corrections with two basis sets, 6-31G^{00} (a slight improvment over 6-31G**) defined in Sect. 2 and 6-31G$^{\alpha\alpha}$ with exponents optimized on molecular polarizabilities. To our knowledge, no ab initio study of complexes formed by ACh itself and aromatic ligands has been published up to now. We present here an extension to the system Ach–benzene of our recent SCFMP2 calculations on TMA– and MMA–benzene [17].

2 Computational details

The ACh–benzene complex has been treated as a supermolecule, using the same theoretical level (SCFMP2) as for its fragments ACh and benzene. The interaction energies are obtained from the electronic energies of the three systems, taking into account the BSSE and the ZPVE, as in our computation for TMA–benzene [17]. The molecular orbitals involved in the MP2 perturbation treatment are obtained as solutions of the Roothaan–Hartree–Fock equations in terms of extended atomic basis sets of Gaussian form: they are split-valence double zeta functions derived from standard 6-31G orbitals modified by applying a scale factor of 1.09 to the most diffuse *s* and *p* components of the quarternary nitrogen, N^+, and augmented by adding polarization functions with energy-optimized exponents, (α_p = 1.22 for H; α_d = 0.83 for C, 0.99 for O, 0.91 for N^+).[1] Thus, the size of the basis set (called 6-31G^{00}) used for the SCFMP2 treatment is 334 for the complex (114 for benzene, 220 for ACh). For the estimation of the ZPVE corrections from scaled SCF vibration calculations and also for a tentative evaluation of the solvent effect on the conformation of ACh by the Onsager model included in Ref. [21], we have omitted the polarization functions.

Complete geometry optimizations at the MP2 level were performed for the ACh and benzene fragments, except for the initial introduction in ACh of equality constraints between the bond lengths and bond angles of the three methyl groups of the trimethylammonium head, reducing the 3*N*-6 variables of the molecule from 72 to 49 (13 lengths, 13 valence angles and 23 dihedral angles). Then, the head and tail geometry parameters were optimized each in turn until the changes were practically negligible. Concerning the geometry of the complex, we have assumed that its two fragments kept their individual bond lengths and angles unchanged, in analogy with the results obtained on TMA–benzene [17], a reflection of the fact that, in such complexes, the separation of the two partners is fairly large. Thus, the sole geometry parameters kept in the iterative determination of the ACh–benzene structure are the following (see Fig. 1 for the atom numbering and for the definitions of the variables):

1. Six variables fixing the position of benzene in the *Z* matrix of the supermolecule; namely, one length parameter *r*, (distance of N2 to the center, X, of benzene), two angular variables θ_1, θ_2 and three dihedral angles, ϕ_1, ϕ_2, ϕ_3, determining the relative disposition of the benzene principal axis and of the N^+C_1 direction in the tail of ACh.

2. Three dihedral variables, τ_1, τ_2, τ_3, in the ACh chain, the bond $C_{23}C_{21}$ being taken as trans with respect to $O_{20}C_{17}$. The active form of ACh is generally considered to be gauche around the dihedral angle τ_2 [22]. A preference for gauche over trans in τ_2 was found in early ab initio SCF STO3G computations using the geometry of the chloride crystal [23, 24] and was confirmed in optimized SCF 4-21G calculations [25]. We thus started our optimization from a gauche form in τ_2.

The computations were performed by means of the program GAUSSIAN 94 [21] running on the CRAY C-90 platform of the Institut de Développement et des Ressources en Informatique Scientifique du Centre National de la Recherche Scientifique. Because we were interested primarily in the evaluation of interaction energies, we choose the total electronic energy of the complex as a convergence criterion for the geometry optimization (i.e. 0.00001 au). Small conformational changes beyond this limit are immaterial for our purposes.

3 Results and conclusion

The essential results of the computations on free ACh and its complex are presented in Tables 1 and 2 and in

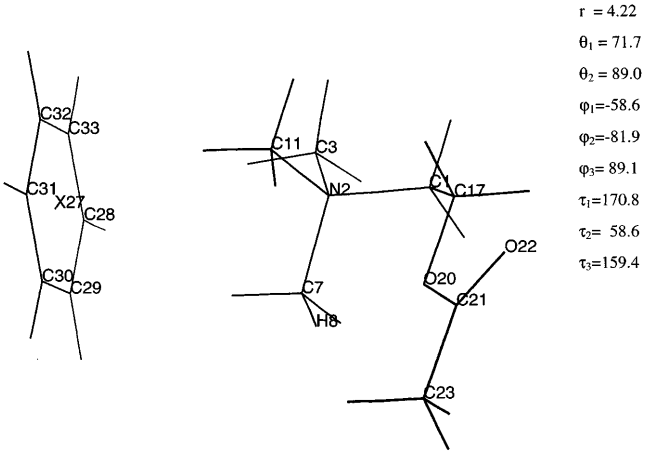

Fig. 1. The acetylcholine–benzene complex with the atom numbering. Geometry variables: $r = N_2X_{27}$; $\theta_1 = X_{27}N_2C_7$, $\theta_2 = C_{28}X_{27}N_2$; $\varphi_1 = X_{27}N_2C_7C_{11}$, $\varphi_2 = C_{28}X_{27}N_2C_7$, $\varphi_3 = C_{29}C_{28}X_{27}N_2$; $\tau_1 = C_{21}O_{20}C_{17}C_1$, $\tau_2 = O_{20}C_{17}C_1N_2$, $\tau_3 = C_{17}C_1N_2C_{11}$. The values in the complex are given on the *right* (distance in angstroms, angles in degrees)

[1] Except for hydrogen, which is Huzinaga's basis [20] with four components contracted 3-1 for consistency

Table 1. Total energy and zero-point vibrational energy (*ZPVE*) computed from self-consistent-field 6-31G wave functions at Møller–Plesset geometry (scaled value on last line, see text) for acetylcholine (*ACh*), benzene (*B*) and their complex (*C*) with and without basis set superposition error (*BSSE*)

	Energy with BSSE (au)	Energy with BSSE (au)	ZPVE (kcal/mol)
ACh	−479.924706	−479.925474	158.63
Benzene	−231.509115	−231.512807	68.42
C	−711.450527	−711.450527	227.56
D = C−(ACh + benzene)	−0.016706	−0.0112245	0.51
D (kcal/mol)	−10.48	−7.68	0.46

Table 2. Net populations in ACh and its complex with benzene. The numbering of the atoms is as in Fig. 1

Atom	ACh	Complex
C_1	0.233	0.229
N_2	−0.287	−0.284
C_3	0.313	0.296
C_7	0.323	0.306
C_{11}	0.313	0.296
C_{17}	0.438	0.433
O_{20}	−0.686	−0.684
C_{21}	0.750	0.750
O_{22}	−0.518	−0.520
C_{23}	0.120	0.117

Fig. 1. The trends in the optimized bond lengths, bond angles and dihedral angles are similar to the SCF results of Ref. [25]. The gauche conformation comprises a relatively short distance $O_{20}H_8$ of 2.22 Å (also found in the SCF results), which corresponds to a privileged interaction. The – very tentative – evaluation of the effect of water by the Onsager model indicates little modification of the conformation, in agreement with simple computations using explicit water molecules [26]. This, however, would need confirmation by a more reliable procedure.[2]

The conformation of the molecule is conserved in the ACh–benzene complex, even though the angles τ_1, τ_2, τ_3 were left free in the optimization of the supermolecule. In the optimum complex, the benzene ring is located in a plane almost perpendicular to the N^+C_1 bond of the tail, with the ring center 4.22 Å from the nitrogen atom.

The BSSE-corrected binding energy is 7.68 kcal/mol for the complex, from which a ZPVE of 0.46 kcal/mol must be substracted. The energy is a little less favorable than the binding energy in TMA–benzene (8.10 kcal/mol with the same basis set [17]).[3]

The electron distribution of the neurotransmitter is not much affected by the complexation with the aromatic: for instance, according to the Mulliken population analysis, the charge on the "head" of ACh (sum of the charges of the nitrogen and of the four surrounding carbon atoms, including their bound hydrogens) varies from +0.896 in the free molecule to +0.843 in the complex, corresponding to an electron transfer to the head so defined of 0.053*e*. (The total transfer from benzene is 0.060*e*. In the case of TMA–benzene the transfer from benzene is 0.063*e*.)

From a computational point of view, the analogies summarized above result from the fact that ACh is made of the junction of two rather well localized electronic systems, an ammonium head very similar to TMA and an acetyl tail, with only slight influence of one on the other. The consequence is that TMA is a very good model for the most favorable cation π interactions likely to involve the polar head of ACh. This is not the case for other cations such as MMA or NH_4^+ or alkali ions.

Note that we have limited our search to the most favorable complex ACh–benzene for obvious reasons of size. It may be inferred from the results on TMA–benzene that secondary minima exist around the head, essentially commanded by interaction with two methyl groups, or even one, instead of three [17]. In the case of ACh, steric hindrance should decrease their energies and also their number, making cation π interactions statistically less favorable than for TMA. The fact that TMA is an inhibitor [29] of the enzyme seems in agreement with this observation.

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[2]A recent Monte Carlo study was performed on the effect of water on the dihedral angle τ_1 [27] but did not touch on the problem of τ_2, assumed to be gauche

[3]As concerns the numerical values of the binding energies, due to the number of atoms and variables involved, we could not utilize our best 6-31G$^{2\alpha}$ basis set which was shown to reproduce very satisfactorily the value of the enthalpy of binding of benzene to TMA measured in the gas phase [28]. The present results should be scaled upwards by an approximate factor of 1.12 to reach the corresponding accuracy

References

1. Galzi JL, Revah F, Bessis A, Changeux JP (1991) Annu Rev Pharmacol 31: 37
2. Changeux JP, Revah F (1987) Trends Neurosci 10: 245
3. Galzi JL, Changeux JP (1994) Current Opin Struct Biol 4: 554
4. Quinn DM (1987) Chem Rev 87: 955
5. Sussman JL, Harel H, Frolow F, Oefner C, Goldman A, Toker L, Silman I (1991) Science 253: 872
6. Hucho F, Tsetlin VI, Machold J (1996) Eur J Biochem 239: 539
7. Furois-Corbin S, Pullman A (1989) Biochim Biophys Acta 984: 339
8. Bertrand D, Changeux JP (1995) Semin Neurosci 7: 79
9. Dougherty DA, Stauffer DA Science (1990) 250: 1558
10. Gresh N, Pullman B (1980) Biochim Biophys Acta 625: 356
11. Pullman A, Hui X (1994) Biophys J 66: A345

12. Pullman A (1995) In: Pullman A et al (eds) Modelling of biomolecular structures and mechanisms. Kluwer, Dordrecht, pp 11–23
13. Ma JC, Dougherty DA (1997) Chem Rev 97: 1303
14. Kim KS, Lee JY, Lee SJ, Ha TK, Kim DH (1994) J Am Chem Soc 116: 7399
15. Caldwell JW, Kollman PA (1994) J Am Chem Soc (1995) 117: 4177
16. Basch H, Stevens WJ (1995) J Mol Struct (THEOCHEM) 338: 303
17. Pullman A, Berthier G, Savinelli R (1997) J Comput Chem 18: 2012
18. Pullman A, Berthier G, Savinelli R (1998) J Am Chem Soc 120: 8553
19. Nicholas JB, Hay BP, Dixon DA (1999) J Phys Chem A 103: 1394
20. Huzinaga S (1965) J Chem Phys 42: 1293
21. Frisch MJ et al (1994) Gaussian 94. Gaussian, Pittsburgh, Pa
22. Chothia C (1970) Nature 225: 36
23. Pullman A, Port GNJ (1973) Theor Chim Acta 32: 77
24. Port GNJ, Pullman A (1973) J Am Chem Soc 95: 4059
25. Klimkowski VJ, Schäfer L, Scarsdale JN, Van Alsenoy C (1984) J Mol Struct (THEOCHEM) 109: 311
26. Pullman B, Berthod H, Gresh N (1975) C R Acad Sci Paris 280: 1741
27. Margherita C, Corongiu G (1987) J Comput Chem 9: 1
28. Meot–Ner (Mautner) M, Deakyne CA (1985) J Am Chem Soc 107: 469
29. Bergman F,Würtzel M (1953) Biochim Biophys Acta 11: 440