STRUCTURE AND DYNAMIC STABILITY OF CYCLODEXTRIN INCLUSION COMPLEXES WITH 1,4-DISUBSTITUTED BICYCLO-[2.2.2]OCTANES

ULF BERG,* MARCIA BERGLUND, NINA BLADH, ANETTE SVENSSON AND MAGNUS STÖDEMAN[$]

Division of Organic Chemistry 1 and Division of Thermochemistry[$], Chemical Center, Lund University, P.O.Box 124, S-221 00, Lund, Sweden

ABSTRACT

The properties of inclusion complexes of 1,4-di-R-bicyclo[2.2.2]octanes (R = H (**1**), Me (**2**), Cl (**3**), Br (**4**), and OH (**5**)) with cyclodextrins have been studied by NMR, microcalorimetry, and force-field computations. The compounds **2** and **3** (but not the other compounds) give dynamically stable 1:2 guest-host complexes with α-cyclodextrin. Microcalorimetry of **5** in water indicates a moderately strong 1:1 complex with β- but weak complexes with α- or γ-cyclodextrin. The behaviour depends on the subtle interplay of size, polarity, hydrophobicity and type of solvent.

1. INTRODUCTION

Cyclodextrins (CD) act as hosts for a variety of small molecules in water solution and have found use in many fields, such as chromatography, pharmaceutical industry and as potential enzyme mimics,[1] and the phenomenon has proven to be an excellent model system for studying the nature of noncovalent bonding in aqueous solution. In order to study the structure and dynamic stability of such inclusion complexes 1,4-disubstituted bicyclo[2.2.2]octane turned out to possess interesting properties as guest molecules. Thus, the 1,4-dimethyl derivative was found to give a 1:2 complex with α-cyclodextrin in $D_2O/CD_3OD/DMF$-d_7, which exchanges with "free" species with remarkably high barrier.[2] We here present an extended study of a series of analogues in order to gain information of the origin of the unusual dynamic stability of the complexes. The complexes of the analogues, shown in the Scheme, with α-, β- and γ-cyclodextrin have been examined by both experimental and computational methods.

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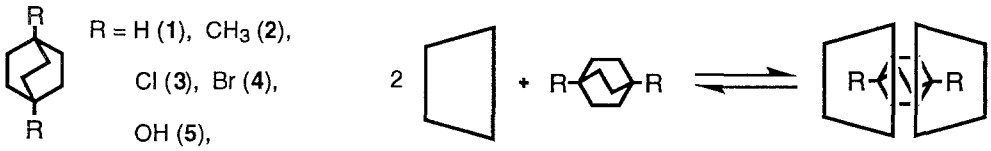

2. MATERIALS AND METHODS

The compounds **1-5** have been described earlier.[3,4] The molecular mechanics calculations were performed using the MM2(91) force field implemented in the MacMimic program package.[5] The microcalorimetric titration technique has been described earlier.[6]

3. RESULTS AND DISCUSSION

3.1 NMR Spectroscopy

The ^{1}H NMR study of **2** and **3** and α-CD in $D_2O/CD_3OD/DMF$-d_7 exhibited broad singlets at room temperature for the methyl and methylene protons, respectively. On lowering the temperature the signals broadened further and at ca. 10 °C decoalesced to three sets of signals as described earlier.[2] With **3** (and even more pronounced with **4**) crystallization occurred at low temperatures, but otherwise it behaved as **2.** The rate constants for the observed exchanges were evaluated by bandshape simulations,[7] and the corresponding free energies of activation were calculated as 13.4 ± 0.1 kcal/mol for **2** and 13.2 ± 0.2 kcal/mol for **3.** None of the other bicyclooctanes showed similar behaviour, nor did any of them with β- or γ-CD. We interpret the phenomenon as the slow exchange between "free" species and 1:2 guest-host complex (Scheme). Evidence in terms of peak intensities, ROESY spectra, behaviour of α-CD 2-monotosylate and computations have been presented.[2] The ROESY spectrum of **2** allowed a precise determination of the structure of the complex in which half of the guest molecule has penetrated into each of the CD cavities.[2] Thermodynamic parameters of **2** for the process in the Scheme derived from NMR peak intensities were: $\Delta H^o_{app} = -16.3 \pm 1.0$ kcal/mol and $\Delta S^o_{app} = -41 \pm 5$ cal/K·mol, values far from the pattern for the classical hydrophobic effect.

3.2 Microcalorimetry

Isothermal microcalorimetric titration of **5** in water at 25 °C gave the results shown in Table 1. The other compounds in the series could not be studied in water due to solubility problems. The calorimetric data was fitted to a 1:1 model using nonlinear regression methods. A complex of moderate stability was found with β-CD and complexation with α- and γ-CD was very weak. There was no indication of 1:2-complexation. Experiments to determine the temperature dependence of ΔH^o (ΔC^o_p) are in progress.

TABLE 1. Results from the microcalorimetric titration of **5** at 25.01 °C using a 1:1 model.

CD	K_c (M^{-1})	ΔG° (kcal/mol)	ΔH° (kcal/mol)	ΔS° (cal/K·mol)
α	< 100	–	–	–
β	1460 ± 72	– 4.32 ± 0.03	– 4.27±0.04	0.17±0.13
γ	< 50	–	–	–

3.3 Force-field modelling

The gas-phase 1:1 complexes of the compounds **1-5** with α-CD were calculated by molecular mechanics using the MM2(1991) force field. A snug fit of the bicyclo[2.2.2]octane molecule accomponied with large negative enthalpy was obtained. However, the 1,4-substituents prevent penetration of the guest such that half of the guest is exposed to the exterior for **2, 3** and **4**, enabling for complexation with another host molecule. On the other hand, **1** and **5** penetrate too deep into the cavity to allow for 1:2-complexation. The results are shown in Table 2 and in Figure 1.

TABLE 2. Molecular mechanics calculations for gas-phase docking with α-CD. The distance is between the centre of the CD cavity and the rear bridgehead carbon.

Guest	Distance (Å)	ΔE (kcal/mol)
1	4.14	–10.5
2	5.20	–11.3
3	5.14	–11.0
4	5.45	–12.2
5	4.47	–14.5

4. CONCLUSION

The computations indicate a favourable interaction between the guests and α-CD, in the cases of **1** and **2** solely as a result of dispersion forces. The structure of **2**-α-CD is in excellent agreement with the ROESY data and with the stability of the 1:2 complexes for **2** and **3** observed in the NMR experiments. However, computations indicate strong 1:1 complex of **5** in the gas phase. Experiments in water show a different picture: weak interactions with α-CD and γ-CD, but a relatively strong 1:1 binding to β-CD.

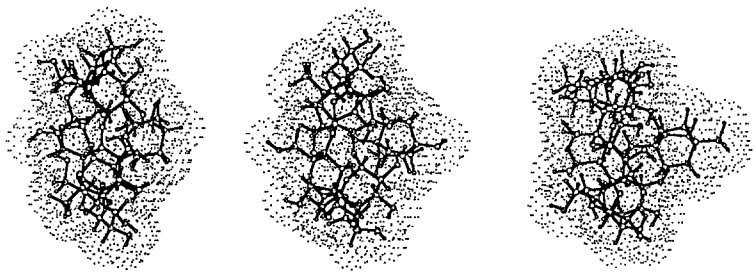

Figure 1. MM2 minimized structures of α-CD complexes with from left **1**, **5** and **2**, with added van der Waals radii, showing the variation of the non-covered parts of the guests.

We have observed 1:2 complexes only with **2** and **3** with α-CD, which is reasonable considering the degree of penetration of the guests in the cavity (Fig. 1). Less obvious is the origin of the high dynamic stability of these complexes; small uncharged molecules notoriously exchange with much higher rate. Considering the available data, we propose that the main cause to the high barrier to complex formation is the dissymmetrical development of enthalpy and entropy along the reaction coordinate. The entropy contribution ($-T\cdot\Delta S$) increases earlier than the enthalpy term decreases. Probably, the solvent mixture also plays a crucial role, the finer details of which we have not so far been able to settle, although further addition of methanol or DMF increases the exchange rate.

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