A computational study of the interaction of [7]-helicene with alkali cations and benzene

Sangeeta Saini[a] & B M Deb[b,c,*]

[a]Solid State and Structural Chemistry Unit, Indian Institute of Science, Bangalore 560 012, India

[b]S.N. Bose National Centre for Basic Sciences, JD Block, Sector III, Salt Lake, Kolkata 700 098, India

and

[c]Jawaharlal Nehru Centre for Advanced Scientific Research, Bangalore 560 012, India

Email: bmdeb@yahoo.co.in

Ab initio calculations, using restricted Hartree-Fock, density-functional (DFT) and Moeller-Plesset perturbation theories, have been performed to study the cation-π interactions between alkali cations and [7]-helicene as well as the interaction between [7]-helicene and benzene. The helical molecule's two terminal benzene rings give the profile of 'crocodile's jaws' which open up to receive the cations, exhibiting the stability of the complexes increasing in the order $Na^+>K^+>Cs^+$. The binding energies in these cation-π complexes comprise mainly electrostatic, polarization (including dispersion) and charge transfer contributions. According to DFT, the electrostatic contribution alone is 43% for Na^+, 60% for K^+ and 75% for Cs^+. However, even DFT shows very little stabilization for the helicene-benzene complex so that this interaction between a helical and a neutral molecule cannot serve as a model for DNA-drug interactions due to very little overlap between the π clouds of the two molecules.

Helicenes constitute a class of exotic and fascinating ortho-fused polycyclic aromatic hydrocarbons[1] in which all the benzene rings are angularly arranged. Due to the resultant overcrowding of the benzene rings, the molecules acquire a helical structure from [5]-helicene onwards. By virtue of their helical structure, the presence of powerful inherently chiral chromophores and the possibility of *trans*-annular electronic interactions[2,3] between overlapping rings, helicenes exhibit a number of interesting and unusual properties such as high optical rotation[4], nonlinear optical properties[5], etc. which have technological potential. Furthermore, these molecules are structural analogues to biological helical macromolecules such as nucleic acids and proteins. In recent years, several experimental and theoretical studies have been carried out on helicenes and related molecules including the determination of their racemization barriers[6,7], aromatic character[8] and nonlinear optical properties (e.g., of tetrathia-helicenes[5]). However, interactions between helicenes and atoms/ions as well as other molecules do not appear to have been studied. This is attempted in the present investigations.

Figure 1 shows the reason why [7]-helicene ($C_{30}H_{18}$) alone has been chosen for the present work.

The profile of the molecule depicted from crystallographic data[9], shows the two terminal overlapping benzene rings in the form of a crocodile's jaws. Other helicenes do not have such a profile. Therefore, it would be worthwhile to investigate the nature of the interactions of [7]-helicene with: (i) cations of alkali metals, and (ii) other molecules, e.g. benzene itself. In other words, how do the ions and molecules slide into the `jaws' of [7]-helicene and how do the `jaws' open up to receive the `food'? Such
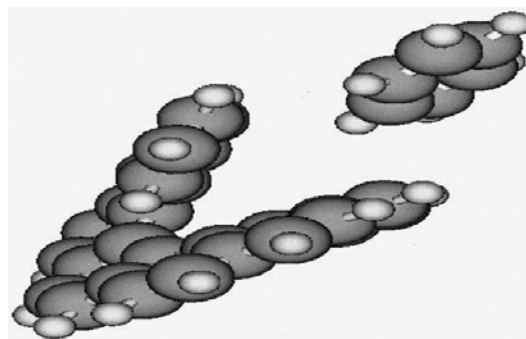

Fig. 1—Profile of [7]-helicene (the molecule on the left) from crystallographic data, seemingly trying to 'devour' benzene molecule.

Table 1—Comparison of calculated C-C bond lengths (Å) in the optimized geometry of [7]-helicene at various levels
of theory with the corresponding crystallographic data[9]

C-C bond length	Crystal structure	AM1	RHF/MIDI	RHF/3-21G*	RHF/6-31G**	DFT/BHHLYP/6-31G**
Terminal rings	1.392 ± 0.030	1.403 ± 0.020	1.391 ± 0.025	1.393 ± 0.025	1.394 ± 0.030	1.394 ± 0.025
Inner bonds	1.421 ± 0.004	1.414 ± 0.004	1.398 ± 0.002	1.400 ± 0.005	1.401 ± 0.006	1.411 ± 0.005
Inner helix	1.437 ± 0.007	1.443 ± 0.001	1.454 ± 0.004	1.457 ± 0.004	1.448 ± 0.025	1.439 ± 0.020
Outer helix[a]	1.33 and 1.41	1.36 and 1.43	1.34 and 1.42	1.34 and 1.42	1.35 and 1.43	1.35 and 1.45

[a]The C-C bonds along the outer helix alternate between the values gives in each column

an interaction might also be able to model, e.g. drug-DNA interactions. It has long been known through crystallographic studies of the DNA-actinomycin D interacting system[10] that as the drug slides into DNA, DNA first opens up to receive the incoming molecule and then `bites down' on it through stretching, bending, sliding and unwinding motions of the sugar-phosphate backbone via the corresponding normal modes. For [7]-helicene to mimic such interactions, it would be of interest to see whether this relatively smaller molecule has adequate flexibility in its backbone in the case of its interaction with, e.g. benzene.

The interaction of [7]-helicene with alkali cations brings in the important problem of cation-π interactions[11-13] which constitute a general non-covalent binding force and are widely prevalent in chemical and biological systems, e.g. gas-phase ion-molecule complexes, proteins, certain enzymes and the molecular mechanisms through which they catalyze biochemical reactions, ion selectivity in K^+ channels, etc. Consequently, cation-π interactions constitute an important general force for molecular recognition in biological receptors.

Materials and Methods

Ab initio geometry optimizations for [7]-helicene itself as well as for the interacting [7]-helicene + alkali cations and [7]-helicene + benzene systems were performed by using the GAMESS (General Atomic and Molecular Electronic Structure System) software package[14]. The employed *ab initio* methods were restricted Hartree-Fock (RHF) and density functional theory (DFT) with B3LYP and BHHLYP exchange-correlation functionals. All the *ab initio* calculations were performed by using either 3-21G* or 6-31G** basis sets or both, except for a large cation like Cs^+ where the MIDI level basis set was employed. Single-point Moeller-Plesset (MP2/6-31G**) calculations were also performed at the

equilibrium geometries obtained with DFT/BHHLYP/6-31G**. The input geometry of [7]-helicene, for purposes of optimization by the *ab initio* methods, was the optimized geometry calculated according to the AM1 method. Earlier, DFT/B3LYP calculations with 6-31G* and 6-311G** basis sets had been performed to study cation-π interactions between tetramethylammonium cation and benzene[15]. Another possible method is CCSD(T). However, to the best of our knowledge, CCSD(T) calculations on cation-π calculations as well as on a large molecule like [7]-helicene do not appear to have been attempted so far. Because of the relative ease in computation and interpretation, DFT has been a preferred method for studying non-covalent interactions (see also ref. 16) unless one calculates a potential energy surface involving bonds with hydrogen atoms where CCSD(T) may have a slight advantage over DFT[17]. The present work, however, does not involve the calculation of a potential energy surface.

Results and Discussion

Table 1 compares different types of experimental C–C bond lengths in the [7]-helicene molecule with the corresponding optimized values according to AM1 and *ab initio* calculations. All the calculations yield values close to the experimental ones. However, the AM1 optimized geometry has slightly higher energy (-1146.560 a.u.), compared to the RHF optimized energy (-1146.574 a.u.), both energies calculated at the 6-31G* level. Overall, DFT/BHHLYP/6-31G** gives the best results (Tables 1 and 2).

Now, in order to study the complexes of [7]-helicene with alkali cations, it is first necessary to ascertain the preferred direction of approach of the monopositive cations towards the helicene molecule. This can be done by visual inspection of the color-coded electrostatic potential (ESP) maps of [7]-helicene itself[18,19]. These maps provide reliable

Table 2—Energies in hartrees (1 hartree = 627.5 Kcal mol^{-1}) of non-interacting (isolated) systems, using different methods and different basis sets (MP2 calculation for [7]-helicene was performed only at the equilibrium geometry given by DFT/BHHLYP/6-31G**)

System	RHF/MIDI	RHF/3-21G*	RHF/6-31G**	DFT/B3LYP/ MIDI	DFT/B3LYP/ 3-21G*	DFT/BHHLYP/ 6-31G**	MP2/6-31G**
Helicene	-1139. 75644	-1140. 26511	-1146. 60653	-1146. 59843	-1147. 05886	-1153. 40730	-1150. 53386
Na+	_	-160. 67435	-161. 65929	_	-161. 03383	-162. 06390	-161. 66078
K+	_	-596. 00665	-598. 97190	_	-596. 67178	-599. 72563	-598. 98235
[a]Cs+	-7530. 46378	_	-19. 47928[a]	-7532. 83360	_	-19. 68283[a]	-19. 51332[a]
Benzene	_	-229. 45300	-230. 71386	_	-230. 84673	-232. 11040	-231. 50458

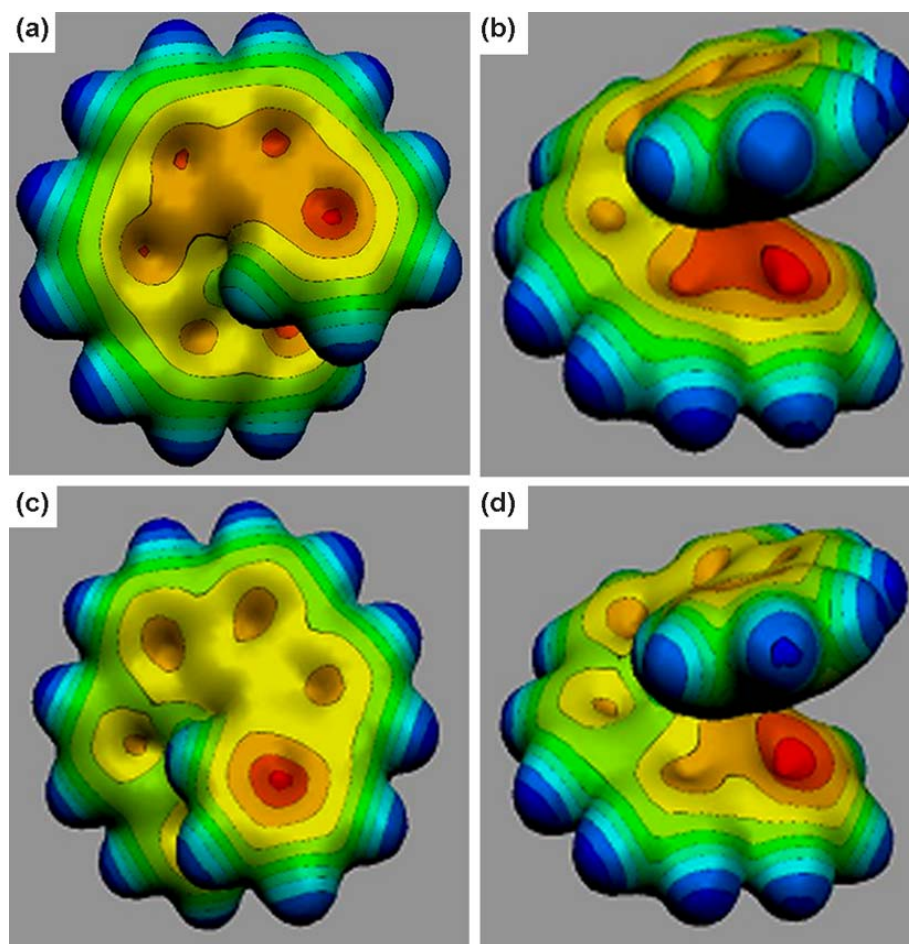[a]Using Hay-Wadt ECP + Glendering polarization[25]

Fig. 2—Colour-coded ESP maps of uncomplexed [7]-helicene. (a) and (b) depict views of the top (along helix axis) and along 'jaws' of the molecule, respectively according to RHF/6-31G** calculations while (c) and (d) depict the same according to DFT/BHHLYP/6-31G** calculations. For (a) and (b), the colour code is (in a.u.): Red, -0.12; light red, -0.090; orange, -0.073; green, -0.022; blue, 0.055. For (c) and (d), the colour code is (in a.u.): Red, -0.074; light red, -0.057; orange, -0.046; green, -0.013; blue, 0.037.

information on the strength of cation-π interactions, a more negative ESP indicating a stronger interaction. Figure 2 shows the color-coded[18] ESP maps, at the RHF/6-31G** (Figs 2a, 2b) and DFT/BHHLYP/6-31G** (Figs 2c, 2d) level, by viewing the molecule from the top (or bottom) along the helix axis (z-axis) and along the `jaws' ($x$-axis). It is clear from Fig. 2 that the cation prefers to approach helicene along the $x$-direction because the ESP is most negative (red regions) within the `jaws'. In contrast, the top view of the molecule (Fig. 2) indicates less negative (orange regions) ESP. The picture is the same for both levels of theory. Nevertheless, in view of cation-π interactions between alkaline earth cations and benzene[11,12], the possibility of an alkali cation also gravitating towards any of the terminal benzene rings in [7]-helicene cannot be ruled out.

Table 2 lists the energies of the non-interacting, isolated systems, viz., [7]-helicene at its equilibrium geometry according to the particular method employed, the cations (Na^+, K^+, Cs^+) and benzene. The last molecule was chosen to explore the feasibility of employing helicene + other molecule systems for modeling drug-nucleic acid interactions. Table 3 lists the energies of the helicene-cation and helicene-benzene complexes along with the respective stabilization energies, according to different methods and basis sets (Limitations on computer time prevented full geometry optimizations using the MP2 method. Instead, single-point MP2 calculations were performed at the optimized geometries given by DFT/BHHLYP/6-31G**). These data indicate that the order of stability of the complexes is: helicene-Na+ > helicene-K+ > helicene-Cs+ > helicene-benzene. Interestingly, among successive alkali cation complexes, there is a near-constant stability difference of ≈0.03 hartree (19 kcal mol⁻¹). The interaction energy with benzene is about one-tenth of that with Cs^+.

Before one analyzes the nature of binding in these complexes, it is necessary to look at the geometry changes in the helicene molecule as a result of the interactions. The space-filling models[20] of the three helicene-cation complexes (Fig. 3) show that as a cation approaches helicene, the terminal rings move apart in space. In other words, the helicene `jaws' open up to receive the `food'. This effect is most pronounced with Na^+. Even the terminal-ring C–C bond lengths in helicene-Na⁺ suffer an increase of 0.008 Å while the inner C–C bond lengths and those

Table 3—Energies in hartrees(1 hartree = 627.5 Kcal mol⁻¹) of complexes of [7]-helicene with alkali cations and benzene, after geometry optimization (Table 2 gives the energies of non-interacting isolated systems)

Complex	Sum of non-interacting energies (A)	Energy of complex (B)	Stabilization energy (B-A)
Helicene-Na⁺	-1300.93946[b]	-1301.03846[b]	-0.09900[b]
	-1308.26582[c]	-1308.34556[c]	-0.079740[c]
	-1308.09269[e]	-1308.20021[e]	-0.10752[e]
	-1315.47120[f]	-1315.56000[f]	-0.08880[f]
Helicene-K⁺	-1736.27176[b]	-1736.33344[b]	-0.06168[b]
	-1745.57843[c]	-1745.63138[c]	-0.05295[c]
	-1743.73064[e]	-1743.79798[e]	-0.06734[e]
	-1753.13293[f]	-1753.19290[f]	-0.05997[f]
	-1749.51621[g]	-1749.57700[g]	-0.06079[g]
Helicene-Cs⁺	-8670.22022[a]	-8670.24856[a]	-0.02834[a]
	-1166.08581[c,h]	-1166.11693[c,h]	-0.03112[c,h]
	-8679.43203[d]	-8679.46279[d]	-0.03076[d]
	-1173.09013[f,h]	-1173.12543[f,h]	-0.03530[f,h]
Helicene-Benzene	-1369.71811[b]	-1369.72098[b]	-0.00287[b]
	-1377.90559[e]	-1377.90776[e]	-0.00217[e]
	-1377.32039[c]	-1377.32219[c]	-0.00180[c]
	-1385.51770[f]	-1385.52000[f]	-0.00230[f]
	-1382.03844[g]	-1382.04369[g]	-0.00525[g]

[a]RHF/MIDI; [b]RHF/3-21G*; [c]RHF/6-31G**; [d]DFT/B3LYP/MIDI; [e]DFT/B3LYP/3-21G*; [f]DFT/BHHLYP/6-31G**; [g]MP2/6-31G**, single-point calculation at the equilibrium geometry according to (f); [h]using Hay-Wadt ECP + Glendering polarization for Cs⁺ (ref. 25).

in the inner helix increase by 0.004 and 0.003 Å, respectively as a result of the `jaw-opening' (Table 1). There is no change in the C–C bonds in the outer helix.

The equilibrium distances of the cations from the origin indicate the closeness of their approach to the helicene molecule. These distances decrease in the order Na^+ <K^+ <Cs^+. The stabilization energies (Table 3) follow the trend Na^+ >K^+ >Cs^+ indicating that electrostatic interactions[21] play a significant role in binding in these complexes for which the attractive interactions consist of mainly electrostatic and polarization (including dispersion) interactions while the repulsive electronic interactions arise due to the penetration of electrons of one partner into the space of the other partner. Table 4 gives the ESP values for [7]-helicene at distances along the x-axis, corresponding to the equilibrium positions of the cations from the origin in the respective complexes. The ESP plays a dominant role (74.6%) in stabilizing the helicene-Cs⁺ complex, compared to the helicene-K⁺ complex (59.9%) and the helicene-Na⁺

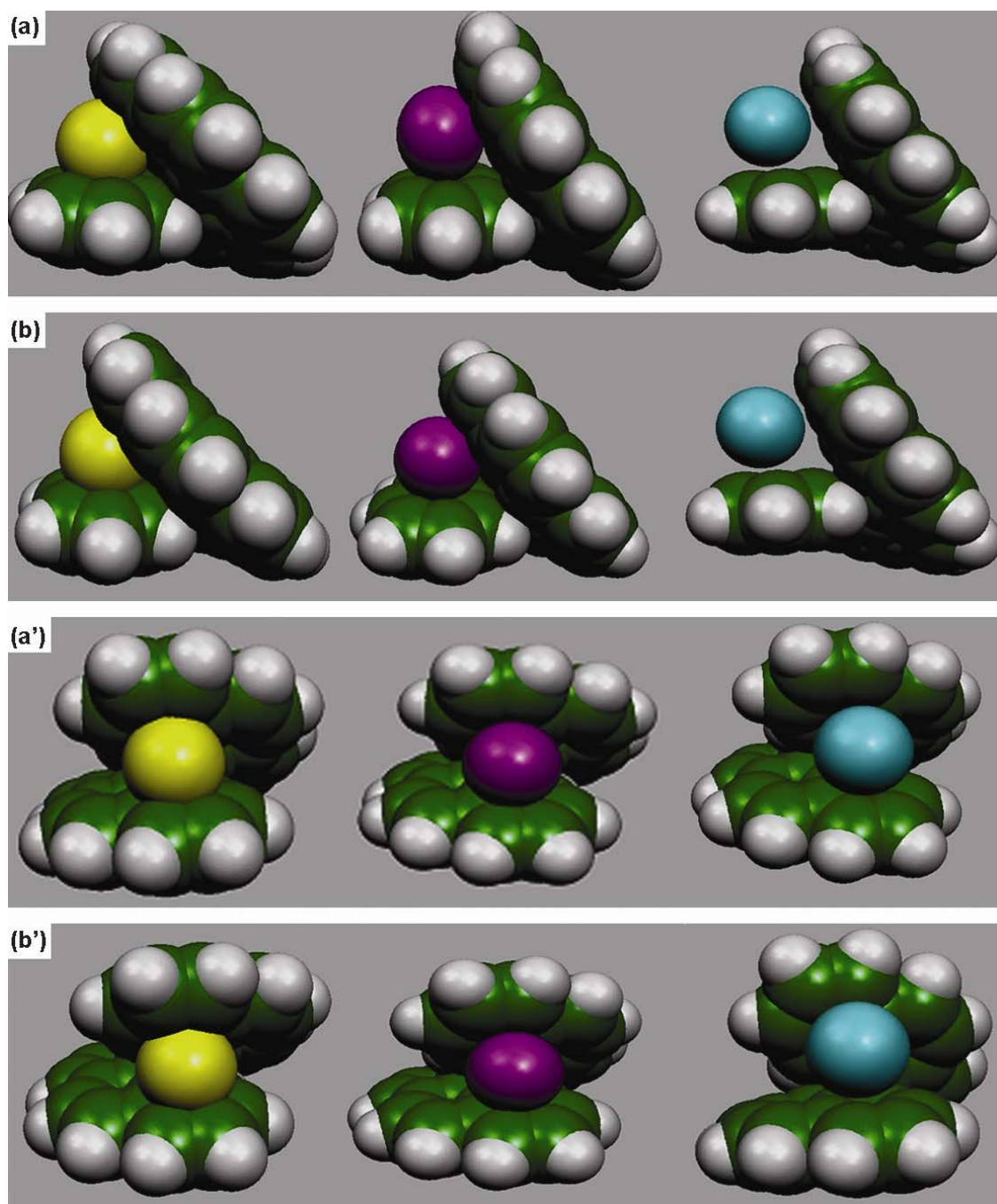Fig. 3—Space-filling models of [7]-helicene-cation complexes, with Na^+ (left), K^+ (middle) and Cs^+ (right), at RHF/6-31G** [(a): side view, (a′) front view, and DFT/BHHLYP/6-31G** (b): side view, (b′) front view] levels of theory.

complex (42.8%), the percentages coming from DFT/BHHLYP/6-31G** calculations. Other methods in Table 4 also show similar trends. However, the actual magnitudes of the ESP values themselves increase in the same order as the stabilization energies. The Na^+ cation, with its greatest positive charge density, polarizes the π cloud of the helicene more than the other cations. Hence, for the helicene-Na^+ complex, polarization contributes more to binding than electrostatic interactions whereas for the helicene-Cs^+ complex the electrostatic contribution to binding is much more than polarization contribution due to a much lower positive charge density on the cation.
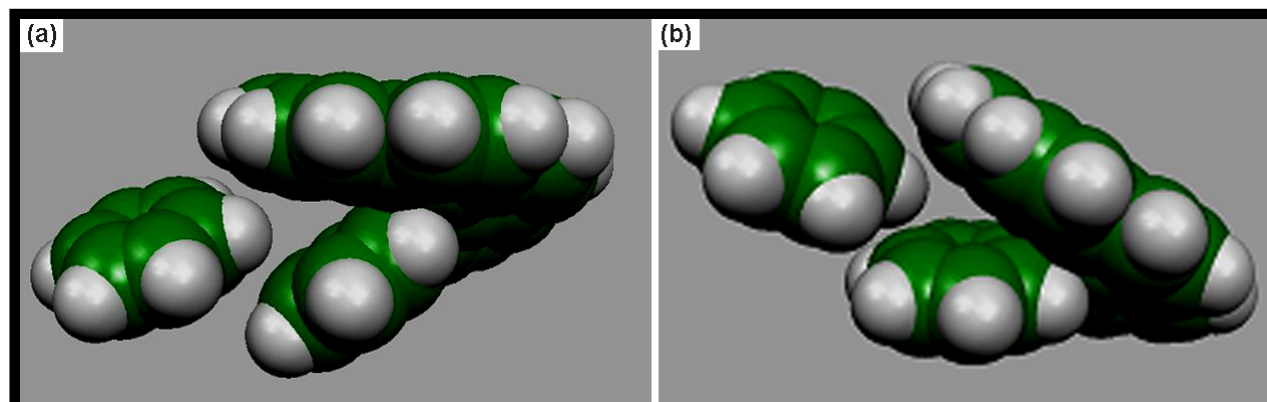
Fig. 4—Space-filling models of the equilibrium geometries of the [7]-helicene•benzene system at: (a) RHF/6-31G**, and (b) DFT/BHHLYP/ 6-31G** levels of theory.

Table 4—Electrostatic potentials(ESP) in hartrees (1 hartree = 627.5 Kcal mol^{-1}) for [7]-helicene at distances corresponding to the equilibrium positions of the cation nuclei in the complexes of [7]-helicene with alkali cations. The cation nuclear distances from the origin are calculated along the x-axis of [7]-helicene. Numbers in parentheses denote the ratio (100 × ESP) / (Stabilization energy) (see also Table 3)

Complex	RHF/3-21G*		RHF/6-31G**		DFT/BHHLYP/6-31G**	
	Cation Distance (Å)	ESP	Cation Distance (Å)	ESP	Cation Distance (Å)	ESP
Helicene- Na$^+$	2.806	-0.0526 (53.1)	2.981	-0.0420 (52.7)	2.892	-0.0380 (42.8)
Helicene- K$^+$	3.457	-0.0458 (74.3)	3.570	-0.0368 (69.4)	3.288	-0.0359 (59.9)
Helicene- Cs$^+$	-	-	4.308	-0.0254 (81.8)	4.096	-0.0262 (74.6)

Besides electrostatic and polarization interactions, charge transfer also plays a role in the binding in these complexes. Table 5 indicates the extent of π charge donation from helicene to a cation, the extent decreasing rather approximately in the ratios of squares of their ionic radii, using the results from DFT/BHHLYP/6-31G**. Thus, using Mulliken atomic charges[22] of helicene-cation complexes and free helicene respectively, Na$^+$, K$^+$ and Cs$^+$ receive π electronic charge of 0.52, 0.27 and 0.12, respectively according to DFT/BHHLYP/6-31G**. Note that of the three methods in Table 5, inclusion of electron correlation makes the DFT results more reliable. However, the LYP correlation functional was designed at equilibrium molecular geometries and does not have satisfactory long-range behavior indicating that dispersion interactions[23] are unlikely to be adequately represented by LYP. For such interactions, the local Wigner correlation functional[24] might provide better results. It may also be noted that no population analysis, whether Mulliken or Löwdin, is unique[22]. Hence, the relative atomic charges values in Table 5 represent at best a trend.

Table 5—Charge transfer (in a.u.) from [7]-helicene to the cations in the complexes of [7]-helicene with alkali cations

Complex	Charge transferred to cation		
	RHF/ 3-21G*	RHF/ 6-31G**	DFT/BHHL YP/6-31G**
Helicene-Na+	0.13	0.39	0.52
Helicene-K+	0.087	0.22	0.27
Helicene-Cs+	0.024	0.099	0.12

Figure 4 depicts the [7]-helicene-benzene system, with benzene approaching helicene along the x-axis, at RHF/6-31G** and DFT/BHHLYP/6-31G** levels. A comparison of the stabilization energies according to these two methods, -1.13 and -1.44 kcal mol^{-1}, respectively (Table 3), indicates that apart from basis set superposition error, there is at most dispersion interaction between the molecules. Since, neither of the two methods would describe this interaction well (note that RHF does not include electron correlation), a single-point MP2 calculation was performed with the DFT/BHHLYP/6-31G** optimized geometry of the interacting system. The corresponding stabilization energy was enhanced to –3.29 kcal mol^{-1}.

Overall, there is thus little overlap between the π electron clouds of benzene and [7]-helicene. This does not favor the entry of benzene molecule inside the helicene, indicating that this particular interaction cannot serve as a model for drug-nucleic acid (host-guest) interactions.

Conclusions

The expectation that [7]-helicene might open up its crocodile-like `jaws' to form complexes with alkali cations has turned out to be correct, with the stability of the complexes increasing in the order $Na^+ > K^+ > Cs^+$. The binding energies in these cation-π complexes mainly consist of electrostatic, polarization (including dispersion) and charge transfer contributions. For Cs^+ and K^+ complexes, the electrostatic contribution is the major part, being 75% and 60%, respectively of the total binding energy whereas it is only 43% for the Na^+ complex, according to DFT/BHHLYP/6-31G**. However, the interaction between [7]-helicene and benzene is not favourable since there is very little overlap between the two π electron clouds. Therefore, one needs to take a larger helical molecule which would have adequate flexibility in its backbone in order to model DNA-drug interactions.

Acknowledgement

References

1   Martin R H, *Angew Chem Int Ed Engl,* 13 (1974) 649.
2   Obenland S & Schmidt W, *J Am Chem Soc,* 97 (1975) 6633.
3   Deb B M & Kavu G, *Canad J Chem,* 58 (1980) 258.
4   Furche F, Ahlrichs R, Wachsmann C, Weber E, Sobanski A, Vögtle F & Grimme S, *J Am Chem Soc,* 122 (2000) 1717.
5   Daul C A, Ciofini I & Weber V, *Int J Quant Chem,* 91 (2003) 297.
6   Janke R H, Haufe G, Würthwein E U & Borkent J H, *J Am Chem Soc,* 118 (1996) 6031.
7   Grimme S & Peyerimhoff S D, *Chem Phys,* 204 (1996) 411.
8   Schulman J M & Disch R L, *J Phys Chem A,* 103 (1999) 6669.
9   Beurskens P T, Beurskens G & Van den Hark T E M, *Cryst Struc Comm,* 5 (1976) 241.
10 Sobell H M, *Scient Ameri*, 231 (1974) 82.
11 Tan X J, Zhu W L, Cui M, Luo X M, Gu J D, Silman I, Sussman J L, Jiang H L, Ji R Y & Chen K X, *Chem Phys Lett,* 349 (2001) 113.
12 Ma J C & Dougherty D A, *Chem Rev,* 97 (1997) 1303.
13 Sunner J, Nishizawa K & Kebarle P, *J Phys Chem,* 85 (1981) 1814.
14 GAMESS: *General Atomic and Molecular Electronic Structure System,* Schmidt M W, Baldridge K K, Boatz J A, Elbert S T, Gordon M S, Jensen J H, Koseki S, Matsunaga N, Nguyen K A, Su S J, Windus T L, Dupuis M & Montgomery J A, *J Comput Chem,* 14 (1993) 1347 (and the references cited therein. Grateful acknowledgement is made for permission to use GAMESS).
15 Felder C, Jiang H -L, Zhu W -L, Chen K -X, Silman I, Botti S A & Sussman J L, *J Phys Chem A,* 105 (2001) 1326.
16 Sceats E L & Green J C, *J Chem Phys,* 125 (2006) 154704.
17 Datta A & Sherrill C D, *J Chem Phys*, 118 (2003) 1610.
18 Bonaccorsi R, Scrocco E & Tomasi J, *J Chem Phys,* 52 (1970) 5270.
19 Politzer P & Daiker K C, in *The Force Concept in Chemistry*, edited by B M Deb (Van Nostrand-Reinhold Co , New York) 1981.
20 Portmann S & Luethi H P, *Chimia,* 54 (2000) 766.
21 Cioslowski J & Lin Q, *J Am Chem Soc,* 117 (1995) 2553.
22 Szabo A S & Ostlund N S, *Modern Quantum Chemistry* (Dover Publications, New York) 1996, pp.151.
23 Berry R S, Rice S A & Ross J, *Physical Chemistry* (Oxford University Press, Oxford) 2000, Chap. 10.
24 Roy A K, Dey B K & Deb B M, *Chem Phys Lett,* 308 (1999) 523.
25 Hay P J & Wadt W R, *J Chem Phys,* 82 (1985) 299.