Carbocation−π Interaction: Computational Study of Complexation of Methyl Cation with Benzene and Comparisons with Related Systems

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Abstract: An investigation of the interaction of carbocations with aromatic rings has been initiated by a computational study of complexation of methyl cation with benzene to determine if this is appropriately included as an example of η^6 cation−π interaction. Specifically, electronic structure calculations for three types of π complex of methyl cation with benzene, **1**(η^6), **2**(η^2), **3**(η^1), and the Wheland σ complex **4** have been obtained at several theoretical levels. The results indicate that inclusion of electron correlation is required for accurate calculation of intermolecular distances and binding energies and that the B3LYP/6-31G* level of theory provides a practical, reliable approach for the study of carbocation−π interactions. Although none of the π complexes is an energy minimum, the maximum binding energy of CH_3^+ above the periphery of the ring is more than twice as large as that of optimum binding above the ring centroid. In addition, the association energies in η^2 and η^1 complexes are ca. 80% of the binding energy calculated for the equilibrium σ complex. The comparison of results for C_6H_6- -CH_3^+, C_6H_6- -SiH_3^+, and C_6H_6- -Na^+ with earlier theoretical work and with experiment confirms the reliability of the B3LYP/6-31G* method. An examination of the dependence of binding in complexes **1**−**4** on intermolecular separation was also conducted. The results indicate that at distances >2 Å, a "π approach" toward **2** or **3** has a binding energy which is competitive with the approach to σ complex (**4**) formation. This work also shows clearly that, in contrast to complexes of coordinatively saturated cations with benzene, at intermolecular distances <3.5 Å an η^6 geometry is not the most favorable for π complexation of carbocations. Significantly greater binding energy is obtained anywhere over the periphery of the ring (as in **2** or **3**) at any binding distance less than ca. 3.5 Å. Even at distances >3.5 Å, binding at the periphery of the aromatic system is comparable in energy to η^6 binding. With respect to the postulated stabilization of carbocation intermediates in biochemical reactions via π interactions with aromatic residues, the results show that very substantial stabilization can be afforded to carbocations positioned appropriately over any portion of a benzene ring and at distances considerably greater than typical covalent bonding distances. Thus, an enforced separation between carbocation and aromatic amino acid side chain residue to avoid unwanted covalent bond formation between protein and substrate would still allow substantial stabilization via carbocation−π interaction.

Introduction

It has been proposed, originally in the context of oxidosqualene cyclases,[1−5] that interaction with the π electron systems of aromatic side chain residues can serve to stabilize carbocation intermediates in enzymatic reactions.[6] Such a mechanism of biocatalysis has recently been used[7] to rationalize experimental findings concerning the aging process of methylphosphono acetylcholinesterase conjugates, and the recently reported crystal structures of three terpenoid polyene cyclases all show aromatic residues positioned in a manner consistent with postulation of such a mode of stabilization of putative carbocationic intermediates.[8−10] This hypothesis has the distinct advantage, relative to the earlier proposed electrostatic stabilization of carbocation intermediates by anionic residues,[11] that the aromatic rings involved could also participate in the binding of hydrophobic substrates.

To date, this postulated mode of carbocation stabilization has simply been considered to be an example of the general phenomenon of "cation−π interaction",[12,13] in which a cation is depicted in an η^6 complex with an aromatic ring, with electrostatic attraction as "the defining feature".[13] For various

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ammonium and metal cations such η^6, cation−π interactions have been extensively studied theoretically[14−19] and in model systems,[16] and convincing evidence has been accumulated that they are important in a variety of protein-mediated processes.[12,13]

However, complexes of aromatic rings with carbocations, which are coordinatively unsaturated, might well be expected to be profoundly different in geometry and energy from those of ammonium or metal ions. The bonding interaction of carbocations with π systems, unlike that of ammonium or metal ions, may not be primarily determined by the electrostatic attraction between the cation charge and the quadrupole moment of the aromatic system. Furthermore, binding energies calculated for η^6 π complexes may differ substantially from those of π complexes in which the carbocation is not located above the ring centroid.

One familiar property of carbocations, which clearly distinguishes them from coordinatively saturated cations, is their formation of σ complexes by reaction with aromatic rings. The extensive experimental gas-phase work of Cacace et al.,[20] Kuck,[21] and Fornarini[22] has provided a wealth of information on relative energies of these arenium ions. In addition, solution studies of rearrangements of toluenium,[23] xylenium,[24] and heptamethylbenzenium[25] ions have been reported, but detailed considerations of the transition states involved were not made. Complementary theoretical results for the structures and energies of σ complexes, $C_6H_6CH_3^+$ and $C_6H_6C(CH_3)_3^+$, have been reported at semiempirical[26−29] and ab initio levels.[30,31]

In contrast, little information is available concerning the structures or energies of any kind of π complex of a carbocation.[32−34] Although both η^6 and η^2 π complexes were long ago suggested as intermediates in electrophilic aromatic substitution,[35] evidence for their existence has been obtained only in unusual circumstances,[36] whereas there are large numbers of well-characterized π complexes of metal cations with aromatic rings,[37] including ones having η^6, η^2, and (in at least one case) η^1 [38] geometries. Very recently, Jenson and Jorgensen[39] have reported a computational study of carbocations involved in the cyclization of squalene oxide to lanosterol, including a consideration of the interaction between carbocationic centers and proximate aromatic residues, obtaining optimized structures with η^6 geometry. However, in this work the geometry of both the tertiary carbocation and the aromatic ring were held constant (to preclude σ complex formation), thereby likely favoring the binding to be found in an η^6 cation−π interaction.

To determine whether energy minima corresponding to carbocation−aromatic ring π complexes do exist and how their energies compare to those of σ complexes, one would ideally require a complete mapping of potential energy surfaces for illustrative examples of such complexes. However, even for systems of modest size, it is rarely feasible to determine all the details of the many-dimensional potential energy surface using accurate computational techniques. Such a mapping would clearly be extremely difficult for complexes between aromatic rings and the structurally complex tertiary and substituted allylic cations postulated as intermediates in enzymatic processes.[6]

A consideration of such constraints and the limited theoretical data currently available on any such π complexes indicated that important initial insight into the binding energies of carbocation−aromatic ring complexes having varied geometries could be obtained from a computational study of the interaction of methyl cation with benzene. The modest size and the symmetry of the C_6H_6- -CH_3^+ system allowed us not only to explore substantial regions of the potential energy surface governing the interaction of methyl cation with benzene but also to assess the performance of different levels of theory. It was anticipated

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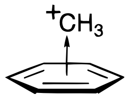
that such an assessment would enable us to define the minimum theoretical level required to provide a reliable description of carbocation−π interactions for future study of interactions between larger cations and benzene. Our explorations of the C_6H_6- -CH_3^+ potential surface have been guided by the known structures of various metal cation−aromatic complexes. Thus, we have conducted a computational study of the σ complex **4** and regions of the energy surface corresponding to the three types of π complex of methyl cation with benzene, **1** (η^6), **2** (η^2), and **3** (η^1). *The results support the premise that carbocation−π interaction is fundamentally different from the π interaction of coordinatively saturated cations and indicate that only at intermolecular separations ≥4 Å does the η^6 geometry provide comparable binding energy.*



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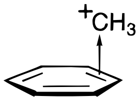

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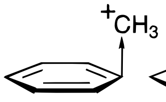

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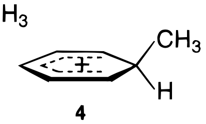

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Computational Details

In initial studies of each π complex, CH_3^+ was constrained to approach in a direction normal to the benzene ring plane and various symmetry elements were maintained. In **1**, the binding axis is the 6-fold axis of the ring, and a C_3 axis was maintained; in **2**, the binding direction is the bisector of a ring C−C bond, and a C_s plane was maintained; and in **3**, the normal intercepts a ring C atom, and a C_s plane was maintained. To establish a reliable basis set for this work, optimized geometries for π complexes **1**−**3** and σ complex **4** were obtained at the Hartree−Fock level with the 6-31G*, 6-31G**, 6-311G*, and 6-31+G* basis sets.[40] Electron correlation effects were then initially investigated by repeating geometry optimizations at the MP2(fu)[41] level using the 6-31G*, 6-31G**, and 6-311+G* sets of atomic functions. A more complete treatment of electron correlation was subsequently made by performing an MP4 calculation for each of the MP2/6-31G* optimized structures. To explore an alternate treatment of electron correlation, geometry optimizations were repeated using the B3LYP variant of density functional theory,[42] employing the 6-31G* and 6-311+G* sets of atomic functions. As a final step, at each level, harmonic vibrational frequencies were determined analytically to characterize each optimized structure and used to compute the zero-point energies (ZPE) for the stationary points located. To obtain approximate estimates of basis set superposition errors (BSSE), counterpoise calculations[43] were made at the MP2(fu)/6-31G* and MP2(fc)/6-311+G* levels. All calculations were performed on IBM RS-6000 workstations using the Gaussian 92 (Revision F.2) software.[40]

Results and Discussion

The C_6H_6- -CH_3^+ System. The computational results for species **1**−**4** in the C_6H_6- -CH_3^+ system are given in Table 1. Since our studies clearly indicate that inclusion of electron correlation effects is required to produce reliable intermolecular distances and binding energies in such complexes, only MP2, MP4, and B3LYP data are reported in Table 1. The results, especially binding energies, do not seem particularly sensitive to the approach used to treat the effects of electron correlation. MP2 and B3LYP calculations of intermolecular distances show differences of up to 0.07 Å and binding energy variations of up to 3−4 kcal/mol. However, such variations are relatively minor when compared with the broad ranges of variation of intermolecular distance and binding energy found. In addition, the performance of the B3LYP method appears to be intermediate between that of MP2 and MP4 and suggests that use of the B3LYP/6-31G* level should provide a reliable, efficient approach for the study of larger carbocation−π complexes.

Table 1. Intermolecular Distances, *R* (Å), and Binding Energies, Δ*E* (kcal/mol), of 1:1 π and σ Complexes of Benzene with Methyl Cation Calculated Including Electron Correlation Effects using Different Levels of Approximation

level	1	2	3	4
MP2(fu)/6-31G*				
R	2.52	1.82	1.80	1.57
ΔE[a]	−25.18	−69.82	−73.03	−86.77
MP2(fu)/6-31G**				
R	2.51	1.81	1.80	1.56
Δ*E*	−25.16	−69.68	−73.25	−86.78
MP2(fc)/6-311+G*				
R	2.56	1.82	1.81	1.57
Δ*E*	−25.20	−68.16	−70.97	−83.10
MP4(fc)/6-31G*				
Δ*E*	−25.10	−67.74	−71.57	−87.59
B3LYP/6-31G*				
R	2.58	1.89	1.83	1.57
Δ*E*	−28.12	−68.38	−73.49	−90.27
B3LYP/6-311+G*				
R	2.62	1.89	1.84	1.57
Δ*E*[a]	−26.01	−64.36	−69.38	−86.20

[a] When ZPE corrections are included, the binding energy of **4** is reduced to −81.54 kcal/mol at the MP2/6-31G* level and to −81.49 kcal/mol at the B3LYP/6-311+G* level.

A fundamental issue to be addressed was whether any of the π complexes **1**−**3** represents an energy minimum. An exploration of the potential energy surface surrounding each of these structures indicates that complexes **1** and **4** are stationary points. Structure **1** was identified as a second-order saddle point with a degenerate imaginary frequency of 976 *i* cm^{-1} at the B3LYP/6-311+G* level, analogous to the recent results for $C_6H_7^+$ [33d] and C_6H_6- -SiH_3^+.[31,44a] For η^6 complex **1**, the binding energy of −25.2 kcal/mol at the MP2/6-31G* level is somewhat greater than that calculated at the same level for the analogous C_6H_6- -NH_4^+ complex (−17.9 kcal/mol)[16] and very similar to the MP2/6-31G* value of −26.6 kcal/mol reported for C_6H_6- -SiH_3^+.[31,45] The σ complex **4** is calculated to be an energy minimum, as expected, with a binding energy of −86.2 kcal/mol. It has an essentially tetrahedral methyl group with a bonding distance (1.57 Å) close to that of a typical C(sp^3)−C(sp^3) linkage and the C_{Me}−C_{ring} bond makes an angle of 137.9° with the ring (Figure 1). The ring structural parameters are very close to those for the analogous structure of protonated benzene, calculated at the B3LYP/6-31G** level,[33d] and similar to the HF/6-31G* values reported by Schleyer et al.[31] for the C_6H_6- -$C(CH_3)_3^+$ Wheland complex.

The results of computations for the η^2 complex **2** show a significant decrease in bonding distance (1.89 Å) when compared with structure **1** (2.62 Å) and a large increase in binding energy (−64.4 kcal/mol vs −26.0 kcal/mol). The constrained

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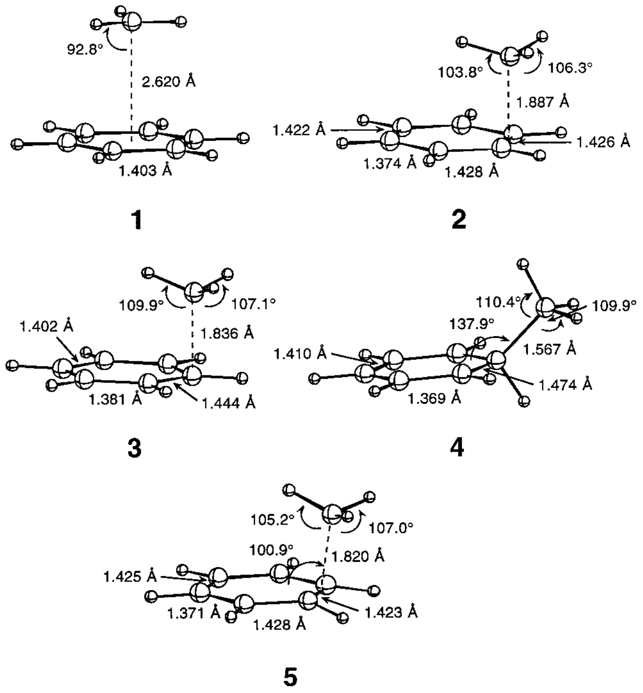

Figure 1. Optimized B3LYP/6-311+G* geometries for C_6H_6- -CH_3^+ complexes **1**−**5**.

Table 2. Intermolecular Distances, *R* (Å), and Binding Energies, Δ*E* (kcal/mol), of the Transition State Structure **5** for the Interconversion of Two σ Complexes Calculated using Different Levels of Approximation

level	*R* (Å)	Δ*E* (kcal/mol)[a]
MP2(fu)/6-31G*	1.76	−73.66
MP2(fu)/6-31G**	1.76	−73.70
MP2(fc)/6-311+G*	1.76	−71.71
MP4(fc)/6-31G*	1.76	−71.55
B3LYP/6-31G*	1.82	−72.34
B3LYP/6-311+G*	1.82	−68.37

[a] When ZPE corrections are included, the binding energy of **5** is reduced to −68.86 kcal/mol at the MP2/6-31G* level and to −63.78 kcal/mol at the B3LYP/6-311+G* level.

optimized geometry of **2** (Figure 1) shows CH_3 slightly tilted toward the center of the ring, presumably to alleviate interactions between its peripheral hydrogens and those on benzene. However, this structure is not a stationary point on the potential surface. Relaxing the constraint that CH_3^+ approach in a direction normal to the ring in **2**, but maintaining a C_s plane of symmetry bisecting the ring C−C bond, and reoptimizing the geometry of the complex leads to the lower energy structure **5** (Figure 1) which *is* a stationary point on the potential energy surface. A B3LYP/6-311+G* vibrational frequency calculation on this structure gave one imaginary frequency (411 *i* cm^{-1}), and an intrinsic reaction coordinate calculation[46] confirmed **5**, with the properties indicated in Table 2, as the transition state structure for interconversion of two σ complexes.[33] Using the B3LYP/6-311+G* vibrational frequencies, an activation barrier was calculated for a methyl shift of 17.3 kcal/mol at 298 K, which is consistent with the 15−22 kcal/mol range reported in solution studies of methyl group migration in methylbenzenes.[21,23−25]

For the constrained η^1 π complex **3**, the calculated binding energy is −69.4 kcal/mol, slightly greater in magnitude than that for the η^2 complex **2**, consistent with the prediction that the electron density in benzene is slightly greater over a carbon atom than over the midpoint of a C−C bond.[47] The optimized geometry of **3** (Figure 1) has a slightly smaller separation of CH_3^+ from C_6H_6 than **2** (1.84 Å), and CH_3 is tilted slightly away from the ring since the two external hydrogens are now staggered with respect to those of benzene. An exploration of the potential energy surface surrounding structure **3** shows that it also is not a stationary point. When the constraint that CH_3^+ approach in a direction normal to the ring carbon in **3** is relaxed but a C_s plane of symmetry which intersects the para C atoms of the ring is maintained, reoptimizing the geometry of the complex results in σ complex **4**. Exploration of other regions of the surface in the vicinity of **2** and **3** failed to locate any other stationary points. Such calculations yield binding energies for CH_3^+ located at distances of 1.8−1.9 Å above the periphery of the ring and in a plane parallel to C_6H_6 which are close to those reported in Table 2 for **2** and **3**. These explorations also suggest that, over a wide range of intermolecular distances, any portion of the periphery of the aromatic ring provides an approximately equally attractive binding region for CH_3^+. Binding energies for complexes **1**−**4** which include BSSE corrections have also been calculated.[43] Although such corrections reduce the binding energies found by 3−7 kcal/mol, they do not significantly change the conclusions concerning the relative binding in complexes **1**−**4**.[48,49]

However, a π complex stabilizing a carbocationic biochemical intermediate might well be constrained to have a separation between the carbocationic center and the aromatic ring substantially greater than the intermolecular distances for **1**−**4** listed in Table 1. Such a constraint might be essential to prevent progression of an enzyme−carbocation complex toward a σ complex. To gain insight into the effect of changing intermolecular distances on binding energies for complexes with the symmetries of **1**−**4**, computations were performed at the MP2/6-31G*//HF/6-31G* level to calculate the energy associated with the approach of CH_3^+ to C_6H_6 along the binding axis in each of structures **1**−**4**. In these calculations, for each of **1**−**4** the intermolecular distance was fixed at the value shown in Figure 2, and the binding axis in **4** was fixed at 133.2° to the plane formed by the three C atoms indicated in Figure 1. All other geometrical parameters were optimized at the HF/6-31G* level, and an MP2/6-31G* energy calculation was performed on each of the geometries thus obtained.[50]

As the results displayed in Figure 2 indicate, at distances >2 Å, a π approach toward **2** or **3** has a binding energy which is competitive with that associated with an approach along the binding axis for the σ complex. At 2.52 Å, the equilibrium bonding distance in η^6 complex **1**, the binding energy in **2** or **3** is just about twice that in **1** (−50 vs −25 kcal/mol). In general, for intermolecular separations in the 2.5−3 Å range, which are considerably greater than typical covalent bonding distances,

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[46] (a) Fukui, K. *Acc. Chem. Res.* **1981**, *14*, 363−368. (b) Gonzalez, G.; Schlegel, H. B. *J. Chem. Phys.* **1989**, *90*, 2154−2161. (c) Gonzalez, G.; Schlegel, H. B. *J. Phys. Chem.* **1990**, *94*, 5523−5527.

[47] HF/6-31G* calculations of electron densities at various points above the periphery of the benzene ring compare closely with the HF/3-21G results previously reported: Francl, M. M.; Hout, R. F., Jr.; Hehre, W. J. *J. Am. Chem. Soc.* **1984**, *106*, 563−570.

[48] Binding energies (kcal/mol) for complexes **1**−**4** which include BSSE corrections calculated at the MP2(fc)/6-311+G* level are **1**: −22.34; **2**: −62.66; **3**: −65.77; **4**: −76.47.

[49] It should be noted that Schwenke, D. W.; Truhlar, D. G. *J. Chem. Phys.* **1985**, *82*, 2418−2426 have not only shown that use of the counterpoise approach overestimates BSSE corrections but also conclude that using a basis set in which counterpoise corrections are small does not guarantee accurate results.

[50] Since it is the intermolecular distance which appears to be the most sensitive to inclusion of the effects of electron correlation, we expect the approach outlined above to give reliable estimates of the dependence of binding energy on intermolecular distance.

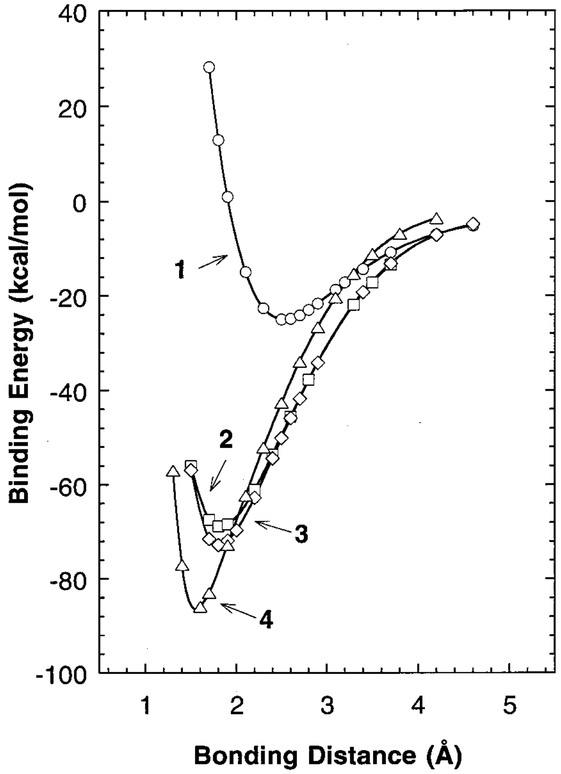
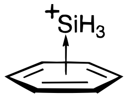


Figure 2. Relative potential energies associated with approach of CH_3^+ to C_6H_6 along the binding axis toward each of the minimized structures for **1**−**4** shown in Figure 1, calculated at the MP2/6-31G*//HF/6-31G* level: ○ ≡ **1**; □ ≡ **2**; ◇ ≡ **3**; △ ≡ **4**.

the strength of binding of CH_3^+ over the edge of the ring is significantly greater than that along the 6-fold axis of the ring. *Only for intermolecular distances ≥4 Å is the strength of binding in the η^6 complex comparable to that over the edge of the aromatic ring.*

Comparison of C_6H_6- -CH_3^+ with C_6H_6- -SiH_3^+. To assess the accuracy of the computational methods used to obtain the results just discussed for C_6H_6- -CH_3^+, it seemed important to compare these results with earlier theoretical and experimental results on the same (σ complex **4**) or closely related species. There have been extensive recent studies[30,44,45,51−56] concerning the nature of silylium cations in aromatic solvents. Although the initial intent of such investigations was to examine the feasibility of obtaining free R_3Si^+ ions in condensed phases, such work has shown that silylium cations are significantly coordinated to aromatic solvent molecules, and several research groups[30,44,45,55] have reported calculated structures and association energies for a variety of silylium cations bound to benzene. These studies therefore provide data which may be usefully compared with our results for the C_6H_6- -CH_3^+ system.

The geometry and binding energy of the η^6 complex for C_6H_6- -SiH_3^+ (**6**) are remarkably similar to those calculated for structure **1**. At the B3LYP/6-311+G* level the calculated intermolecular distance (2.618 Å)[57] in complex **6** is essentially the same as that (2.620 Å) obtained for the η^6 structure of C_6H_6- -CH_3^+, and the ring geometries are identical. The main difference between structures **1** and **6** is that the SiH_3^+ geometry is more pyramidal (∠HSiH = 117.1°) than that in the CH_3^+ moiety, which remains essentially planar (∠HCH = 119.8°). The binding energy of −24.8 kcal/mol calculated for η^6 complex **6** is very similar to the value (−26.01 kcal/mol) reported in Table 1 for structure **1**, and as mentioned earlier, structures **1** and **6** are both second-order saddle points. Furthermore, atomic charges calculated from a natural population analysis[58−60] of the B3LYP/6-311+G* wave functions show that transfer of electron density from the ring to the CH_3^+ moiety in C_6H_6- -CH_3^+ (0.197) is close to that (0.181) calculated for structure **6**.



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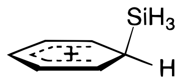

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In marked contrast to the similarities in geometry and binding energy between the η^6 complexes for C_6H_6- -CH_3^+ (**1**) and C_6H_6- -SiH_3^+ (**6**), the equilibrium σ complexes **4** and **7** obtained in these two systems are quite different. In the carbocation case, σ complex structure **4** has an essentially tetrahedral methyl group with a bonding distance (1.567 Å) close to that of a typical $C(sp^3)-C(sp^3)$ linkage, and the ring bond lengths show a pronounced alternation (1.474 Å, 1.369 Å, 1.410 Å) similar to B3LYP/6-311+G* results (1.469 Å, 1.369 Å, 1.410 Å) for the benzenium ion[61] and to the HF/6-31G* results (1.481 Å, 1.355 Å, 1.406 Å)[31] for the C_6H_6- -$C(CH_3)_3^+$ Wheland complex. In contrast, in σ complex **7**, not only is the C−Si bond distance (2.104 Å) calculated at the B3LYP/6-311+G* level considerably longer than the typical C−Si bond length of 1.88 Å found in alkylsilanes,[62] but the silyl group also forms an angle of 106.7° with the benzene ring. These values agree closely with the HF/6-31G* results reported by Olsson and Cremer.[44a] Furthermore, as pointed out by previous authors,[31,44,45,55] the ring bond lengths in C_6H_6- -SiH_3^+ complex **7** show much smaller alternation (1.432 Å, 1.382 Å, 1.402 Å). These bond distances are remarkably similar to the B3LYP/6-311+G* ring bond lengths (1.444 Å, 1.381 Å, 1.402 Å) for structure **3** of C_6H_6- -CH_3^+ and support the suggestion of Cremer et al.[44a] that the silylium complex may be better described as a C-centered π complex rather than as a classical σ complex.[63]

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(52) (a) Olah, G. A.; Rasul, G.; Heiliger, L.; Bausch, J.; Prakash, G. K. S. *J. Am. Chem. Soc.* **1992**, *114*, 7737−7742. (b) Olah, G. A.; Rasul, G.; Li, X-Y.; Buchholz, H. A.; Sandford, G.; Prakash, G. K. S. *Science* **1994**, *263*, 983−984. (c) Olah, G. A.; Li, X-Y.; Wang, Q.; Rasul, G.; Prakash, G. K. S. *J. Am. Chem. Soc.* **1995**, *117*, 8962−8966.

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(56) Pauling, L. *Science* **1994**, *263*, 983.

(57) The B3LYP/6-311+G* intermolecular distance is slightly shorter than that calculated at the HF/6-31G* level (2.751 Å) see ref 44a.

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(60) Glendening, E. D.; Reed, A. E.; Carpenter, J. E.; Weinhold, F. NBO Version 3.1.

(61) These values are in close agreement with those calculated[33d] at the B3LYP/6-31G** level.

(62) Hengge, E.; Keller-Rudek, H.; Koschel, D.; Krüerke, U.; Merlet, P. *Silicon, Gmelin Handbook of Inorganic Chemistry*; Springer: Berlin, 1982; Suppl. Vol. B1.

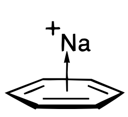
(63) B3LYP/6-311+G* calculations indicate that the optimized structure of C_6H_6- -SiH_3^+ in which the silyl group is constrained to form an angle of 90° with the benzene ring lies only 3.8 kcal/mol higher than structure **7**.

However, the binding energy in the silylium complex **7** is considerably smaller (−52.1 kcal/mol)[64] than that calculated for either structure **4** (−86.2 kcal/mol) or structure **3** (−69.4 kcal/mol) of the carbocation complex. This small binding energy, the relatively long Si−C bond, and the small bond alternation in the aromatic ring have all been rationalized[31,44a] in terms of cationic Si−C hyperconjugation. In a similar manner, the structural and binding energy differences between structures **3** and **4** of C_6H_6- -CH_3^+, reported in Table 2 and discussed above, can be rationalized in terms of cationic C−C hyperconjugation.

The calculated barrier (17.8 kcal/mol) for CH_3 group migration in C_6H_6- -CH_3^+ is much larger than that calculated (5.7 kcal/mol) for SiH_3 group migration in C_6H_6- -SiH_3^+.[44a] In this regard, it is worth noting that a detailed examination of the reaction coordinate for CH_3 group migration (**4** → **5**) shows that the early stages of reaction involve nuclear motions which simultaneously lengthen the C_{Me}−C_{ipso} bond and decrease the angle (137.9°) this bond makes with the plane of the ring in a manner that essentially maintains the molecular C_s plane of symmetry. This motion continues at an energy cost of ~6 kcal/mol until the above angle decreases to ~110° at which point the methyl group moves in a manner that destroys the C_s symmetry. Since the C−Si bond is unusually long and since the silyl group forms an angle of only 106.7° with the benzene ring in the silylium complex **7**, it is reasonable that the barrier for SiH_3 group migration is significantly smaller than that for CH_3 group motion.

Comparison of C_6H_6- -CH_3^+ with C_6H_6- -Na^+. These comparisons of results for C_6H_6- -CH_3^+ with those for C_6H_6- -SiH_3^+ provide reasonable assurance that our use of the B3LYP/6-31G* theoretical level does indeed provide reliable results. It also seemed important to compare our results for various geometries of the C_6H_6- -CH_3^+ system with analogous geometries of a typical coordinatively saturated cation complexed with benzene. Whereas the binding energy in the C_6H_6- -CH_3^+ η^6 complex (−26.0 kcal/mol) is very similar to that for the analogous C_6H_6- -SiH_3^+ complex (−24.8 kcal/mol), it is considerably greater than that (−17.9 kcal/mol)[16] for the analogous η^6 complex of the coordinatively saturated NH_4^+ with benzene, and the potential energy governing the approach of CH_3^+ to C_6H_6 is clearly quite different from that found by Dougherty et al.[12,13,16,18,19] for the approach of alkali metal cations. To explore these differences, we have performed B3LYP/6-31G* calculations of regions of the C_6H_6- -Na^+ potential energy surface analogous to structures **1**, **2**, and **3**.

The η^6 complex **8** is calculated to be a mininum with a bonding distance of 2.37 Å and a binding energy of −28.4 kcal/mol, results which are very similar to those reported previously at the Hartree−Fock level.[18,19] The η^2 and η^1 complexes **9** and **10** have calculated binding energies of −24.2 kcal/mol and −23.3 kcal/mol and intermolecular distances of 2.51 and 2.52 Å, respectively, indicating that the periphery of the benzene ring is in this case slightly less favorable for binding than the 6-fold axis. Neither structure **9** nor structure **10** is a stationary point on the C_6H_6- -Na^+ potential energy surface. Relaxing the constraint that Na^+ approach in a direction normal to the ring in **9** but maintaining a C_s plane of symmetry bisecting the ring C−C bond and reoptimizing the geometry of the complex leads to the η^6 complex **8**. Similarly, relaxing the analogous constraint in **10** and reoptimizing also produces structure **8**.



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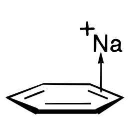

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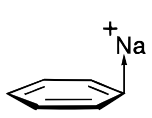

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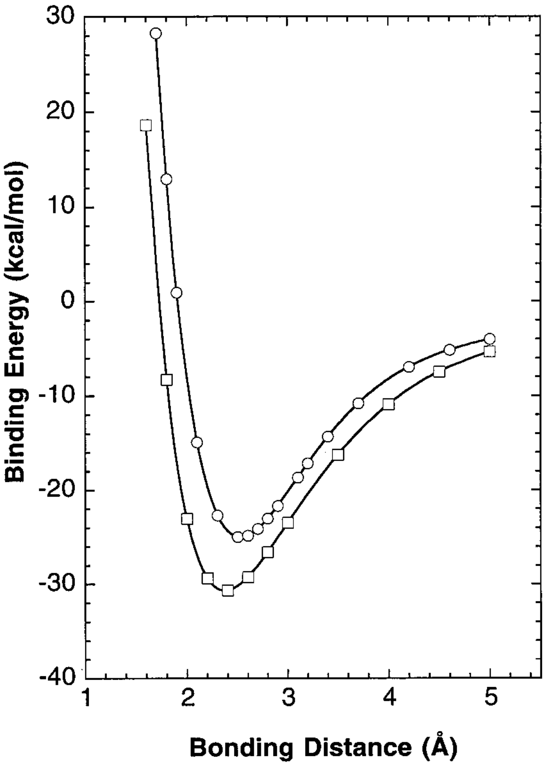

Figure 3. Relative potential energies associated with approach of CH_3^+ and Na^+ to C_6H_6 along the 6-fold axis of the ring, calculated at the MP2/6-31G*//HF/6-31G* level: ○ ≡ C_6H_6- -CH_3^+; □ ≡ C_6H_6- -Na^+.

In addition, to examine the effect of changing intermolecular distance on binding in η^6 complex **8**, MP2/6-31G*//HF/6-31G* level computations were performed to calculate the energy associated with approach of Na^+ along the 6-fold axis of the benzene ring. The results of such computations are displayed in Figure 3 where they are compared with the corresponding η^6 approach potential for C_6H_6- -CH_3^+. The intermolecular distance for optimum η^6 binding in C_6H_6- -Na^+ is close to that found for complex **1**, and the overall curvatures of the potentials are very similar. The slightly weaker optimum binding in C_6H_6- -CH_3^+ is quite reasonable in view of both the considerable delocalization of the net positive charge onto the hydrogen atoms in CH_3^+ and the larger size of the methyl cation.[65] As expected, the effects of such delocalization become much less important as the intermolecular separation increases, and Na^+ and CH_3^+ have very similar η^6 binding energies at intermolecular distances greater than 5 Å. Although these results are qualitatively consistent with the model of electrostatic attraction between the cation charge and the quadrupole moment of the aromatic system proposed by Dougherty et al.,[12,13] it should be noted that a natural population analysis[58−60] of B3LYP/6-311+G* wave functions indicates that there is considerably more transfer of electron density from the benzene ring to the cation in the carbocation case. For the optimized structure of C_6H_6- -Na^+

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[64] The binding energy of −52.1 kcal/mol calculated at the B3LYP/6-311+G* level for silylium complex **7** is similar to the MP2/6-31G*//HF/6-31G* value reported in ref 31.

[65] B3LYP/6-311+G* calculations of the volume inside a contour of density 0.001 electrons/bohr^3 have been used to estimate the sizes of the Na^+ and CH_3^+ cations. At this level, Na^+ and CH_3^+ are computed to have effective radii of 1.47 and 2.14 Å, respectively. This approach is often used to estimate the radius of a solute molecule for use in a solvent reaction field calculation.[40]

with an intermolecular separation of 2.405 Å, the charge on Na is 0.981. In contrast, the net charge on the CH_3^+ moiety in complex **1** is 0.803.

In contrast to the striking similarities between regions of η^6 binding of CH_3^+ and Na^+ to benzene, other regions of the potential energy surface are completely different. For C_6H_6- -CH_3^+, even at intermolecular separations of ca. 2.5 Å, η^2 and η^1 complexes **2** and **3** have binding energies which are much larger than that calculated for η^6 complex **1**, whereas η^2 and η^1 complexes **9** and **10** both have energies which are slightly smaller than the optimum binding energy calculated for **8**. Of course, since Na^+ is coordinatively saturated, there is no possibility of its forming a σ complex.

Implications for Carbocation Intermediates in Biochemical Reactions. There is ample evidence that the η^6 cation−π interaction model accurately describes an important mechanism of stabilization for coordinatively saturated cations in a variety of biochemical contexts.[12,13] The present results indicate, however, that such a model is probably not applicable to carbocations. Considerably greater binding energy is available to a carbocation anywhere over the periphery of an aromatic ring at any intermolecular distance ca. <3.5 Å. For example, even at an intermolecular separation of 3 Å, the strength of CH_3^+ binding over the edge of the benzene ring is approximately 60% larger than that calculated for an η^6 geometry.

For C_6H_6- -CH_3^+, maximum π binding over the periphery of the ring of ca. −70 kcal/mol is obtained in **2** or **3** at a separation of 1.8−1.9 Å and over the ring center in **1** of ca. −26 kcal/mol at a separation of 2.62 Å. Presumably, however, the optimum intermolecular distance will be strongly dependent on the size of the carbocation. This expectation was checked in preliminary studies at the B3LYP/6-31G* level which indicate that the optimum separation for η^6 binding in the C_6H_6- -$C(CH_3)_3^+$ system is 3.74 Å with a binding energy of −8.7 kcal/mol.[66] This binding energy agrees closely with the B3LYP/6-31G*//HF/6-31G* value (−9.1 kcal/mol) reported by Jenson and Jorgensen.[39] It is worth noting that this value also agrees quite closely with the η^6 binding energy in the C_6H_6- -CH_3^+ system at an intermolecular separation of 3.74 Å (see Figure 2). However, as mentioned earlier, in the work of Jenson and Jorgensen,[39] the structures of both C_6H_6 and $C(CH_3)_3^+$ were kept fixed at their isolated geometries and only the intermolecular degrees of freedom were optimized. At the B3LYP/6-31G* level, preliminary work on C_6H_6- -$C(CH_3)_3^+$ in which all geometrical variables are optimized indicates that binding over the edge of the benzene ring is preferable to binding along the 6-fold axis by ca. −1.7 kcal/mol.[66]

Another important consideration for carbocation intermediates in biochemical reactions is that they, unlike metal or ammonium ions, can undergo energetically favorable covalent bond (σ complex) formation with aromatic rings. Obviously, such a presumably irreversible protein−substrate interaction must be prevented in any biochemical reaction mechanism involving carbocation intermediates. This could be achieved by preventing approach of the carbocation toward σ complex formation and/or preventing the significant rehybridization of the carbocation center and geometry changes in the aromatic ring which accompany σ complex formation. One obvious means to this end would be to have an η^6 geometry of interaction dictated by the structure of the enzyme−substrate complex.

On the other hand, as the present study reveals, biochemical reactions involving π complexation of carbocation intermediates with aromatic rings can achieve optimum stabilization with the carbocationic center over the periphery of the aromatic ring. Prevention of σ complex formation could be achieved for η^2 and η^1 geometries of interaction by having sufficient separation between carbocationic center and aromatic ring enforced by other factors in the protein−intermediate complex. It is hoped that our studies in progress of carbocations larger than methyl will help to clarify how the appropriate balance between optimizing binding energy and preventing σ complex formation may be achieved for the types of carbocations (tertiary or allylic) found in biological reactions. *It is already clear, however, from the results of the current study of the* C_6H_6- -CH_3^+ *system, that even if the carbocationic center in an enzyme−intermediate complex is ca. 4 Å away from an aromatic ring, the* η^6 *geometry, although most favorable for binding of a coordinatively saturated cation, offers no energetic advantage for a coordinatively unsaturated carbocation.*

Conclusions

1. One aim of this computational study of the C_6H_6- -CH_3^+ system was to establish the level of theory that could be expected to give reliable results when applied to the interaction of more complex carbocations, such as *tert*-butyl or allyl, with aromatic rings. The studies reported here show that inclusion of electron correlation is essential for accurate calculation of intermolecular distances and binding energies in carbocation−aromatic ring complexes. The extensive comparisons we have made of our results for C_6H_6- -CH_3^+ and similar systems, including C_6H_6- -SiH_3^+ and C_6H_6- -Na^+, with previous experimental and theoretical results for the same systems show very good agreement between our results obtained at the B3LYP/6-31G* level of theory and earlier work. We are thus confident that computations at that level will provide a practical, reliable approach for examining more complex, biochemically relevant, carbocation−π interactions.

2. The results for C_6H_6- -CH_3^+ show that none of the η^6 (**1**), η^2 (**2**), or η^1 (**3**) complexes is an energy minimum. The maximum binding calculated for complexation of CH_3^+ to the periphery of the ring is calculated to be ca. −70 kcal/mol, which is more than twice the optimum strength of binding above the ring centroid (η^6 complex). The optimum association energies in η^2 and η^1 complexes are ca. 80% of the binding energy calculated for the Wheland equilibrium structure (**4**).

3. An examination of the dependence of binding in complexes **1**−**4** on intermolecular separation shows that at distances >2 Å, a π approach toward **2** or **3** has a binding energy which is competitive with that associated with the approach to σ complex (**4**) formation. *The results for* C_6H_6- -CH_3^+ *also show clearly that, in contrast to complexes of coordinatively saturated cations with benzene, at intermolecular distances <3.5 Å an* η^6 *geometry with the cation centered over the aromatic ring is not the most favorable geometry for* π *complexation of carbocations.* Significantly greater binding energy is obtained anywhere over the periphery of the ring (as in **2** or **3**), and even at distances > 3.5 Å, binding at the periphery of the aromatic system is comparable in energy to η^6 binding (Figure 2). Therefore, it is probably misleading to include interactions of carbocations with aromatic rings as examples of cation−π interaction with η^6 geometry, as has been done to date.[12,13]

4. With respect to the postulated stabilization of carbocation intermediates in biochemical reactions via π interactions with aromatic residues, the current results not only redefine the probable geometries of such interactions but also indicate that very substantial stabilization can be afforded to carbocations appropriately positioned over a benzene ring even at distances

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(66) Tetler, J. M.; Ditchfield, R.; Spencer, T. A., unpublished results.

considerably greater than typical covalent bonding distances. This is an important consideration with respect to the stabilization of biochemical carbocation intermediates. However, the results for C_6H_6- -CH_3^+ indicate that in the absence of constraints, any type of π complex will collapse without a barrier to the σ complex. Clearly, such unwanted σ complex formation between the substrate and protein must be prevented in biochemical reactions. This could be achieved, for example, by an enforced separation between the carbocation and an aromatic amino acid side chain residue. Further study will be required to achieve a full understanding of how the carbocation−π interaction can function successfully to stabilize carbocation intermediates in enzymatic reactions without permitting irreversible σ complex formation.

Acknowledgment. The authors are grateful to the Richter Memorial Trust for a Research Grant to P.C.M. in support of his undergraduate honors thesis research and to Dr. Holy Razafinjanahary-Cremillieux for valuable discussions of density functional methods.

Supporting Information Available: Energies and optimized geometries in Cartesian coordinate form at the B3LYP/6-311+G* level for CH_3^+, SiH_3^+, C_6H_6, and complexes **1**−**7** and energies for optimized structures of CH_3^+ and C_6H_6 at the MP2(fu)/6-31G*, MP2(fu)/6-31G**, MP2(fc)/6-311+G*, MP4(fc)/6-31G*, and B3LYP/6-31G* levels. (6 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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