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Solvent- and Temperature-Tuned Orientation of Ferrocenyl Azide Inside β-Cyclodextrin

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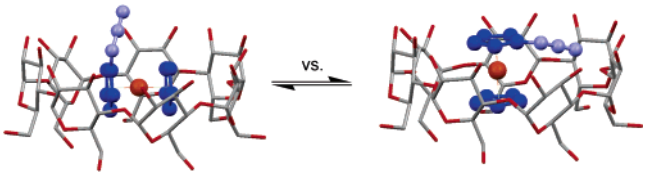
Received January 18, 2006



An induced circular dichroism (ICD) solution study on the orientation of ferrocenyl azide within the β-cyclodextrin cavity is described. In DMSO, ferrocenyl azide prefers an axial inclusion, whereas in ethylene glycol and DMSO/H_2O = 50/50 an equatorial alignment dominates. As shown by temperature-dependent ICD spectra, at lower temperatures ferrocenyl azide adopts preferentially an equatorial arrangement, whereas at higher temperatures an axial one is favored. Temperature and solvent effects on the co-conformation of ferrocene noncovalently bound to cyclodextrin have never been observed before.

For the study of solution structures of achiral chromophoric guests with chiral host molecules, induced circular dichroism (ICD) has been employed as a sensitive spectroscopic tool. The method is particularly useful for the structural analysis of cyclodextrin (CyD) complexes.[1] Knowledge of solution structures of host−guest complexes contributes to the understanding of molecular recognition phenomena in enzyme−substrate interaction or catalysis. In supramolecular chemistry, it also helps to advance structure−reactivity relationships.

In recent years, we have focused on supramolecular carbene chemistry. The reactive species were generated photolytically from diazirine precursors within the cyclodextrin cavity.[2] In contrast, examples concerning supramolecular nitrene chemistry are rare.[3] Because the chemistry of azides as nitrene precursors entrapped in host matrixes has not yet been examined extensively, we decided to investigate the ferrocenyl azide FcN_3@β-CyD complex. Moreover, the chemistry of FcN_3 in solution has already been described.[4] Here we wish to report the solution structure of the FcN_3@β-CyD complex with special emphasis on how solvent properties and temperature influence the alignment of FcN_3 in the β-CyD cavity.

The structures of ferrocene (FcH)−cyclodextrin complexes have been determined by X-ray diffraction analysis.[5] Naturally, the solid state structure of a complex may differ from that in a solution.[6] Because ferrocene β-CyD complexes are barely soluble in water,[7] studies have been conducted in organic solvents or in mixtures of organic solvents and water. Aprotic polar solvents such as DMSO and DMF comprise the best solubilizing properties for CyDs and also their complexes, unfortunately at the expense of low association constants.[8] Among aqueous solutions, the combination of DMSO/H_2O has been applied.[9] Ethylene glycol was found to be a preferred solvent compromising relatively good solubilizing and binding properties.[10−13]

The alignment of the guest molecule within the CyD host molecule may be inferred from ICD. Thus, Harata established a rule[14] which states that the ICD of a chromophore inside the cyclodextrin's cavity will be positive, when the electric transition dipole moment is aligned parallel to the cyclodextrin's principal axis. In contrast, the ICD will be negative, when the alignment of the transition dipole moment vector is perpendicular to the

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Published on Web 03/16/2006

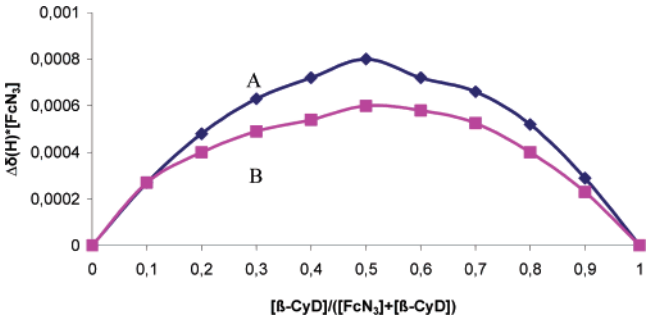

FIGURE 1. ^{1}H NMR Job's plot of the FcN_3@β-CyD complex in DMSO-d_6. The change in chemical shift of the α- and β-protons (A and B curves, respectively) of the ferrocenyl azide multiplied by the concentration of ferrocenyl azide is plotted on the ordinate. [FcN_3] + [β-CD] = 0.1 M, T = 27 °C.

cyclodextrin's principal axis. Later, Hatano et al.[15] calculated a "transit" angle at 54°, at which the signs of the ICD peaks reverse.[16] Kodaka's treatment shows that the situation is exactly the opposite outside the cyclodextrin cavity.[17] It has to be noted that these rules were derived on the basis of strong $\pi-\pi^*$ transitions of the guest's chromophore. However, they have been successfully validated for weak $n-\pi^*$ transitions of diazirines,[18] azoalkanes,[19] and even weak d−d transitions (400−550 nm) of ferrocenes.[11,20]

Ferrocene produces in ethylene glycol a positive ICD band for β-CyD and a small negative one for γ-CyD in the range of its d−d transition band of FcH.[11,12] Therefore, two different dominant orientations were proposed for FcH in β-CyD and in γ-CyD. The axial arrangement of ferrocene was attributed to β-CyD and the equatorial one to the FcH@γ-CyD complex.[11] This assignment was corroborated later by comparing the ICD spectra of bridged ferrocenophanes in the presence of β-CyD with those of FcH in β- or γ-CyD.[13]

The stoichiometry of the FcN_3@β-CyD complex in solution was determined by the method of continuous variation (Figure 1).[21] Its maximum at 0.5 clearly indicates a 1:1 stoichiometry.

The structure of the guest molecule−ferrocenyl azide was determined by X-ray single-crystal analysis (Figure 2).

Also of interest was the effect of the azido functional group on the association constant (K_a) in comparison to unsubstituted ferrocene. ICD titration in ethyl glycol afforded a K_a for the FcH@β-CyD complex at 510 M^{-1}.[22] We determined K_a of the

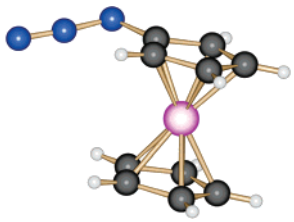

FIGURE 2. Structure of ferrocenyl azide based on X-ray single-crystal analysis.

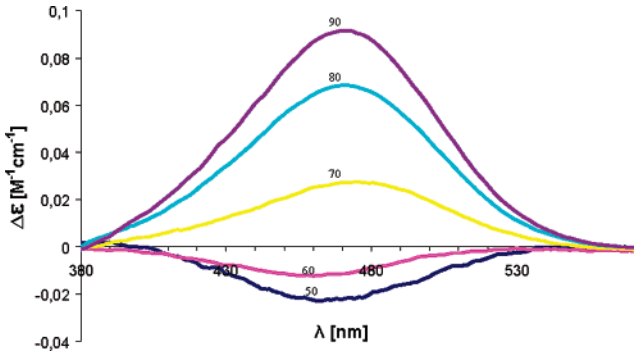

FIGURE 3. ICD signal dependence on the DMSO content (% v/v) of the aqueous solution. T = 25 °C.

FcN_3@β-CyD complex in ethylene glycol by two methods. An iterative Scatchard plot[23] based on ICD titrations afforded a value of 180 ± 5 M^{-1}. Benesi−Hildebrand treatment[24] of the UV−vis titration data furnished a value of 190 ± 20 M^{-1}. Thus, the azido group causes K_a to be reduced by a factor of about 3. The association constant for the FcH@β-CyD complex in DMSO has been determined at 40 and 60 M^{-1} by ICD and cyclic voltametric titration, respectively.[8b] Determination by polarimetry afforded a value of 50 M^{-1}.[8a] Moreover, the association constant of the FcN_3@β-CyD complex was determined by us by ^{1}H NMR titration in DMSO-d_6 utilizing a Benesi−Hildebrand plot. This led to K_a < 5 M^{-1}. Thus, in DMSO, FcN_3 is about 10 times more weakly bound than unsubstituted FcH.

Next, the conformation of FcN_3 in the β-CyD cavity was investigated. The polarization direction of the symmetry forbidden d−d band of FcH has been established by single-crystal UV−vis spectroscopy and was found to be axial along the Cp−Fe−Cp vector of FcH.[25] Inclusion of FcN_3 gives rise to a negative ICD signal in DMSO/H_2O = 50/50 (v/v), but a positive one in DMSO (Figure 3).

A negative band was also observed for ethylene glycol solutions. In contrast, in all solvents studied, FcH produces a positive ICD band (see the Supporting Information).

In accordance with Harata's rule, from the band signs it can be assumed that the transition dipole moment of the FcN_3 molecule is oriented parallel to the principal axis of β-CyD in

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(16) If the chromophore transition dipole moment adopts this angle, zero rotatory strength was calculated. In a real solution, it may be assumed, no ICD signal should be observed, if the band of the guest's chromophore would consist of only one single transition. And that despite of the presence of a complex!

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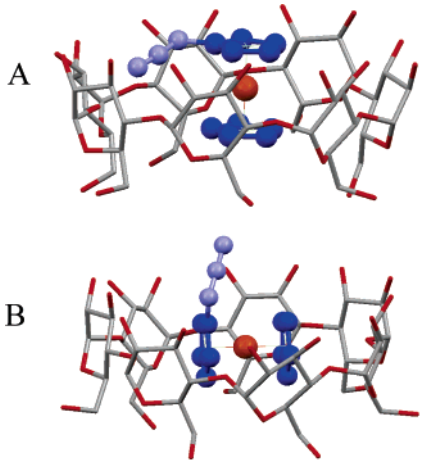

FIGURE 4. Proposed orientation of ferrocenyl azide inside the β-cyclodextrin cavity according to ICD. (A) axial, (B) equatorial arrangement. The geometry of the complex components, each is based on a single-crystal X-ray diffraction analysis (Experimental Section), is shown.

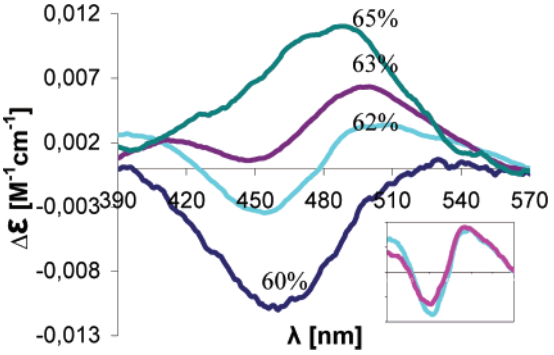

FIGURE 5. ICD signal dependence on the DMSO content (% v/v) of the aqueous solution. $T = 25$ °C. The inset represents a comparison of ICD spectra at equal DMSO content (62%) but with different concentration of the complex.

ethylene glycol and DMSO/H_2O = 50/50 (v/v) (Figure 4B), whereas it is perpendicular for neat DMSO (Figure 4A).[26]

Other mechanisms could account for a ICD band reversal as well: in a dynamic equilibrium, two (or more) complex co-conformations can exist. Each one produces a different ICD band. The overlay of these bands is observed as an experimental ICD spectrum. Dependent on the conditions, the differently weighted populations of the co-conformers can lead to an ICD sign reversal as well as to a mutual cancellation of the ICD signals.

Figure 5 represents a search for a suitable ratio of DMSO and H_2O in which the transition dipole moment adopts the above-mentioned transit angle, at which no ICD signal should be observed.

At 62% of DMSO, however, the signal splits into two components with a trough at 455 nm and a hill at 500 nm. This splitting is well-known, even from the spectroscopy of chiral ferrocenes and indicates participation of two transitions.[27] To exclude that the curve profile exhibiting a positive as well as a negative ICD signal at 62% of DMSO arose at random, the measurement was conducted with a lower concentration of the complex (Figure 5, inset, purple curve). No remarkable concentration effect on the intensity change or wavelength shift was observed.

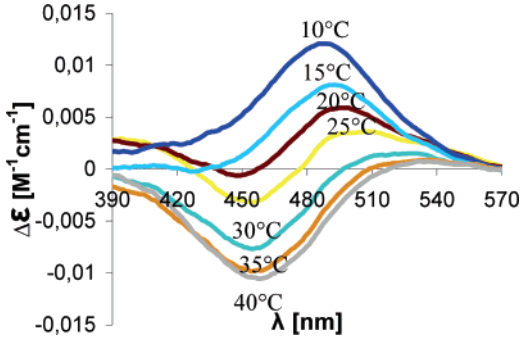

FIGURE 6. Temperature effect on the ICD spectra sign at a constant solvent composition, DMSO/H_2O = 62/38 (v/v), [FcN_3] = 0.0049 M, [β-CyD] = 0.0496 M.

It is well-known that solvents can control the orientation of guest molecules within the CyD cavity.[20e,28] However, for a ferrocene *noncovalently* bound to cyclodextrin a solvent composition-dependent ICD signal sign reversal is described here for the first time.

Next, the temperature effect on the ICD spectrum of the FcN_3@β-CyD complex was investigated (Figure 6).

At 10 °C, the complex produces a positive ICD band within the investigated wavelength range. A temperature increase up to 40 °C caused a continuous sign reversal with a final nearly all negative ICD spectrum (Figure 6). Applying Harata's rule, it is assumed that at higher temperatures the ferrocenyl azide adopts preferentially an equatorial arrangement (Figure 4B) and at lower temperatures an axial one (Figure 4A) is favored.[29] At ~25 °C, we deduce that the molecular axis of ferrocenyl azide adopts the "transit" angle. As mentioned above, population contribution of two co-conformers might account for the ICD sign reversal as well.

A temperature effect on the ICD spectra of ferrocene *covalently* bound to β-CyD has already been described.[20e] To the best of our knowledge, the here demonstrated temperature effect on the orientation of a *noncovalently* bound guest inside a cyclodextrin has never been observed before.

In summary, application of Harata's rule on the FcN_3@β-CyD complex allowed inspection of the changes of the orientation of ferrocenyl azide inside the β-CyD cavity caused by temperature and solvent property altering. At lower temperatures, ferrocenyl azide adopts axial inclusion, whereas at higher temperatures an equatorial one is preferred. Enhancing

(26) The ^{1}H NMR titration with β-CyD in DMSO-d_6 caused a change of chemical shift of the α- and β-protons of ferrocenyl azide speaking in favor of inner inclusion. Nevertheless, there exists a risk that the sign reversal observed in the ICD spectra originates from a translation of the guest along the principal axis of the cyclodextrin host.

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(29) For simplification, neglection of a temperature effect on the binding constant was assumed. An increase of temperature could also bring about a relocation of the guest beyond or beneath the CyD's cavity. Thus, the fact that the observed ICD sign reversal may have originated from a translation of the guest along the principal axis of cyclodextrin ultimately cannot be excluded.

the DMSO content in aqueous DMSO solution invoked axial alignment, whereas a higher water content leads to an equatorial one. In ethylene glycol, the proposed structure might be similar to the one in DMSO/H_2O. Further insight into the co-conformation variability should come from QM/MM calculations, which are currently in progress.

Experimental Section

The structures of the complexes presented in the Abstract graphic and in Figure 4 were drawn on the basis of the single-crystal X-ray structure analysis of the complex components. The structure of β-CyD was adopted from the literature.[30] For the determination of the association constants by NMR and ICD titration, the errors of the regression analyses were expressed as standard deviations.

Ferrocenyl azide was prepared according to the literature.[31] β-CyD was recrystallized two times from water and dried at 80 °C at 15 mmHg for 24 h. The composition was determined by elemental analysis (97.17% w/w). Deionized MQ water (conductivity 18 MΩ·cm) was used. Commercial p.a. quality DMSO and ethylene glycol were used.

Circular dichroism spectra were recorded in thermostated (±0.5 °C) quartz cuvettes (1 cm path length). For ICD, the integration time was set to 1 s, and each spectrum was repeated four times (ICD titrations) and two times for the temperature and solvent dependencies. The averaged spectra were then smoothed according to need and corrected to zero baseline at the longest wavelength.

A 250 MHz NMR instrument was used for recording ^{1}H NMR spectra at 27 °C. The residual solvent peak was set as a reference (DMSO, quintet, $\delta = 2.50$ ppm).

Acknowledgment. This work was financially supported by the Fonds zur Förderung der wissenschaftlichen Forschung in Österreich (Project P12533-CHE). We kindly thank Prof. Harald Lehner for the interpretation of the ICD spectra splitting and Dr. Daniel Krois and Dr. Jean-Luc Mieusset for helpful discussions.

Supporting Information Available: CIF file of FcN_3 for the crystallographic data, the Scatchard and Benesi−Hildebrand plots for the K_a determinations, additional data, and details. This material is available free of charge via the Internet at http://pubs.acs.org.

JO060102T

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