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Luis A. Godínez[a]; Brita G. Schulze-fiehn[a]; Sonal Patel[a]; Cecil M. Criss[a]; Jeffrey D. Evanseck[a]; Angel E. Kaifer[a]
[a] Chemistry Department, University of Miami, Coral Gables, FL, U.S.A.

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Communication

Observation and Interpretation of Anomalous Inorganic Anion Binding with α- and β-Cyclodextrins in Aqueous Media

LUIS A. GODÍNEZ, BRITA G. SCHULZE-FIEHN, SONAL PATEL, CECIL M. CRISS, JEFFREY D. EVANSECK and ANGEL E. KAIFER*

Chemistry Department, University of Miami, Coral Gables, FL 33124-0431, U.S.A.

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The binding constants for hexafluorophosphate, perchlorate and triflate with α- and β-cyclodextrins were quantified using calorimetry and fluorescence spectroscopy experiments in aqueous media as well as molecular orbital calculations. The association of α- and β-cyclodextrin with three commonly used counterions of large organic cations or as supporting electrolyte systems, proved to be large enough to produce significant interferences in complexation studies. In particular, the binding constant of hexafluorophosphate and β-cyclodextrin was measured to be ten times larger than the previously reported value. The enthalpies and entropies of complexation of the two receptors with the three anions under study were directly evaluated using calorimetric measurements in aqueous media. The PM3 semiempirical molecular orbital method was employed to rationalize the enhanced binding between β-cyclodextrin and hexafluorophosphate. The computed results from several energy minimizations show that inclusion complexes of β-cyclodextrins have a complicated energy surface with many possible energy minima. The binding of octahedral hexafluorophosphate originates from a loose yet complementary host-guest geometric fit that provides for three strong hydrogen bonds with primary hydroxyls of β-cyclodextrin.

The cyclodextrins (CDs) constitute a well-known family of cyclic oligosaccharide compounds that are widely used as molecular receptors.[1] Their ability to encapsulate nonpolar guests in their hydrophobic cavities, combined with their relatively high solubility in aqueous media, have made them very popular hosts and led to several scientific and technological applications.[2] In order to fully understand the forces that drive the complexation of CDs in aqueous media, several binding studies have been recently carried out using a combination of different techniques and a wide variety of nonpolar guests.[3–7] Among these, large organic cations in which the positive charge readily improves the aqueous solubility of the molecule have been frequently used as suitable guests for CDs. Prototypes of such cationic molecules are tetraalkylammonium derivatives of ferrocene.[8,9] However, the counterions of such cationic guests, or the anions of the supporting electrolyte system used to

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*Corresponding author.

maintain a constant ionic strength, are generally not considered to interact with the CD receptors. This assumption, usually justified, is based on the fact that the reported binding constants of these types of complexes in aqueous media are usually very low (in the range of 0–20 M^{-1}).[10–16]

While studying the complexation in aqueous media of a cationic ferrocene derivative with β-cyclodextrin by calorimetry,[9] we observed different thermograms for the system depending on the counterion of the ferrocene derivative (chloride or hexafluorophosphate). Further measurements of the electrochemical response of both salts using rotating disk voltammetry experiments (in which the diffusion coefficient of the electroactive ferrocene cation was determined as a function of the concentration of β-CD), confirmed the interference of the hexafluorophosphate ion in the complexation experiments. As a consequence of these observations, we have studied the association in aqueous media of α- and β-cyclodextrin with three anions: hexafluorophosphate, perchlorate and triflate.

In the first part of this study, the thermodynamic parameters of complexation of PF_6^-, ClO_4^- and $CF_3SO_3^-$, with the two cyclodextrin receptors were measured using flow-calorimetry in aqueous NaCl 0.2 M. The supporting electrolyte system was chosen based on previous measurements[12] that clearly indicated the absence of a detectable interaction between the chloride ion and the CD receptors even when it is present in concentrations as high as 1M. The details on the experimental calorimetric technique as well as the treatment of the resulting data have been discussed elsewhere.[9]

In Table I, the thermodynamic parameters for the complexation of β-CD with the three anions in 0.2 M NaCl at 298 K are presented. As one can see from the values of the binding constants, PF_6^- and $CF_3SO_3^-$ bind β-CD with enough strength to cause interference when present as counterions of cationic organic guests or as a part of the supporting electrolyte system (whose concentration is usually very high).

In fact, the binding constants for these two systems seem to be the largest ones reported for complexes of β-CD with inorganic anions in aqueous media.[10] Moreover, the measured binding constant of the PF_6^- anion with β-cyclodextrin is 10 times larger than the previously reported value.[10] In good agreement with literature results,[12,17] the measured binding constant of the β-CD-ClO_4^- complex falls close to 10 M^{-1} showing the lowest stability of the group.

In terms of the enthalpies and entropies of association, the stabilization of the three systems seems to follow the general pattern of complexation of nonpolar guests with CDs in aqueous media.[18] The complexation processes are enthalpy driven and the entropy changes are small and in some cases even negative, which supports the widely accepted idea that the association process is basically controlled by the desolvation of the CD cavity and intramolecular CD rearrangement.[19,20]

In order to elucidate if the detected interaction between the inorganic anions and the β-CD receptor was of the inclusion type, we decided to perform fluorescence displacement experiments as described by Park and co-workers.[21] In a typical experiment, the emission intensity of the fluorescent probe 1-anilino-8-naphthalenesulfonate (ANS, analytical concentration 5 μM, λ_{exc} = 350 nm) in the presence of 1 mM β-CD at different

TABLE I Thermodynamic parameters for the complexation of β-CD with the three anions under study in 0.2 M NaCl at 298 K

Anion	K (M^{-1})	ΔG° (kcal/mol)	ΔH° (kcal/mol)	$T\Delta S^\circ$ (kcal/mol)
PF_6^-	85 ± 5	−2.63 ± 0.03	−5.31 ± 0.21	−2.68 ± 0.21
$CF_3SO_3^-$	57 ± 2	−2.40 ± 0.02	−4.83 ± 0.19	−2.43 ± 0.19
ClO_4^-	12 ± 1	−1.50 ± 0.05	−3.94 ± 0.15	−2.45 ± 0.15

concentrations of the anion under study gave rise to a well defined binding isotherm (see Figure 1). In the absence of β-CD, the surveyed anions had no effect on the fluorescence emission of ANS. In the presence of β-CD however, the observed decrease in the fluorescence emission of the solution, caused by the displacement of the ANS probe from the cavity of the receptor by the inorganic anion, provided not only an additional way to measure the binding constants of the three anions with β-cyclodextrin, but also suggested that the complexation of the inorganic guests by the CD receptor is of the inclusion type. In Figure 1, for instance, the binding isotherm for the PF_6^--β-CD system is shown along with the calculated curve that best fits ($K = 88 \pm 6\ M^{-1}$) the experimental data. Notice the excellent agreement of this value with that reported in Table I, which was obtained by an entirely different procedure.

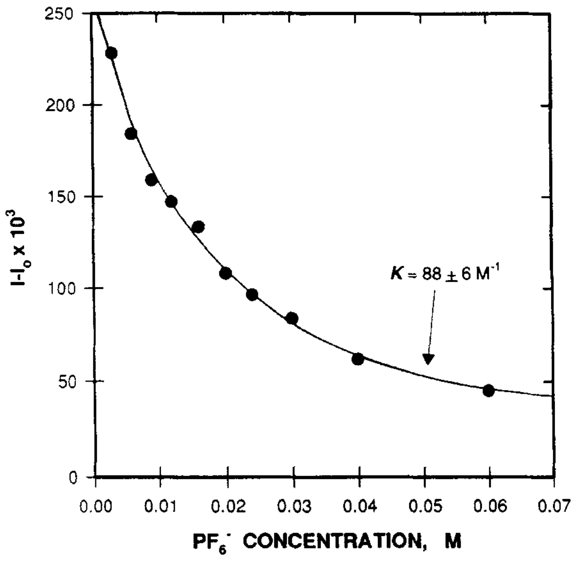

FIGURE 1 Fluorescence displacement binding isotherm for the PF_6^--β-CD complex in aqueous medium at 298 K. I-Io is the difference in the emission intensities of ANS in the presence of β-CD 1 mM at different concentrations of the anion (I) and in its absence (Io). The concentration of 1-anilino-8-naphthalenesulfonate (ANS) and β-CD are 5 μM and 1 mM respectively. λ_{exc} = 350 nm.

An important factor to be considered in studies on CD complexation is obviously concerned with the relative sizes of the host cavity and the guest molecule. In the particular case of the PF_6^--β-CD system, the reported size in aqueous medium of the octahedral hexafluorophosphate anion ranges between 5.82–6.12 Å,[22] while the internal diameter of the β-CD cavity has been reported to be 6.2 Å on average.[2] In order to better understand the three dimensional structure of the β-CD and hexafluorophosphate complex, energy minimization using the PM3[23] semiempirical molecular orbital method within the Spartan 4.1 program[24] was carried out. The crystal structure of β-CD[25] was used as the starting point for energy minimization. Separately, the hexafluorophosphate was constructed in an octahedral configuration. The energy minimized structures for both β-CD and hexafluorophosphate were superimposed using the Spartan graphics interface. At first, hexafluorophosphate was arranged in the center of the β-CD to give it the choice of either primary or secondary hydroxyl hydrogens for binding. During energy minimization, the anion moved towards the narrow end of β-CD where its fluorine atoms formed only weak electrostatic interactions (2.42 to 2.70 Å) with hydrogen atoms at C5 carbons of the sugar moieties of the β-CD, resulting in a binding enthalpy of −12.45 kcal/mol. It seemed unlikely that hexafluorophosphate would interact with hydroxyl groups from the wide rim of β-CD, because the anion is too small and the hydroxyl groups are too rigid to allow any close interaction. Therefore, our further investigation focused on the interactions between hexafluorophosphate and the narrow rim of β-CD.

We assumed that in solution there will be unhindered rotation of the CH_2OH groups at the C5 carbon atoms; therefore, we modified the orientation of these methylene hydroxyl groups to probe the potential energy surface of the inclusion complex. Several complexes with significantly lower energy were found. By forming one strong hydrogen bond (F-H distance = 1.74 Å) and four medium-range hydrogen bonds (2.47 to 2.64 Å), the energy of the minimized complex dropped to −18.26 kcal/mol (Fig. 2A). The lowest energy configuartion resulted with the formation of three strong hydrogen bonds (1.75 Å) and two weak hydrogen bonds (2.54 to 2.74 Å). The resulting complex has a binding enthalpy of −23.74 kcal/mol (Fig 2B). The weakest binding was observed when all primary hydroxyl groups are oriented away from the cavity (ΔH = −10.94 kcal/mol, not shown).

A maximum of five primary hydroxyl groups can simultaneously rotate inwards far enough for an appreciable interaction with the guest, but the most significant contribution to the binding enthalpy of the inclusion complex comes from close-range interactions (less than 2 Å, see Fig. 2). This can only result from a significant shift of the guest from the center of the cavity, as shown Fig. 2B. Due to its octahedral geometry, only the hexafluorophosphate ion (compared to perchlorate or triflate) is able to form three close-contact hydrogen bonds, which rationalizes its enhanced binding affinity over the other guests considered. For the other two ions, perchlorate and triflate, only two close-range hydrogen bonds are possible, which makes them less stable than the PF_6-inclusion complex.

The large values for complexation energy, as compared to experiment, are consistent with our recent report using the same computational methods for aromatic guest binding with a cyclophane receptor in the gas-phase.[26] The neglect of solvent typically enhances the energy of complexation by a factor ranging from three to four.

The thermodynamic values for the complexation process of α-CD with the three anions under study are presented in Table II. In excellent agreement with previous results,[11–13] the association constant of the ClO_4^- ion indicates a preferential binding with α-CD over the other two anions which in this case seem to be rather big for the receptor's cavity.

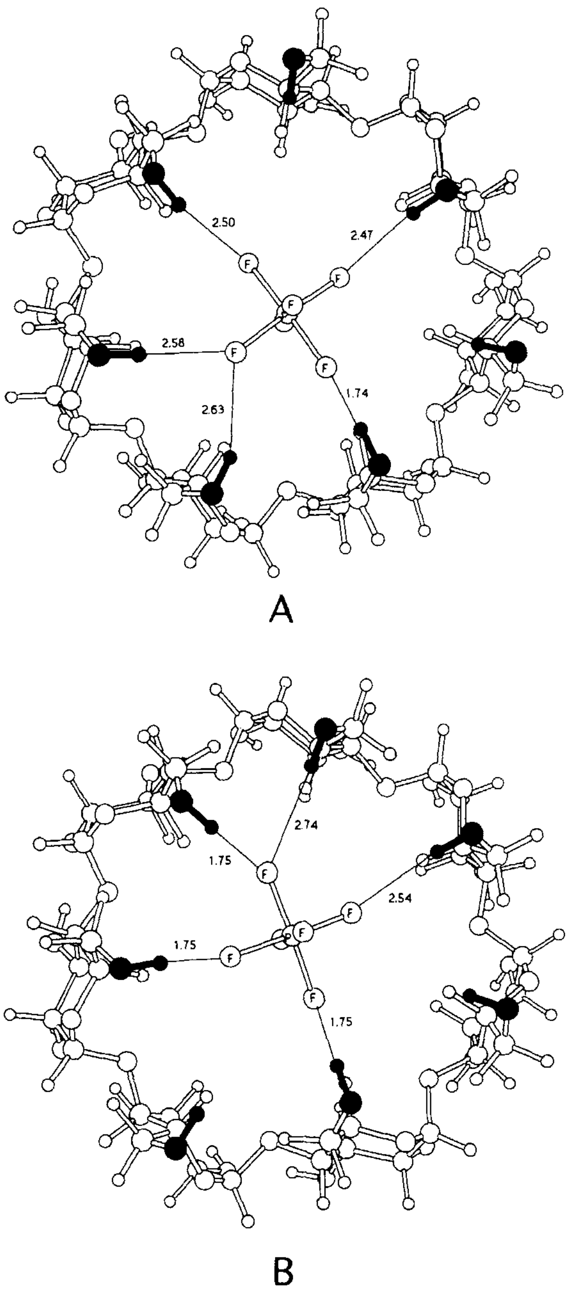

FIGURE 2 Top-view of the minimized structure of the PF_6^- - β-CD complex showing (a) the distances H-F in Å and (b) the Mulliken and Natural atomic charges in e units on the anomeric carbon hydrogens of the β-CD receptor and four of the fluorines of the PF_6^- anion.

The measured enthalpy and entropy values for the α-CD- ClO_4^- complex are however very different from the previously reported numbers

TABLE II Thermodynamic parameters for the complexation of α-CD with the three anions under study in 0.2 M NaCl at 298 K

Anion	K (M^{-1})	ΔG^0 (kcal/mol)	ΔH^0 (kcal/mol)	$T\Delta S^0$ (kcal/mol)
PF_6^-	40± 5	−2.18 ± 0.07	−6.08 ± 0.66	−3.91 ± 0.66
$CF_3SO_3^-$	38±10	−2.15 ± 0.14	−1.93 ± 0.53	0.22 ± 0.53
ClO_4^-	66± 5	−2.48 ± 0.04	−3.77 ± 0.24	−1.29 ± 0.24

($\Delta H^0 = -6.3$ kcal/mol and $T\Delta S^0 = -4.0$ kcal/mol).[12] In those cases however, the determination of the relevant binding constants were always carried out using indirect methods. Furthermore, the enthalpies and entropies of complexation were determined from Van't Hoff plots in which, as pointed out by Dougherty,[27] heat capacity effects are neglected. On the other hand, the thermodynamic complexation values presented in Table II were obtained directly from calorimetric data.

In summary, we have reported the thermodynamic values for the complexation by α- and β-CD of hexafluorophosphate, perchlorate and triflate in aqueous media. The binding constants as well as the heats of complexation (in the case of calorimetric experiments) of these anions with α and β-cyclodextrin, prove to be large enough to merit consideration in complexation studies of other species. In particular, the measured binding constant of hexafluorophosphate anion with β-cyclodextrin resulted to be 10 times larger than the previously reported value. Based on fluorescence displacement experiments as well as semiempirical molecular orbital theory, we also showed that the complexation of hexafluorophosphate by β-CD takes place by partial inclusion of the anion into the hydrophobic cavity of the receptor.

Acknowledgments

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References

[1] Bender, M. L.; Komiyama, M. "Cyclodextrin Chemistry", Springer-Verlag, Berlin, **1978**.
[2] Wenz, G. *Angew. Chem. Int. Ed. Engl.* **1994**, 33, 803.
[3] Matsue, T.; Evans, D. H.; Tetsuo, O.; Kobayashi, N. *J. Am. Chem. Soc.* **1985**, 107, 3411.
[4] Örstan, A.; Ross, J. B. A. *J. Phys. Chem.* **1987**, 91, 2739.
[5] Eftink, M. R.; Andy, M. L.; Byström, K.; Perlmutter, H. D.; Kristol, D. S. *J. Am. Chem. Soc.* **1989**, 111, 6765.
[6] Cromwell, W. C.; Byström, K.; Eftink, M. *J. Phys. Chem.* **1985**, 89, 326.
[7] Ueno, A.; Kuwabara, T.; Nakamura, A.; Toda, F. *Nature*, **1992**, 356, 136.
[8] Isnin, R.; Salam, C.; Kaifer, A. E. *J. Org. Chem.* **1991**, 56, 35.
[9] Godínez, L. A.; Patel, S.; Criss, C. M.; Kaifer, A. E. *J. Phys. Chem.* **1995**, 99, 17449.
[10] Taraszewska, J.; Wójcik, J. *Supramol. Chem.* **1993**, 2, 337.
[11] Cramer, F.; Saenger, W.; Spatz, H. Ch. *J. Am. Chem. Soc.* **1967**, 89, 14.
[12] Gelb, R. I.; Schwartz, L. M.; Radeos, M.; Laufer, D. A. *J. Phys. Chem.* **1983**, 87, 3349.
[13] Hoiland, H.; Hald, L. H.; Kvammen, O. J. *J. Solution Chem.* **1981**, 10, 775.
[14] Sanemasa, I.; Fujiki, M.; Deguchi, T. *Bull. Chem. Soc. Jpn.* **1988**, 61, 2663.
[15] Rohrbach, R. P.; Rodríguez, L. J.; Eyring, E. M.; Wojcik, J. F. *J. Phys. Chem.* **1975**, 79, 2251.
[16] Lewis, E. A.; Hansen, L. D. *J. Chem. Soc. Perkin Trans. 2*, **1973**, 2081.
[17] Buvari, A.; Barcza, L. *Inorg. Chim. Acta* **1979**, 33, 179.
[18] Inoue, Y.; Hakushi, T.; Liu, Y.; Tong, L.; Shen, B.; Jin, D. *J. Am. Chem. Soc.* **1993**, 115, 475.
[19] Saenger, W.; Noltemeyer, M.; Manor, P. C.; Hingerty, B.; Klar, B. *Bioorg. Chem.* **1976**, 5, 187.
[20] Harata, K.; Tsuda, K.; Uekama, K.; Otagiri, M.; Hirayama, F. *J. Incl. Phen.* **1988**, 6, 135.
[21] Park, J. W.; Song, H. J. *J. Phys. Chem.* **1989**, 93, 6454.
[22] Van-Wazer, J. R. "Phosphorus and its Compounds", Interscience Publishers, New York, **1958**.
[23] Stewart, J. J. P. *J. Comp. Chem.* **1989**, 209, 221.
[24] Spartan 4.1, Wavefunction, Inc. Irvine, CA.
[25] Betzel, C.; Saenger, W.; Hingerty, B. E.; Brown, G. M. *J. Am. Chem. Soc.* **1984**, 106, 7545.

[26] Castro, R.; Berardi, M. J.; Córdova, E.; Ochoa de Olza, M.; Kaifer, A. E.; Evanseck, J. D. *Submitted to J. Am. Chem. Soc. February 29, 1996.*

[27] Stauffer, D. A.; Barrans, R.; Dougherty, D. *J. Org. Chem.* **1990**, 55, 2762–2767.