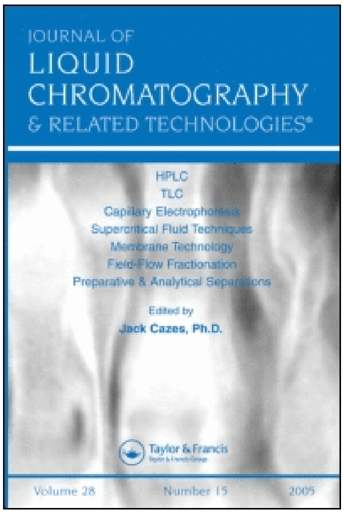

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Investigation of the Complexation Between Quinidine Carbamate and the Enantiomers of 3-Chloro-1-phenyl-propanol by Circular Dichroism and UV Spectroscopy

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Abstract: UV and circular dichroism spectroscopic measurements showed that the molecular interactions in hexane/ethyl-acetate solutions between dihydroquinidine tert-butylcarbamate, used as a model for the quinidine carbamate chiral selector (QD), and 3-chloro-1-phenyl-propanol are too weak to affect the corresponding spectra of these compounds. The weak interactions between QD and 3-chloro-1-phenyl-propanol are probably masked by the formation of self-associated dimeric structures in solution.

Keywords: Chiral selector, Enantiorecognition, Job's method, Mole-ratio method

INTRODUCTION

Recently, it was found that the enantiomers of 3-chloro-1-phenyl-propanol (3CPP) could be separated on silica bonded quinidine carbamate.[1] This result suggested that complexes of different stability may form between the chiral bonded selector and the two enantiomers, (*R*)-(+)- and (*S*)-(−)-3CPP. Therefore, it was of interest to study this complexation process, in an effort to ascertain the stoichiometry of these complexes and the retention mechanism. To avoid the serious difficulties associated with the direct

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investigation of complexation reactions taking place on a solid surface, we decided to study this equilibrium in solution, using dihydroquinidine tert-butylcarbamate (QD) as a model of the silica bonded chiral selector. Job's method and the mole-ratio method were used. These methods are both known to be simple and powerful techniques to establish the composition of complexes in solution.[2–4]

EXPERIMENTAL

Materials

Solvents (hexane and ethyl acetate) were purchased from Fisher Scientific (Fair Lawn, NJ, USA) and were HPLC grade. Both 3-chloro-1-phenyl-propanol enantiomers were from Aldrich (Milwaukee, WI, USA). Dihydroquinidine tert-butylcarbamate was synthesized as reported earlier[5] and was a gift from Wolfgang Lindner and Norbert Maier.

Methods

Circular dichroism (CD) measurements were carried out on an AVIV Circular Dichroism Spectrometer, Model 202 (Aviv Instruments, Lakewood, NJ) at 20°C, using a quartz cell with an optical path length of 0.25 cm. For Job's method experiments, the samples were prepared by mixing stock solutions of QD and of either one of the enantiomers having equal molar concentrations (0.2 or 0.25 mM). Six samples with ratios from 0.2/0.8 to 0.8/0.2 were prepared. The samples used for the mole-ratio method experiments were prepared by mixing 1 mL of a 1 mM QD solution with 0.25, 0.5, 1, 1.5, 2, 2.5, 3, and 3.5 mL of a 1 mM stock solution of either enantiomer in a 5 mL volumetric flask. Each sample was scanned twice and the average spectrum was used in the calculations. Since the measurements were made with a single-beam spectrometer, the prerecorded spectrum of pure hexane was subtracted from the recorded spectrum of each solution.

The UV spectra were recorded at ambient temperature using a BioMate 5 UV-spectrometer (ThermoSpectronic, Rochester, NY) and quartz cells with an optical path length of 1 cm. In order to determine the Job plots, the solutions of QD and the 3CPP enantiomers in the ratios listed above were prepared from 1 mM stock solutions of the reagents in either n-hexane or n-hexane + ethyl acetate (95/5, v/v). For the mole-ratio method, the samples used had the same composition as for the circular dichroism experiments. For the Job's method experiments, the pure solvent and, for the mole-ratio method, a 0.2 mM QD solution in the pure solvent were used as the reference solutions.

RESULTS AND DISCUSSION

UV Measurements

The method of Job is based on the determination of the molar concentration of the reagents that corresponds to the maximum yield of complex formation. The plot of the absorbance (A) of the complex versus the ratio C_L/C_T (where C_L and C_T are the concentrations of the ligand in the solution and its total concentration in the system, respectively) has an extremum, the abscissa of which gives unambiguously the stoichiometry of the complex.[3] When the components of a mixture absorb themselves, the value Δ is used instead of A, Δ being the difference between the absorbance of the mixture and the sum of the partial absorbances of the initial components at the corresponding concentrations. The stoichiometric coefficient found by Job's method must be validated by the mole-ratio method. In the latter, the dependence of A (or Δ) on the concentration of one of the component at constant concentration of the other one is determined. The salient point of such graphs indicates the ratio of the stoichiometric coefficient of the component in the complex.

The spectra that were recorded for solutions of QD and 3CPP in n-hexane are reported in Figure 1. These experiments did not show any Job's correlation in the entire wavelength range under investigation, neither for (*R*)-3CPP nor for (*S*)-3CPP. The data provided by the mole-ratio method (not shown) confirmed the absence of any visible influence of interactions between either one of the 3CPP enantiomers and QD on their UV spectra in both hexane and hexane—ethyl acetate solutions.

Concerning QD, Beer-Lambert's law was fulfilled within the wavelength range from 240 to 380 nm but it was dramatically broken below 240 nm, as shown in Figure 2. We suggest that the self association of QD is the reason of that effect. The existence of self associated dimeric carbamoylated quinidine moieties in solutions was suggested in.[6] By switching from the

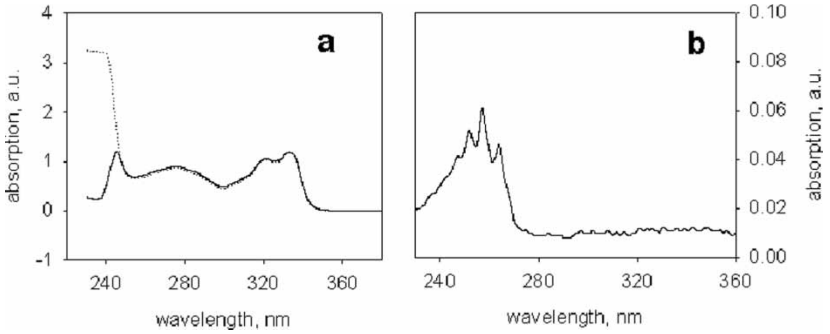

Figure 1. UV spectra of QD (0.25 mM) in n-hexane (dotted line) and n-hexane + ethyl acetate (95:5, v/v, solid line) (a) and of (*R*)-3CPP (0.25 mM) in n-hexane (b).

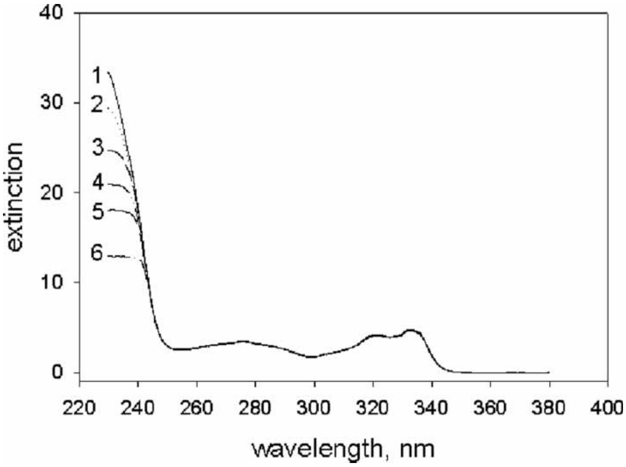

Figure 2. Extinction ($A/[C\ 1\,\mathrm{cm}]$) as a function of wavelength for the solutions of QD in n-hexane. Concentration: 0.075 mM (1), 0.1 mM (2), 0.125 mM (3), 0.15 mM (4), 0.175 mM (5), 0.25 (6).

solvent hexane to an hexane—ethyl acetate solution, a broad band in the QD spectra, at a wavelength lower than 240 nm, was turned into the narrow band with a maximum at 246 nm (Figure 1). Inter-, intra-molecular interactions or interactions of both types may take place between the functional groups of the QD molecule and be responsible for this effect. From this point of view, the solvation of the QD molecule functional groups by ethyl acetate shields them from interactions with each other, resulting in the observed change in the absorption spectra. This can be considered as an indirect confirmation of the suggestion about the dimerization of QD in n-hexane. Note also, that the intensity of the absorption band in the binary solvent becomes significantly lower, which confirms the validity of the supposition that ethyl acetate solvates QD, preventing the formation of an easily excited self associated form.

CD Measurements

In CD spectrometry, the differences between the absorption of left and right circularly polarized light are measured as a function of the wavelength.[7] Assuming additivity of the contributions of the different optically active components of a mixture to the total CD spectrometer signal of the solution, the value of the differential dichroic absorption (*DA*) of the mixture is related to the concentration of these components (C_i) as:

$$DA(\lambda) = \sum_i (\varepsilon(\lambda)_{L,i} - \varepsilon(\lambda)_{R,i}) \cdot C_i \cdot l \tag{1}$$

where $\varepsilon(\lambda)_L$ and $\varepsilon\ (\lambda)_R$ are the molecular extinction coefficients for left and right circularly polarized light at the wavelength λ, and l is the optical path length of the measuring cell. The formation of a complex between two chiral molecules must lead to a change of the differential dichroic absorption, as predicted by Eq. (1). This is due to a decrease of the concentrations C_i of the reagents and, possibly, to the apparition of a new term, related to the newly formed complex (if this complex has its own optical activity). By analogy with Job's method in UV spectrometry, this change will be largest at the point of maximal yield of the complex, at the stoichiometric ratio of the concentrations of the reagents. Since the terms $(\varepsilon(\lambda)_{L,i} - \varepsilon\ (\lambda)_{R,i})$ for different components of the solution can have opposite signs, Job's curve can be either a normal parabola or an inverted one.

The design of the CD spectroscopic measurements was based on the following two assumptions:

- The existence of a complex between quinidine carbamate and the enantiomers of 3CPP is proven by the chromatographic data. The chiral centers of either enantiomeric molecules and of the chiral selector participate in the formation of this complex, which is proven by the separation of (*R*)- and (*S*)-3CPP on the quinidine carbamate stationary phase.[1]
- CD spectroscopy can be more sensitive to the consequences of the formation of a diastereoisomeric complex than UV spectroscopy since

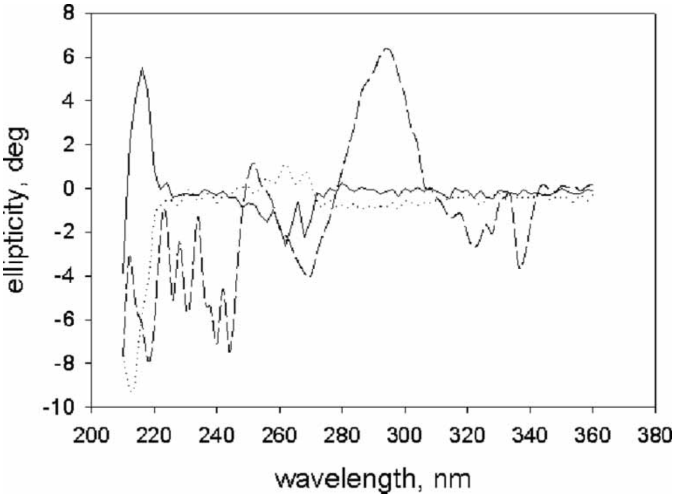

Figure 3. CD spectra of QD (0.2 mM; dashed line), (*R*)-(+)-3CPP (0.25 mM; solid line), and (*S*)-(−)-3CPP (0.2 mM; dotted line). The spectra are reported as the dependence of the ellipticity, measured by the CD spectrometer, on the wavelength; the ellipticity is equal to 32.99 *DA*.

only the bonds that are responsible for the chiral dichroism effect take part in that process.

The CD spectra of QD and of the two enantiomers of 3CPP are reported in Figure 3. The spectrum of QD at wavelengths lower than 250 nm is characterized with a large noise and irreproducible absorption profile, both resulting, obviously, from the large absorption of UV light by QD in this region (Figure 1). The preliminary experiments showed a straight proportionality between the response of the spectrometer and the concentration of reagents, both for QD and for the two 3CPP enantiomers in the wavelength range from 250 to 360 nm. Thus, in this wavelength interval, Eq. (1) can be employed to estimate the value of *DA* for hypothetical mixtures of non-interacting compounds, in order to calculate the difference between experimental and hypothetical *DA*s.

The data obtained with Job's and with the molar ratios methods were treated at all the wavelengths of each absorption band in Figure 3. No meaningful correlations were found. The results obtained in several instances are reported in Figure 4.

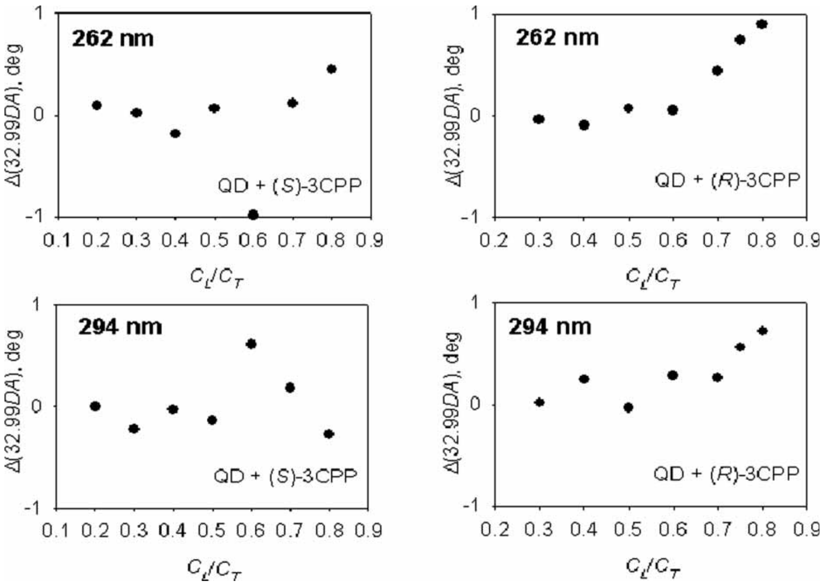

Figure 4. Job plots for solutions of QD and (*S*)-3CPP or (*R*)-3CPP at different wavelengths. Δ(32.99 *DA*) in the *y* axis indicates the differences of the measured ellipticity and that calculated from Eq. (1), assuming no interactions. Note that, in general the difference of ellipticity fluctuates around zero, within the interval of experimental error (0.1–0.2 deg).

CONCLUSIONS

The results obtained show that the molecular interactions between QD and 3CPP in solutions of n-hexane with no, or small, concentrations of ethyl acetate are too weak significantly to disturb the UV and CD spectra of these components. Because of this weakness, the classical analytical techniques of UV and CD spectroscopy cannot give conclusive results. Beside dimerization of the QD molecules, most probably, takes place in solution, which is suggested by features of the spectra in the wavelength range of 210 to 250 nm. This is probably a more preferable interaction for them than the association with 3CPP molecules. However, these results must not be interpreted as proving the absence of interactions between QD and 3CPP. The dimerization process cannot take place between immobilized molecules, making the QB—3CPP association more easily possible under HPLC conditions. Indeed, studies based on chromatographic results proved earlier that such enantioselective interactions do take place.

ACKNOWLEDGMENTS

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