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CIRCULAR DICHROISM COTTON EFFECTS INDUCED IN INHERENTLY SYMMETRIC CHROMOPHORES BY DISSYMMETRIC SOLVENTS

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Since the original observation by Mason and Norman (1), other authors have reported circular dichroism induced at the isotropic electronic transitions of racemic or symmetric metal complexes (1,2) and ketones (3,4,5) when optically active alcohols, usually diols, were present in the same solution. This phenomenon has been attributed (1,4) to dissymmetric association via hydrogen bonding, an explanation which was supported by 1) ir and uv spectral evidence of hydrogen bonding (4), 2) failure to observe CD when (-)-bornyl acetate (5) or other (3) non-hydroxylic asymmetric compounds are substituted for the optically active alcohol and 3) failure of nitrites or nitrates, poorer hydrogen bond acceptors, to show CD in (+)-diethyl tartrate (4).

We should like to disclose the results of our own investigations which show that induced CD is a very general phenomenon, that hydrogen bonding is not a prerequisite, and that the effect is not restricted to ketones but is seen also at the n-π^* absorption band of a nitrite and a thioketone. A strong concentration dependence of the induced effect has also been noticed.

The requirements imposed on the optically active solvents (6) (Table 1) were: (a) transparency in the region of absorption of the solute, (b) ready availability, and (c) high optical purity. Particular care was taken to minimize the incursion of instrumental artifacts. In each measurement the CD data were taken with reference to the baseline of the optically active solvent. Solutions at the same concentration in the racemic solvent gave baselines which were superimposable on those obtained using the racemic solvent alone. The Cotton effects induced by (+)-diethyl tartrate and by (-)-diethyl tartrate were of opposite sign and, within experimental error, of the same magnitude. Measurements were made at concentrations and path lengths such that the optical density was less than 1. Signal to noise ratios (T_c = 1 sec.) are indicated by vertical bars in each figure. Measurements were repeated over an interval of several months using freshly prepared solutions and at several concentrations, path lengths, and instrument sensitivities (7).

Table 1

Cotton Effects Induced in Cyclohexanone by Different Optically Active Solvents.

Solvent	Optical Purity %	Concentration (g./l)	CD,λ, nm([θ],deg.mole^{-1}cm^{2})
R-(+)-diethyl tartrate	100	26.2	298 (-32.1)
S-(-)-ethyl lactate	95	54.3	288 (-26.2)
S-(-)-2-methyl-1-butanol	100	110.0	288 (+ 1.5)
R-(-)-2-octanol	96	78.3	287 (+ 3.1)
S-(+)-3-methyl-2-butanol	100	78.6	290 (+ 3.7)

The induced Cotton effects exhibited by a representative series of aliphatic ketones dissolve in (+)-diethyl tartrate are presented in Figure 1. The results of a preliminary survey of the Cotton effects induced in a number of relatively unhindered ketones suggested that although the magnitudes and positions of the Cotton effects induced by a particular optically active solvent might reflect the geometry of the ketone, the sign of the induced Cotton effect would reflect the dissymmetric environment provided by the solvent. That such ketones do not exhibit induced Cotton effects of the same sign in a particular optically active solvent is evident upon comparison of the spectra presented in Figure 1 for acetone, pinacolone, and cyclopentanone (for justification of the use of molar ellipticities, vide infra). The double Cotton effects observed for norcamphor and adamantanone (Figure 1) are reminiscent of the solvent effects, usually attributed to asymmetric solvation, observed (8) for some structurally related optically active ketones in symmetric solvents.

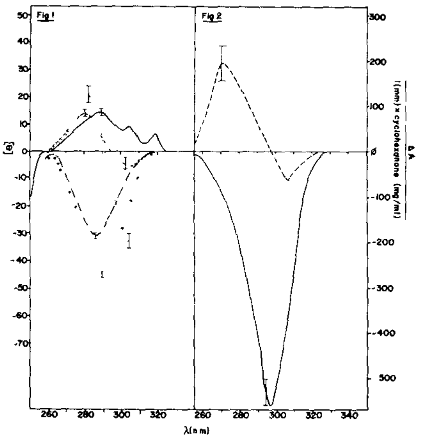

Fig. 1. Cotton effects induced in some aliphatic ketones by (+)-diethyl tartrate. Cyclopentanone ———; norcamphor -----; adamantanone .....; acetone -.-.-, pinacolone °°°°°. Concentrations are approximately 8 mole percent and the pathlength 1 mm.

Fig. 2. Cotton effects induced in cyclohexanone by (+)-diethyl tartrate in the presence of CCl_4. ——— 301 mg. cyclohexanone, 327 mg. (+)-diethyl tartrate, 0 ml. CCl_4 ----- 97.4 mg. cyclohexanone, 93.1 mg (+)-diethyl tartrate, 4 ml. CCl_4.

An investigation of the system cyclohexanone/(+)-diethyl tartrate revealed that the intensity of the induced Cotton effect is concentration dependent. The value of $\frac{\Delta A}{A}$ (ΔA = differential absorbance) increased with decreasing cyclohexanone concentration until a plateau was reached at a mole ratio of about 0.2. This observation suggests that an optimum dissymmetric environment is not attained until there are several solvent molecules per solute molecule and provides a basis (i.e., the use of molar ellipticities (9)) for the comparison of intensities of the Cotton effects induced in cyclohexanone by the several solvents in Table 1. Examination of the data collected in Table 1 shows that the magnitudes of the induced Cotton effects are several orders of magnitudes smaller than those exhibited by optically active ketones in symmetric solvents. Although it was anticipated that diethyl tartrate would be the most efficient solvent, the large effect observed for ethyl lactate suggested that the gem-diol function was not as important as had been supposed. Whereas the Cotton effects induced by the hydroxyesters are large and negative, the ones induced by the optically active monoalcohols are much smaller (9) and positive. It is of interest to note that the hydroxyl group need not be attached directly to the asymmetric carbon (e.g., 2-methyl-1-butanol).

Since induced Cotton effects could be observed in diethyl tartrate at moderately high dilutions, the effects obtained using solutions of cyclohexanone and diethyl tartrate in an inactive solvent were examined. Although polar solvents such as methanol, dioxane, and chloroform were found to drastically reduce the induced Cotton effects, interesting results were obtained at rather high dilution in carbon tetrachloride. Cyclohexanone exhibits only a single negative $\underline{n}-\pi^*$ CD maximum at 298 nm in (+)-diethyl tartrate but two oppositely signed Cotton effects (10) are clearly evident in solutions diluted with CCl_4 (Figure 2). That the negative Cotton effect exhibited by the undiluted solution is also composed of at least two (unresolved) Cotton effects is supported by the fact that its maximum is bathochromically shifted by some 9 nm in comparison to its absorption maximum.

The induced Cotton effects exhibited by n-butylnitrite, fluorenone, and p,p'-dimethoxythiobenzophenone in (+)-diethyl tartrate presented in Figure 3a demonstrate that these induced Cotton effects are not peculiar to the $\underline{n}-\pi^*$ transitions of saturated aliphatic ketones (12). Since p,p'-dimethoxythiobenzophenone exhibited very large induced Cotton effects and since the $\underline{n}-\pi^*$ transition of the thione chromophore is found in the visible region of the spectrum, this compound was utilized as a gauge for investigating the nature of the dissymmetric associative forces provided by different optically active environments. A conveniently available nonhydroxylic solvent was the acetonide of (+)-dimethyl tartrate (11). Although the Cotton effect(s) induced by this acetonide (Figure 3a) is much weaker (9) than the one induced by (+)-diethyl tartrate itself, the observation of even a small Cotton effect suggests that one must consider associative forces other than hydrogen bonding (e.g., dipole-dipole) in a general treatment. Further evidence for this statement is provided by observation of a Cotton effect (Figure 3b) at the thioketone absorption near 600 nm in a mixture of p,p'-dimethoxythiobenzophenone and (+)-camphor in CCl_4 solution.

We are hopeful that the investigations now in progress will lead to a more complete understanding of the origins of these effects and their dependence on solvent stereochemistry.

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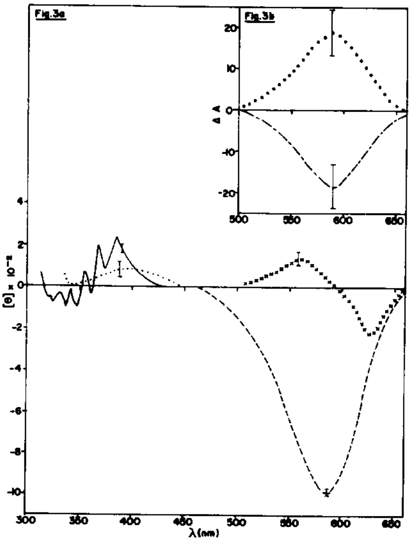

Fig. 3. (a) Cotton effects induced in other chromophores. ——— *n*-butylnitrite (c=12.5 g/l in (+)-diethyl tartrate); ..... Fluorenone (c= 7.98 g/l in (+)-diethyl tartrate); ----- p,p'-dimethoxythiobenzophenone (c=11.1 g/l in (+)-diethyl tartrate; +++++ p,p'-dimethoxythiobenzophenone (c=7.75 g/l in the acetonide of (+)-dimethyl tartrate).
(b) ooooo p,p'-dimethoxythiobenzophenone and (+)-camphor in CCl_4 (8.79 mg., 630.3 mg., 1 ml.); -.-.- p,p'-dimethoxythiobenzophenone and (-)-camphor in CCl_4 (9.91 mg., 601.1 mg., 1 ml.). Pathlength 1 mm.

References

1. S. F. Mason and B. J. Norman, *Chem. Comm.*, 335 (1965).
2. B. Bosnich, *J. Am. Chem. Soc.*, **88**, 2606 (1966).
3. B. Bosnich, *ibid.*, **89**, 6143 (1967).
4. J. Bolard, *J. Chim. Phys.*, **66**, 389 (1969).
5. L. D. Hayward and R. N. Totty, *Chem. Comm.*, 676 (1969).
6. We are grateful to Professor H. S. Mosher and Mr. James Dale for a gift of the optically active alcohols and to Professor C. Djerassi for his encouragement.
7. A modification of our JASCO ORD/UV/CD-5 made by Sproul Scientific Instruments, Boulder Creek, Calif., through Durrum Instruments Corp., Palo Alto, California, permitted the use of sensitivities of 2 x 10^{-5} ΔA/cm when required.
8. A. Rassat in "Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry" (edited by G. Snatzke), Heyden and Son, Ltd., 1967, Chapter 16.
9. It should be noted that our use of [θ] for comparing the results obtained with different solvents and chromophores may not be justified.
10. For a detailed discussion of overlapping CD Cotton effects see: K. M. Wellman, P. H. A. Laur, W. S. Briggs, A. Moscowitz, and C. Djerassi, *J. Am. Chem. Soc.*, **87**, 66 (1965).
11. M. Carmack and C. J. Kelley, *J. Org. Chem.*, **33**, 2171 (1968).
12. Alternatively, the nitrite CD may represent transesterification by active alcohol; *cf.* L. D. Hayward and R. N. Totty, *Chem. Comm.*, 997 (1969).