

STRUCTURE AND SPECTROSCOPIC PROPERTIES OF CYCLODEXTRIN INCLUSION COMPLEXES.

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ABSTRACT

We compare spectroscopic properties of higher order complexes of organic guests (e.g. naphthalene, phenols, indole, C₆₀-fullerene) with cyclodextrins (CDx) to results of molecular modeling investigations. Naphthalene 1:2 complexes with α -CDx show high spectral resolution and peculiar triplet properties. Molecular simulations and calculation of the experimentally measured induced circular dichroism (ICD) provide detailed structural information.

1. INTRODUCTION

Self-assembly of macromolecular systems is of great importance in chemistry and molecular biology. A valuable model system to study molecular self-assembly is inclusion complex formation of cyclodextrins as hosts with appropriate organic guest molecules. CDx's are most suitable for spectroscopic studies extending into the far u.v., as they show no absorption in this region. Besides electronic absorption and fluorescence, circular dichroism induced in the u.v. absorption band of an aromatic guest by the chirality of the glucose subunits of the macromolecular host is used to study complexation.

Additionally to spectroscopic studies molecular docking between CDx and various guests is performed by a Dynamic Monte Carlo (DMC) approach. Solvation effects are included by a continuum model. Sign and strength of the resulting ICD of complexes are calculated by the Kirkwood-Tinoco exciton chirality method for the obtained geometries.

2. MATERIALS AND METHODS

2.1. Experimental Section

Experimental details are given in [1]. Triplet-Triplet transient absorption spectra and triplet quantum yields were measured by laser flash photolysis, using a frequency quadrupled Nd-YAG laser (QuantaRay DCR-1) at 266 nm under right angle conditions.

2.2. Theoretical Methods

Molecular Mechanics calculations are performed using Allinger's MM3-92 force field within the program package MolDoc[2]. The reference geometries for α - and β -CDx are obtained by minimizing crystallographic geometries. γ -CDx is modeled as a symmetric cone and optimized within [2]. Low energy complex geometries are located by calculating complexation pathways (defined stepwise transfer of guest molecules through the CDx cavity) and by Dynamic Monte Carlo simulations. Solvation effects are considered by a continuum approximation. Energetic contributions based on both, potential energies and solvation energies, are represented within a modified Metropolis criterion. For a detailed description of the methods see reference [3-6].

Induced circular dichroism spectra of complexes are calculated by the Kirkwood-Tinoco exciton chirality method. ICD is the most direct method to determine association constants and is used to study structural properties of host-guest systems. It results from dipole-dipole interactions between the transition moment of the guest and induced transient dipoles in the bonds of the chiral groups of the host, i.e. of the glucose subunits of CDx. This technique provides, therefore, direct information on the relative position of the achiral guest in the CDx cavity. Details of the formalism of ICD calculations are reported in reference [3].

3. RESULTS AND DISCUSSION

3.1. Experimental Results

Absorption and fluorescence spectra of aqueous naphthalene become highly structured upon inclusion in α -CDx, similar to those obtained in hydrocarbon solutions (see fig. 1). Two lifetimes are recovered, one in agreement with that in aqueous solution and a second long one, identical to non-aqueous solvents. The α -CDx concentration dependence of their relative weight suggests the formation of 1:2 guest:host complexes.

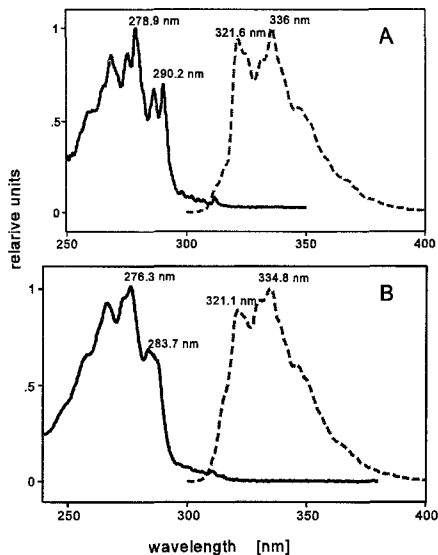


Fig. 1: Absorption (full line) and fluorescence (broken line) spectra of naphthalene 1:2 complexes with α -CDx (A) and of naphthalene in saturated aqueous solution (B).

Transient absorption spectroscopy has been used to study the effect of complexation with cyclodextrins (α -CDx and β -CDx) on spectroscopic and kinetic properties of naphthalene triplets. The main results are:

- CDx complexation induces a marked red shift and line narrowing of T-T absorption. Narrowing is very marked in α -CDx complexes, the band width being strongly temperature dependent (see fig. 2). A value of 5.7 nm is found at 12 °C, which is significantly below that obtained in hexane solution (8.1 nm).
- Triplet decay is slowed down in complexes, in particular with α -CDx. This fact can be used to study the complexation equilibrium. Predominance of a 1:2 naphthalene- α -CDx complex is obtained over a wide CDx concentration range.
- Both, association constant and triplet decay kinetics are strongly temperature-dependent. An activation energy of 66 kJ mol⁻¹ is obtained for the quenching of α -CDx-complexed triplets by molecular oxygen.

1:2 complex formation with α -CDx is found generally for molecules with appropriate shape and cause comparable effects on spectroscopic and kinetic properties. Further examples are 2-naphthol, p-substituted phenols and indole [1,7-8].

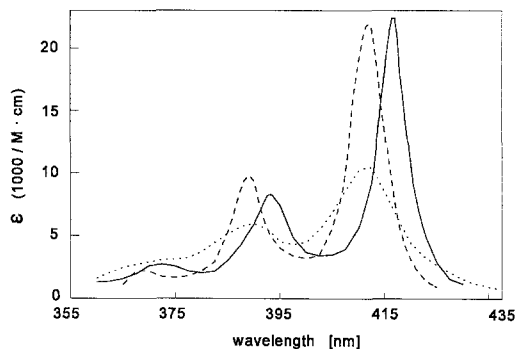


Fig. 2: Triplet-triplet absorption spectra of naphthalene in hexane (broken line), water (dotted line), and aqueous 0.06 M α -CDx (full line), measured at T=22°C.

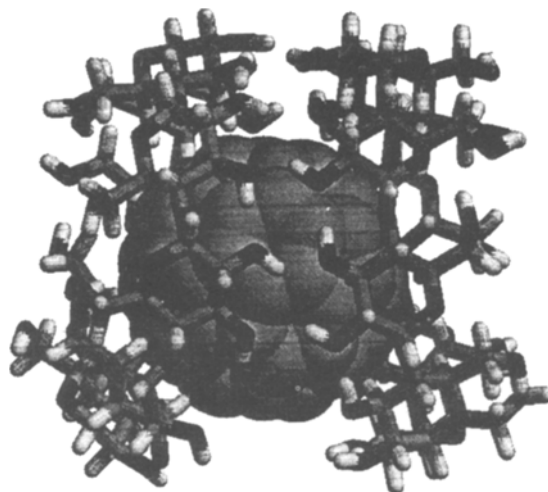


Fig. 3: Low energy 1:2 C_{60} -fullerene - γ -CDx complex

3.2 Molecular Modeling and Calculation of Spectral Properties:

Complexation between a host and a guest molecule can formally be characterized by a two step process: surface properties of host and guest entail molecular recognition and the dynamic properties of the complex defines the final inclusion geometry and its structural distribution. In the case of cyclodextrins, recognition is generally unspecific, despite of possible intermolecular hydrogen bond formation as shown for the phenol - β -CDx system [3] and results mainly from electrostatic and van der Waals interactions. However, CDx molecules as hosts are highly dynamic species, and especially β -CDx shows a strong internal asymmetry [5]. As the complexation process imposes strong constraints on the dynamics of the host, the conformational space of the complex differs completely from the respective space of the host molecule alone, and this was shown for the 2-naphthol - β -CDx complex in some detail [5].

Dynamic Monte Carlo (DMC) simulations proved a good tool for the determination of correct complex structures when solvation effects, especially hydrophobic interactions, are taken into account [3,6-9]. Figure 3 shows exemplarily a low energy geometry of a 1:2 C_{60} -fullerene complex with γ -CDx. This structure is the result of a 1000 step DMC simulation performed at 300 K. Potential energy is calculated by the force field, and solvation energy of hydrophobic surfaces is considered. This model follows a classical view of the hydrophobic effects, i.e. the conception of 'minimizing' the hydrophobic contact surface with water molecules, and reaches a structure prediction capacity for CDx inclusion complexes of over 90 %. This is verified by the calculation of the respective rotatory strength of the final, low energy structures, which were found in agreement with value and sign of the experimentally determined ICD signal [3,4].

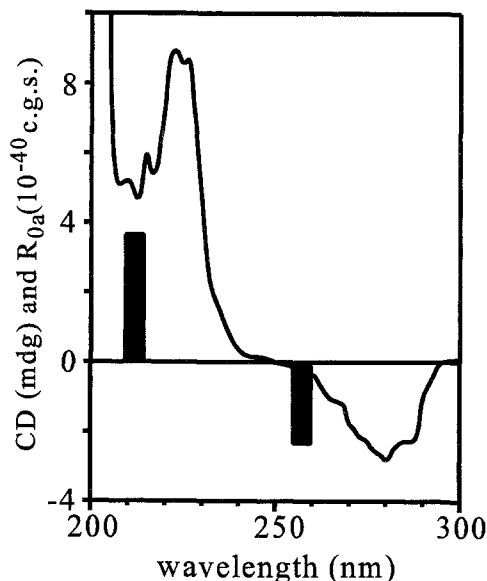


Fig. 4: Induced circular dichroism (CD) and calculated rotatory strength (R_{0a}) of p-cresol in β -CDx complexes (for more details see text).

4. CONCLUSION

The main results are summarized as follows:

- Optical absorption, induced circular dichroism and fluorescence spectra of inclusion complexes of simple aromatic compounds with cyclodextrins show generally more vibronic features than in aqueous solutions or in other polar solvents. A single fluorescence lifetime is found for these complexes, and its value varies in accordance with environmental effects observed when water is replaced by alcohols or ethers as solvent. Spectroscopic and photophysical properties of higher order complexes, like the 1:2 naphthalene - α -CDx complex, have more similarities to gas phase spectra than to those observed in hydrocarbon solution.
- The sign of induced circular dichroism spectra of such inclusion complexes can be predicted. Solvation reduces the highly complex conformational space of inclusion complexes and selects these structures which yield the correct ICD spectra. Another important dynamic feature is the stability of the intramolecularly hydrogen bonded, secondary hydroxylic rim of CDx.
- These complexes have well defined structures within narrow geometrical limits.
- The main structural constraint arises from hydrophobic interactions in aqueous solution, which can be described by minimization of the hydrophobic molecular surface area.

Higher order complexation, i.e. formation of complexes composed of at least one guest and two host molecules, appears as an intrinsic feature of inclusion complex formation resulting from the unspecific recognition process with appropriately shaped guests. These complexes gain essential stabilization energy from hydrogen bonding between the rim of the CDx subunits and formation of even larger structures, as e.g. self-assembled tubes, might be proposed from the experimental and theoretical results. Figure 5 shows such a structure of a molecular, self-assembled tube, consisting of four α -CDx and five indoles as obtained from computer simulation.

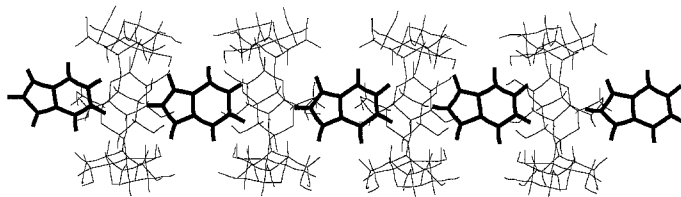


Fig. 5: Molecular tube based on indole - α -CDx complexes

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