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Induced Circular Dichroism of Cyclodextrin Inclusion Complexes: Examining the Cavity with a Bilateral Probe

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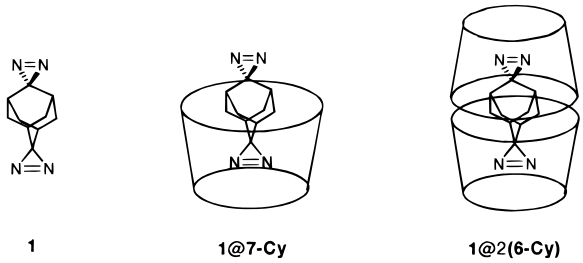
ABSTRACT

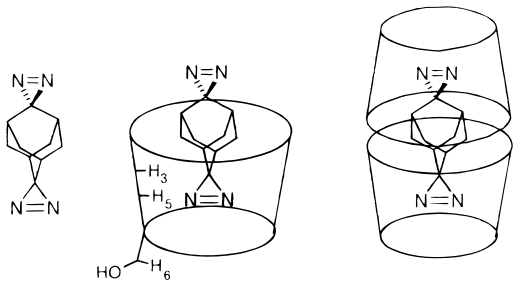


1 1@7-Cy 1@2(6-Cy)

The induced circular dichroism (ICD) of 1@7-Cy gives rise to an unusual spectrum which can be explained by a positive and a negative contribution of two identical chromophores. This finding is in agreement with rules predicting the ICD of chiral supramolecular systems.

Suitable methods of obtaining structural information for cyclodextrin inclusion complexes are currently needed to rationalize molecular processes that occur during supramolecular reactions within host molecules. In addition to NMR spectroscopy, induced circular dichroism (ICD) is a sensitive analytical tool for elucidation of the structure of these complexes in solution.[1] Recently, the properties of the inclusion complexes of 2-aziadamantane in α-, *β*-, and *γ*-cyclodextrin were investigated by ICD.[2] Diazirines, which are important carbene precursors, exhibit a variety of surprising reactions when encapsulated within cyclodextrins.[3,4] The expectation of similarly interesting results led us to investigate the chiroptical properties of 2,6-diaziadamantane[5] (**1**) and its inclusion complex with α- (**6-Cy**) and *β*-cyclodextrin (**7-Cy**) (Figure 1).

The prediction of the sign and magnitude of induced circular dichroism has been the subject of several experimental and theoretical studies.[6−8] Theoretical treatments



1 1@7-Cy 1@2(6-Cy)

Figure 1. 2,6-Diaziadamantane and its inclusion complex with *β*- and α-cyclodextrin.

(1) Schneider, H.-J.; Hacket, F.; Rüdiger, V.; Ikeda, H. *Chem. Rev.* **1998**, *98*, 1755. Connors, K. A. *Chem. Rev.* **1997**, *97*, 1325.
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based on the Kirkwood−Tinoco theory of coupled oscillators[9] led to rules that predict the arrangement of the inclusion compounds on the basis of circular dichroism.[10] These rules are solely grounded on aromatic $\pi-\pi^*$ transitions in which a dipole−dipole coupling mechanism is responsible for the generation of optical activity; very little information is available for other chromophores.[11] The system investigated here adds to our knowledge of how chromophores are influenced by different chemical environments. Furthermore, the scope and limitation of the rules to predict the molecules' arrangement can be tested.

The highly symmetric molecule (D_{2d} symmetry) **1** possesses two diazirine chromophores that are aligned perfectly perpendicular to each other.[12] Diazirines are structurally related to azo compounds and absorb in the UV−vis region around 370 nm with a characteristic fine structure in apolar solvents, which can be attributed to a uniform $n_-\!-\!\pi^*$ transition of the N═N double bond.[13] The weakly allowed transition ($\epsilon \sim 200$ L mol^{-1} cm^{-1}) was determined to be *x*-polarized[13] (Figure 2). This transition is well separated from

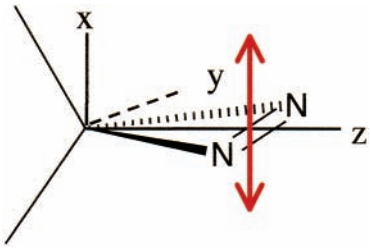

Figure 2. The arrow shows the orientation of the transition dipole moment of the diazirine $n_-\!-\!\pi^*$ transition.

any other transition observed. The UV−vis spectra and the ICD spectra were recorded in water/ethanol mixtures ($^7/_3$) and are depicted in Figure 3.[14]

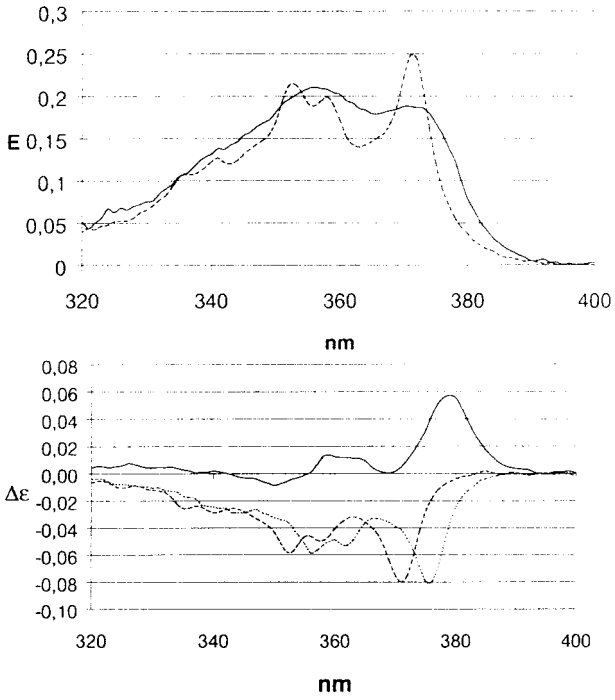

Figure 3. Top: UV−vis spectra of **1**@**7-Cy** (—) and **1**@2(**6-Cy**) (---). Bottom: CD spectra of **1**@**7-Cy** (—), **1**@2(**6-Cy**) (---), and 2-aziadamantane@2(**6-Cy**) (...)^2 (the last two spectra are reduced in size by factors of 18 and 9, respectively).

Comparison of the ICD spectrum of the complex of **6-Cy** with 2-aziadamantane and of **6-Cy** with **1** shows that the phenotypes of the curves are identical. No concentration dependence for the phenotype of the ICD curve was observed. The maximum $\Delta\epsilon$ of the ICD recorded for the complex of **1** with **6-Cy** is −1.18. The extrapolated $\Delta\epsilon$ for quantitative complexation of **1** with 2 equiv of **6-Cy** was determined to be −1.43, following a slight modification of the procedure described in ref 2. NMR experiments show that the complex formed with **6-Cy** has a 1:2 (guest:host) stoichiometry and is symmetric with respect to the guest included (Figure 1). This corresponds to the arrangement determined for the inclusion complex of 2-aziadamantane with **6-Cy**.[2,4] Moreover, as expected, the shape of the CD spectrum of **1** with **6-Cy** is also similar to the shape of the corresponding UV−vis spectrum.

This is *not* the case for the spectrum of **1**@**7-Cy** (Figure 3). The CD spectrum of this complex exhibits one maximum at 379 nm. The UV−vis spectrum, in contrast, possesses two broad maxima at 356 and 371 nm. In addition, the association constant of **1** with **7-Cy** was measured to determine the stoichiometry of the complex. Scatchard plot analysis[15] revealed a linear dependence in υ (υ = fraction of complexed **1**). The association constant was determined to be 2900 ± 300 M^{-1} (Figure 4).

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(10) The first attempts to correlate the orientation of a guest molecule inside **7-Cy** with its ICD were performed with naphthalene and led to the formulation of Harata's rule (ref 7).

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(14) **1**@**7-Cy** is only sparingly soluble in pure water. The addition of ethanol increases the concentration range for the measurements.

(15) Cantor, C. R.; Schimmel, P. R. *Behavior of Biological Macromolecules, Part III*; Freeman: San Francisco, 1980; p 849. For experimental details see ref 2.

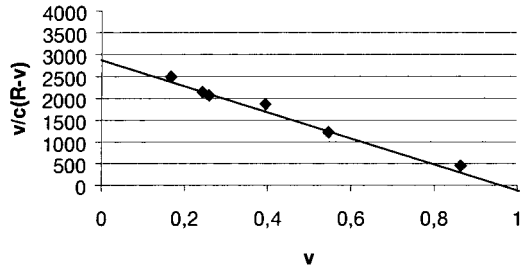

Figure 4. Scatchard plot of the ICD of **1**@**7-Cy** at different concentrations in water/ethanol $^{7}/_{3}$. The intercept and the negative slope of the extrapolated line equal the association constant.

The linearity of the Scatchard plot shows that the ICD spectra observed derive from a complex with 1:1 stoichiometry.[2,15] Thus, the ICD spectrum of **1**@**7-Cy** is caused by association of **1** with only one cyclodextrin molecule. The explanation for the observed signal must therefore be sought in **1** itself or in the geometry of the arrangement with a single **7-Cy**. Because the CD spectra of **1**@2(**6-Cy**) and of the complex of 2-aziadamantane with two **6-Cy** possess an identical phenotype (Figure 3), energy transfer between the two separated chromophores, for instance via exciton coupling, can be ruled out. This is not surprising, since the chromophores are perfectly perpendicularly oriented with respect to each other, and the forces involved in complexation usually are too small to induce significant geometric changes in a guest molecule.[16] Another possible explanation for the phenotype of the ICD spectrum of **1**@**7-Cy** is that a superposition of two independent spectra is observed. The ICD spectra of a complex with a uniform conformation should be expected to match the corresponding UV−vis spectrum (Figure 5).[17] Indeed, the phenotype of the spectrum

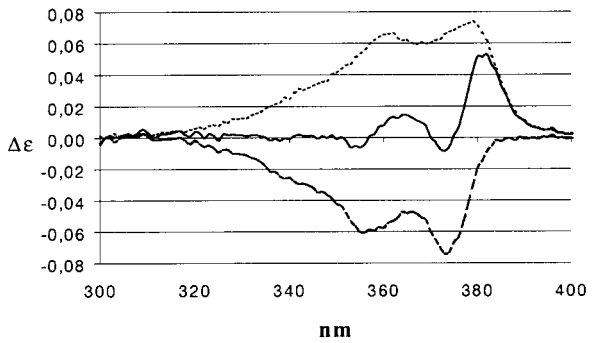

Figure 5. Positive (...) and negative ICD of a diazirine complexed with **7-Cy** (- - -),[17] superposition thereof (—).

can be very well reproduced by the difference spectrum of a **Cy**-complexed diazirine which gives rise to a positive ICD and a different diazirine complex, which produces a negative ICD. The maxima of the positive spectrum depicted are shifted by approximately 6 nm to longer wavelengths. This shift surpasses the usual solvatochromic effect of the n−π* transition of diazirines, which does not exceed 3 nm even for drastic changes in solvent polarity.[2]

This demonstrates that **1** possesses *two independent* chromophores, which exhibit ICD spectra of *opposite sign*. NMR spectroscopy of **1**@**7-Cy** shows NOE enhancement of the guest molecule to both inner protons of the cyclodextrin, *i.e.*, H-3 and H-5 (Figure 1). The latter signals are weaker for all guest protons. No cross-peaks were observed for the H-6 protons of **7-Cy**. This suggests an encapsulation at the wider side of the host, as depicted in Figure 1. Because of the ellipsoid shape of the guest molecule, the symmetry axis of **1** should be aligned with the principal axis of the cyclodextrin. This arrangement effectively positions one diazirine ring deeply inside the cavity of **7-Cy**. The other chromophore is, therefore, located near the wider aperture on the outside of the cyclodextrin.

The structural information obtained makes the systems studied ideal candidates to test the applicability of Harata's[7] and Kodaka's[8] rules. Harata's rule 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. The ICD will be negative when the alignment of the transition dipole moment vector is perpendicular to the cyclodextrin's principal axis. Kodaka's treatment shows that the situation is reversed outside the cyclodextrin cavity. In that case the ICD of a perpendicularly polarized transition will be positive and a parallel transition dipole moment will result in a negative signal.

In addition, one has to consider the differences in the chromophores discussed. The asymmetry in aromatic π−π* transitions is induced by a dipole−dipole coupling mechanism.[18] For n−π* transitions of carbonyl compounds, however, two different mechanisms are considered to account for the induction of chirality.[18] First, a single-electron process can be envisioned. Second, the μ−m mechanism might be involved. Both mechanisms exhibit a strong quadrupole moment, which is absent in the dipole-coupling mechanism of the π−π* transition and not represented by the theoretical treatment in Harata's rule or Kodaka's modification thereof. The similarity of the diazirine chromophore to the carbonyl group[19] suggests that rather the single-electron or the μ−m mechanism than the dipole−dipole coupling mechanism prevails. This could result in signs and magnitude of the ICD of the n−π* transition of the diazirine in cyclodextrin complexes different than those predicted by Harata's and Kodaka's theories. Therefore, one should be reluctant to apply the rules without independent structural information.

The CD spectrum of the complex of **1** with two **6-Cy** demonstrates that both chromophores experience an identical

(16) Rekharsky, M. V.; Inoue, Y. *Chem. Rev.* **1998**, *98*, 1875.

(17) This is the case for the spectra of 2-aziadamantane@**7-Cy** (positive ICD spectrum of Figure 5) and of 2-azi-5-phenyladamantane@**7-Cy** (negative ICD spectrum of Figure 5). Since the maxima of the UV−vis spectra of 2-aziadamantane and **1** in organic solvents differ by approximately 4 nm, the ICD spectrum of 2-aziadamantane@**7-Cy** depicted was corrected to a shorter wavelength by 4 nm.

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(19) Shustov, G. V.; Varlamov, S. V.; Rauk, A.; Kostyanovsky, R. G. *J. Am. Chem. Soc.* **1990**, *112*, 3403.

environment. The intensity measured is twice the intensity found for the complex with 2-aziadamantane,[2] and the value of the $\Delta\epsilon$ measured is well within the range of values for chiral diazirines.[19] Since both chromophores are aligned perpendicular to **6-Cy**'s principal axis and are located inside the hosts' cavity, the negative Cotton effect observed is in agreement with Harata's rule. Similar results were obtained recently with azo chromophores in **7-Cy**.[11]

The experimental data presented here for **1**@**7-Cy** show for the first time that the Cotton effects of the n$-\pi^*$ transition of a diazirine, positioned near **7-Cy**'s principal axis inside and outside the cavities, possess different signs. This is in line with Kodaka's calculations,[8] which predict inversion of the sign of the ICD, when the guest molecule moves from inside the cavity to the outside of the cyclodextrin. According to his theory, the chromophore inside **7-Cy** causes the negative contribution, while the diazirine outside the cavity is responsible for the positive contribution to the net signal observed. At this point, however, the experimental evidence does not allow an assignment of the positive or negative contribution to each diazirine ring.

Conclusion. The findings presented here demonstrate that the ICD spectra of the model systems studied are in agreement with the rules previously discussed. The inversion of the sign of the ICD inside and above **7-Cy**'s cavity takes place also in nonaromatic chromophores such as diazirines. Moreover, the ICD of **1**, when complexed with **6-Cy**, follows the theoretical predictions. Although at this point the chiroptical properties of n$-\pi^*$ transitions seem to match those of $\pi-\pi^*$ transitions, further investigations of aliphatic chromophores will be needed to fully test the potential of the rules discussed for guests other than aromatic molecules in cyclodextrin inclusion complexes.

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Supporting Information Available: Table with concentrations and ICD's measured and NMR data of **1**@**7-Cy** and **1**@2(**6-Cy**). This material is available free of charge via the Internet at http://pubs.acs.org.

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