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Induced-fit conformational changes in the cation–π complexes of pyxophane: a DFT study †

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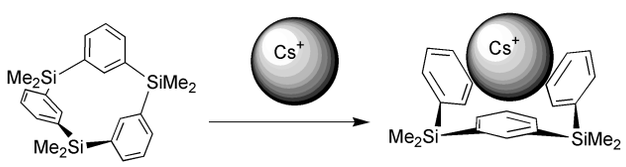
In contrast to the proposed structures of 1 : 1 complexes of the chair-form pyxophane‡ 1 with Na^+ and 'external' 2 : 1 complexes with K^+, DFT calculations suggest that 1 prefers the saddle-form in the complexes due to the induced-fit conformational change and that 1 forms an 'internal' 2 : 1 complex with K^+.

In recent years, the cation–π interaction has attracted much attention, not only in many biological systems but also in artificial host–guest complexes, because the noncovalent interaction plays a key role in many molecular recognition processes.[1] The interaction is considered to be the origin of the selectivity of protein channels,[2] and a large number of studies of synthetic receptors have also demonstrated the importance of the cation–π interaction.[3]

Induced-fit is often important for the understanding of the structures of cation–π complexes. We have recently investigated the cation–π interaction of the silicon-bridged [1$_n$]metacyclophanes as silicon analogues of calix[*n*]arenes.[4,5] The cation–π complexation of these compounds with Cs^+ was observed by electrospray mass spectrometry (ESI-MS). The *ab initio* calculations of the resulting π-complexes show that the most stable conformation in the uncomplexed form is not always the preferred conformation of the π-complexes.[5,6] For instance, trisila[1$_3$]metacyclophane, which adopts the saddle structure in the uncomplexed form, changes its conformation into the cone one during cation inclusion (Scheme 1). The calculations



Scheme 1

show the induced-fit conformational change easily occurs by cation–π complexation.

In this communication, we indicate by DFT calculations that the induced-fit is also important for another artificial π-receptor. Recently, Gokel and co-workers reported the synthesis of the novel π-receptor **1**, namely pyxophane, possessing two arenes held rigidly face-to-face at a distance appropriate to bind an alkali metal cation.[7] The structure of molecule **1** is shown in Fig. 1. They have found that **1** shows unique ion selective dimerization in the cation–π complexes. They stated that the molecular size of **1** estimated by X-ray crystallography was

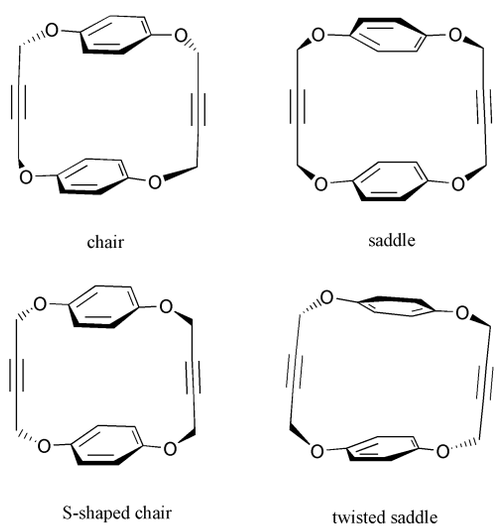
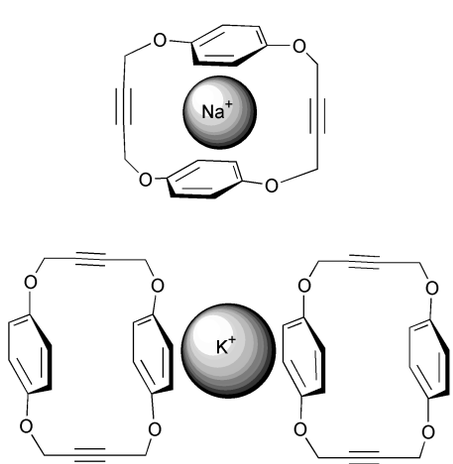


Fig. 1 Four stable conformations of pyxophane **1** in the gas phase.

suitable for a selective Na^+ inclusion. Indeed, the intense signal corresponding to the 1 : 1 complex of **1** and Na^+ was clearly observed using ESI-MS. The compound **1** did not form such a 1 : 1 complex with larger K^+, but forms a 2 : 1 complex instead. They tried to explain the selectivity by speculation that metal ions larger than Na^+ could not go into the cavity of **1** and 'external' dimer complex formation was likely to occur (Scheme 2). They did not consider the induced-fit conformational change to estimate the structures of the complexes. Our DFT calculations, however, indicate that the induced-fit is significantly



Scheme 2

† Electronic supplementary information (ESI) available: diagrams showing conformations of cyclophane **1**. See http://www.rsc.org/suppdata/p2/b1/b102759j/

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Table 1 Calculated relative energies of four conformers of **1** with alkali metal cations[a]

Cation	Conformation	E_{rel}[b]	E_{def}[c]	E_{bind}[d]
None	Chair	0		
	Saddle	2.5		
	S-shaped chair	4.3		
	Twisted saddle	4.8		
Na^+	Chair	3.4	4.9	−40.5
	Saddle	0	3.4	−43.9
	S-shaped chair	2.7	6.8	−41.2
	Twisted saddle	2.7	6.8	−41.2
K^+	Chair	6.8	9.2	−24.8
	Saddle	0	4.0	−31.6
	S-shaped chair	4.0	6.1	−27.6
	Twisted saddle	3.3	6.3	−28.3
Rb^+	Chair	10.4	10.2	−17.9
	Saddle	0	3.9	−28.3
	S-shaped chair	4.9	6.5	−23.4
	Twisted saddle	4.3	6.4	−24.0

[a] Energy in kcal mol^{-1}. Geometries are optimized at the BP/DZVP level. [b] Relative energy difference among the four possible conformations. [c] Increases of the energies by the deformation of the geometry from the isolated chair form to the deformed geometries in the π-complexes. [d] Calculated binding energies of π-complexes.

important for the cation–π complexes of **1**. We have found that **1** prefers the *saddle* conformation in the cation–π complexes and that **1** forms an 'internal' 2 : 1 complex with K^+, in which the K^+ is included in the cavity of the spherical dimer of **1**.

The DFT calculation was performed with the program DGauss 4.1.[8] The gradient corrected Becke'88-Perdew'86 (BP) functional was used with a standard DZVP valence basis set.[9] The BP/DZVP calculation gave four possible conformations for **1** in the gas phase as shown in Fig. 1. These are the chair, saddle, S-shaped chair and twisted saddle conformation, respectively. The geometries of the four conformations were optimized with or without alkali metal ions. In the uncomplexed form, the chair conformation was the most stable as shown in Table 1. The order of stability was chair > saddle > S-shaped chair > twisted saddle, which is in reasonable agreement with the observed chair structure in the X-ray crystallography. The calculation of the π-complexes with alkali metal ions, however, showed that the saddle conformation was more stable than the others. As for Na^+ complexes, the order of stability is saddle > twisted saddle = S-shaped chair > chair, which is completely different from that in the uncomplexed form. In the cases of K^+ and Rb^+ complexes of **1**, the deformation energies of the chair conformation are the largest among the four conformers in agreement with the proposed difficulty in the inclusion of large metal cations. However, the deformation energy of the Na^+ complex of the chair form is still 1.5 kcal mol^{-1} larger than that of the saddle one. The larger deformation energy of the chair form was derived from the following geometrical changes. In comparison with the uncomplexed chair form, the arene–arene distance in the Na^+-complex with the chair form was widened by 0.34 Å and the alkyne–alkyne distance was shortened by 0.38 Å, respectively. All four methylene parts rotated around the C–O axis by *ca.* 18° from the connecting benzene plane, which was energetically disadvantageous judging by the torsional potential of anisole.[11] Therefore, in contrast to the initial expectation, the cavity size of the chair conformation of **1** is not appropriate even for small Na^+. The wide V-shaped cavity of the saddle form is suitable for the inclusion of metal cations, although the saddle conformation is less stable than the chair one in the uncomplexed form. Consequently, the saddle structure was the most stable for all the possible π-complexes of **1**. The results were interpreted by the induced-fit mechanism, resulting in the smallest loss in the deformation energy and the largest gain in the binding energy during the cation–π complexation.

In order to investigate the ion selective dimerization of **1**, we have examined the optimized structures of Na^+ and K^+ complexes of **1** with the saddle conformation as shown in Fig. 2. It is clear that Na^+ enters more deeply into the cavity of **1** than K^+ does. Na^+ is located 0.61 Å below the mean plane of four sp^2-carbons at the edges of two arenes of **1**. On the other hand, K^+ lies 0.07 Å above the mean plane and thus K^+ is almost coplanar with the four carbons. The structure of the K^+ complex of **1** suggests that K^+ can easily bind another saddle-formed **1** and produce the spherical 'internal' dimer complex shown in Fig. 3. The energies of the 'internal' and 'external' dimer complexes with K^+ calculated by the BP/DZVP method showed that the 'internal' dimer complex of **1** was much more stable than the 'external' one by 14.2 kcal mol^{-1}. We also calculated the energies of the dimer complexes of Na^+ and Rb^+. We found that the internal dimer is always more stable than the external one by 11.6 kcal mol^{-1} for Na^+ and by 16.2 kcal mol^{-1} for Rb^+. However, in the internal dimer complex of Na^+, the ion is not located at the center of the cavity. Na^+ is closer to one of the two pyxophanes, indicating that the cavity size of the dimer is too large to fit Na^+. The binding energy of a second pyxophane to the monomer complex of Na^+ is −13.7 kcal mol^{-1}. The binding energy is smaller (less negative) than that to the monomer complex of K^+ (−16.8 kcal mol^{-1}) and is only one-third of the binding energy of the first pyxophane with Na^+. The monomer complex of Na^+ would be easily solvated as observed in ESI-MS.[7] The coordination of the second pyxophane **1** is thus regarded as an exchange reaction (1).

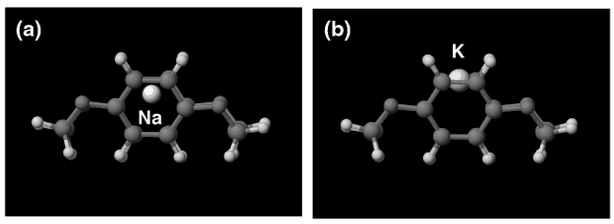

Fig. 2 Side views of the most stable π-complexes of **1** (saddle conformation); (a) with Na^+, (b) with K^+.

$$[Na^+ + \mathbf{1} + (solvent)] + \mathbf{1} \longrightarrow [Na^+ + \mathbf{1}_2] + solvent \quad (1)$$

Na^+ has a larger solvation energy than K^+.[12] The larger solvation energy of Na^+ and the smaller binding energy of the monomer complex of Na^+ with the second pyxophane would be the causes of the difficulty in the formation of the dimer complex of Na^+.

The optimized structure of the internal complex of K^+ suggests that the complex is further stabilized by *the intermolecular CH···O interactions*. The optimized structure has eight short CH···O contacts. The averaged interatomic distance between hydrogen and oxygen is 2.67 Å, which is within the expected region (<2.80 Å) of CH···O interaction contacts determined by Desiraju from the X-ray database survey.[13] The averaged intermolecular carbon and oxygen contact distance (*D*) is 3.61 Å, which is also within a 'significant' region (*D* = 3.00–4.00 Å).[13] Eventually, K^+ is fully surrounded by the shell consisting of two saddle-form **1** molecules with multiple CH···O interactions. The dimerization manner of **1** resembles the so-called 'tennis ball assembly' developed by Rebek, in which two identical molecular pieces provide the overall spherical shape of the dimer.[14] This highly organized supramolecular structure is the origin of the significant stability of the internal dimer complex of **1** compared to the external one. Although cation–π and CH···O interactions have been postulated often in many studies of supramolecules,[15] it is interesting that these interactions are observable even in the gas phase and they should be the cause of the unique ion selectivity of **1**.

In conclusion, the present DFT study has revealed that the pyxophane **1** is a π-receptor well-organized to achieve the specific ion recognition by cation–π and CH···O interactions derived from the induced-fit conformational changes.

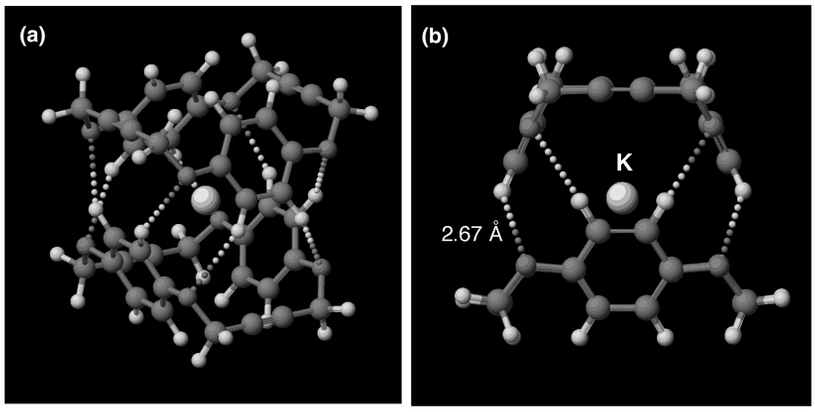

Fig. 3 (a) Optimized structure of the 'internal' dimer complex of **1** with K^+ by BP/DZVP calculations. The averaged K^+–C_{sp^2} contact is 3.33 Å. (b) Side view of the dimer complex of **1**. Dotted lines indicate the intermolecular CH · · · O interaction.

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Notes and references

‡ The IUPAC name for pyxophane is 2,7,9,14-tetraoxa-1,8(1,4)-dibenzenacyclotetradecaphane-4,11-diyne.

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