Studies in Linear Dichroism. III.[1] Application to Molecular Associations

Sir:

Previously we have reported on the application of linear dichroism (LD) measurements to structural problems.[1,2] We wish now to present a further application of LD for studies of association.

When polyethylene film is stretched to its yield point,[3] it becomes directionally oriented.[2] Compounds incorporated in such polyethylene film (either before or after stretching) may become partly aligned, and thus show optical anisotropy.[1] Since the stretched polyethylene is composed of an oriented crystallite phase and an amorphous phase, one may look upon the incorporated molecules as being partitioned between the two phases of polyethylene: the molecules enclosed in the oriented phase being aligned with their long axes parallel to the direction of polyethylene stretching, while the other are completely randomized.[1]

The dichroic ratio (d_0), the ratio of the absorption coefficients in the direction of stretching and perpendicular to it ($\epsilon_\parallel$ and $\epsilon_\perp$), depends both on the fraction of aligned molecules (f) and on the angle (α) between the transition moment and the long axis of these molecules as shown in eq 1.[4]

$$d_0 = \frac{\epsilon_\parallel}{\epsilon_\perp} = \frac{f\cos^2\alpha + \frac{1}{3}(1-f)}{\frac{1}{2}f\sin^2\alpha + \frac{1}{3}(1-f)} \qquad (1)$$

On association both the geometrical isotropy of the incorporated molecules and the direction of their molecular axes are likely to change. Since these changes will affect both f and α (eq 1), they will be reflected in the resulting d_0 values.

We have measured the LD spectrum of dimedone (**1**)[5] and found that at high dilution[6] (2×10^{-3} M),[7] the dichroic ratio of the band λ_{max} 253 nm is smaller than 1 ($d_0 = 0.87$) (Figure 2), and does not change with decrease of concentration. It may be deduced from our previous results[1] that the transition moment of this π-π^* absorption band is in the direction as indicated in Figure 1. It is evident from eq 1 that when $d_0 < 1$, the angle between transition moment and the long axis of the absorbing species, α, is greater than 55°.

The monomeric form of dimedone (**1a**) is likely to be isotropic in its dichroic behavior since methyl and ethyl ethers of dimedone which possess similar geometrical isotropy were found not to exhibit linear dichroism. Thus the lack of concentration effect in the LD and the observed d_0 value point to the preponderance of the dimeric cyclic form (**1b**) (Figure 2) in this concentration range. As expected, methylenebisdimedone (**2**) (Figure 2), whose structure resembles that of the dimeric form of dimedone (**1b**), shows similar LD spectrum ($d_0 = 0.715$ at λ_{max} 258 nm).

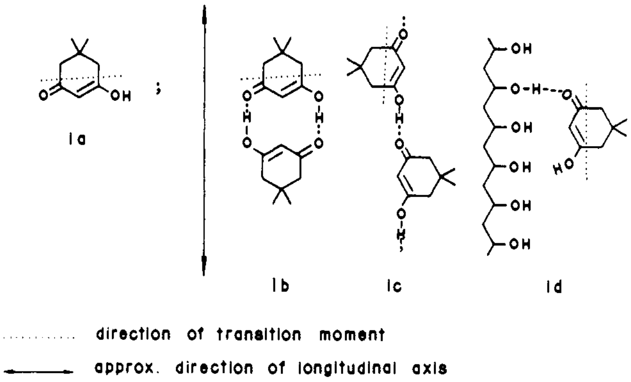

Figure 1.

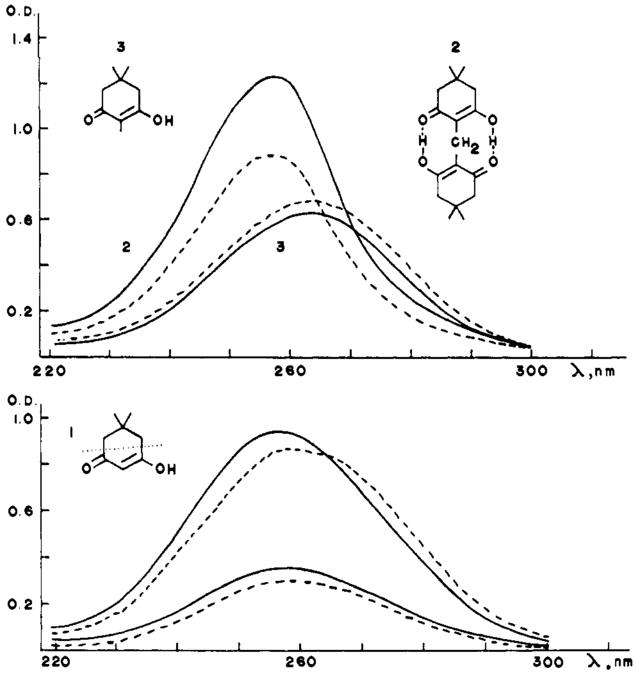

Figure 2. The linear dichroic spectra of **2**, **3**, and **1** (the latter in two concentrations) measured with dichroism accessory CD-HC:[5] ---, the curve of the interpolated optical densities obtained by light polarized in the direction of stretching; ——, the curve obtained by light polarized perpendicular to the direction of stretching.

On increasing concentration (from 2×10^{-3} M to 2×10^{-2} M),[7] the uv spectrum of dimedone (**1**) remained practically unchanged, while its LD spectrum altered gradually. At the concentration of 2×10^{-2} M,[7] the LD spectrum of dimedone (**1**) has the shape shown in Figure 2 (lower part). This spectrum does not change on further increase in the concentration. It may be seen from Figure 2 that at the longer wavelength part of the absorption band the dichroic ratio is greater than 1 ($d_0 = 1.5$). The absorption responsible for this linear dichroism is likely to be due to a higher degree of association which is noncyclic and therefore the concentration dependence.[8] The λ_{max} of this

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(1) Part II: A. Yogev, J. Riboid, J. Marero, and Y. Mazur, *J. Amer. Chem. Soc.*, **91**, 4559 (1969).

(2) A. Yogev, L. Margulies, D. Amar, and Y. Mazur, *ibid.*, **91**, 4558 (1969).

(3) *Cf.* T. O. J. Kresser, "Reinhold Plastics Application Series I, Polyethylene," Reinhold, New York, N. Y., 1957, p 55.

(4) This equation was proposed by M. Beer, *Proc. Roy. Soc., Ser. A*, **236**, 136 (1956), for oriented films and was shown by us to be valid also for materials incorporated in stretched polyethylene films: *cf.* ref 2.

(5) The instrument used was a dichroism accessory Model CD-HC produced by Rehovoth Instruments Ltd. (for a description see J. H. Jaffe, J. Jaffe, and K. Rosenheck, *Rev. Sci. Instr.*, **38**, 935 (1967)); the polyethylene films were Suprathen 200 (0.2-mm thickness), of Kalle and Co. A.G.

(6) For the concentration dependence of the uv spectra of dimedone *cf.* A. Yogev and Y. Mazur, *J. Org. Chem.*, **32**, 2162 (1967), and references cited therein.

(7) This concentration was calculated from the measured OD in stretched films (0.09-mm thickness) assuming ϵ 15,000 for the enol form of dimedone.

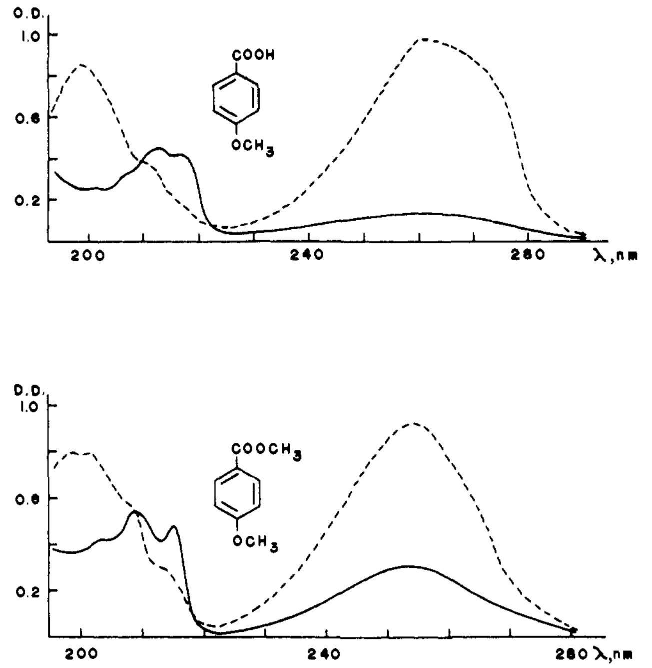

Figure 3. The linear dichroic spectra of *p*-methoxybenzoic acid and methyl *p*-methoxybenzoate measured with dichroism accessory CD-HC:[5] ---, the curve of the interpolated optical densities obtained by light polarized in the direction of stretching; ——, the curve obtained by light polarized perpendicular to the direction of stretching.

enol form, **1c** (Figure 1), is at higher wavelength than that of the cyclic dimeric form, **1b**.

As expected, 2-methyldimedone (**3**), incapable of forming a cyclic dimeric form, owing to the steric interference of the methyl group, shows similar dichroism as **1c** (d_0 = 1.07 at λ_{max} 265 nm) in all concentrations measured, indicating that it exists only in a "polymeric" association form[9] (Figure 2).

Polyethylene gives least interaction with the incorporated compounds, resembling in this respect hydrocarbon solvents. On the other hand, the behavior of compounds incorporated in a stretched polyvinyl alcohol in the uv is similar to their behavior in hydroxylic solvents. Thus, dimedone (**1**) in a stretched polyvinyl alcohol absorbs at λ_{max} 283 nm and shows concentration independent linear dichroism, with d_0 = 1.1. On exposure to HCl vapor this band shifts to shorter wavelength (λ_{max} 260 nm) but leaves the linear dichroism unchanged. The shifts in the λ_{max} are analogous to those observed in alcoholic solutions of dimedone.[10] The linear dichroic behavior indicates that a monomeric dimedone, **1d** (Figure 1), in both ionized and un-ionized forms is anisotropically oriented by hydrogen bonding with polyvinyl alcohol and thus prefers to absorb light polarized parallel to the direction of stretching.

As is well known, benzoic acids associate in nonhydroxylic solvents in the form of cyclic dimers.[11] This association is easily recognized by comparing LD spectra of benzoic acids with their methyl esters incorporated in polyethylene. *E.g.*, *p*-methoxybenzoic acid and its methyl ester, which show almost identical uv spectra (but for a small red shift in the former), differ remarkably in their LD spectra (Figure 3), the dichroic ratio of the electron-transfer band[12] of the free acid (d_0 = 8.8 at λ_{max} 260 nm) being significantly larger than that of its methyl ester (d_0 = 3.3 at λ_{max} 255 nm). Similarly, benzoic acid shows larger d_0 values for the corresponding band (4.7 at λ_{max} 233 nm) than its methyl ester (1.6 at λ_{max} 230 nm).

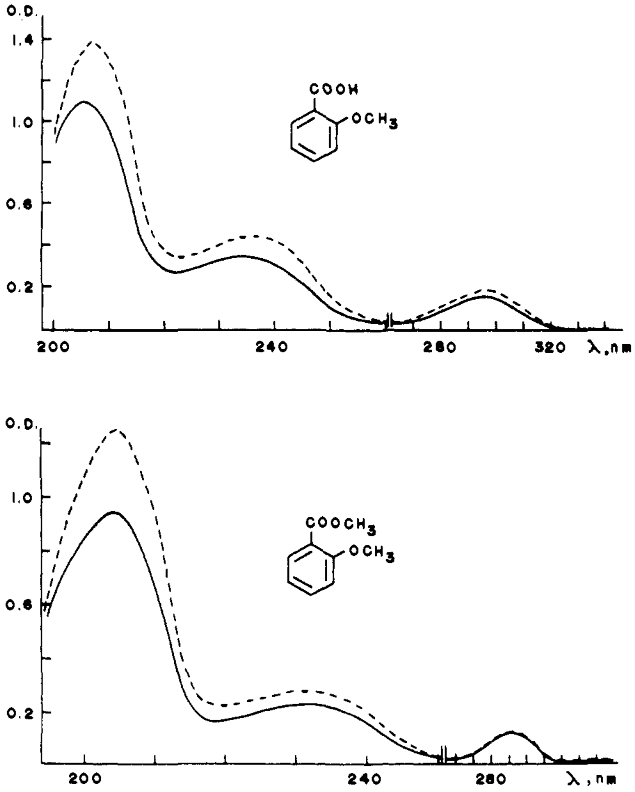

Figure 4. The linear dichroic spectra of *o*-methoxybenzoic acid and methyl *o*-methoxybenzoate measured with dichroism accessory CD-HC:[5] ---, the curve of the interpolated optical densities obtained by light polarized in the direction of stretching; ——, the curve obtained by light polarized perpendicular to the direction of stretching.

The differences between these d_0 values of the electron-transfer bands in acids and their methyl esters point to differences in the geometry of the former and are in agreement with their presence in associated dimeric form. Since the d_0 values of the benzoic acids do not vary with concentration, it is likely that no other association forms exist in polyethylene.

However, much smaller d_0 values were obtained for benzoic acids in polyvinyl alcohol, suggesting that their hydrogen bondings with this alcohol compete with their dimerizations.[10]

On the other hand, the d_0 values of the respective electron-transfer band in *o*-methoxybenzoic acid (1.4 at 236 nm) and its methyl ester (1.2 at 233 nm) are almost identical (Figure 4). This similarity may be

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(8) The constant LD value at high concentration may result from association of dimedone in chains not necessarily linear.

(9) K. Nakanishi, "Infrared Absorption Spectroscopy," Holden-Day, San Francisco, Calif., 1962, p 67.

(10) B. Eistert and W. Reiss, *Chem. Ber.*, **87**, 92, 108 (1954); B. Eistert and F. Geiss, *Tetrahedron*, 7, 1 (1959).

(11) *Cf.* G. C. Pimentel and A. L. McClellan, "The Hydrogen Bond," W. H. Freeman, San Francisco, Calif., 1960, pp 193–206.

(12) *Cf.* J. Tanaka, S. Nagakura, and M. Kobayashi, *J. Chem. Phys.*, 24, 1274 (1956); N. Harada and K. Nakanishi, *J. Amer. Chem. Soc.*, **90**, 7351 (1968); A. I. Scott, "Interpretation of the Ultraviolet Spectra of Natural Products," Pergamon Press, Oxford, 1964, pp 89–136.

explained by an intramolecular hydrogen bonding in this acid competing with its intermolecular association.

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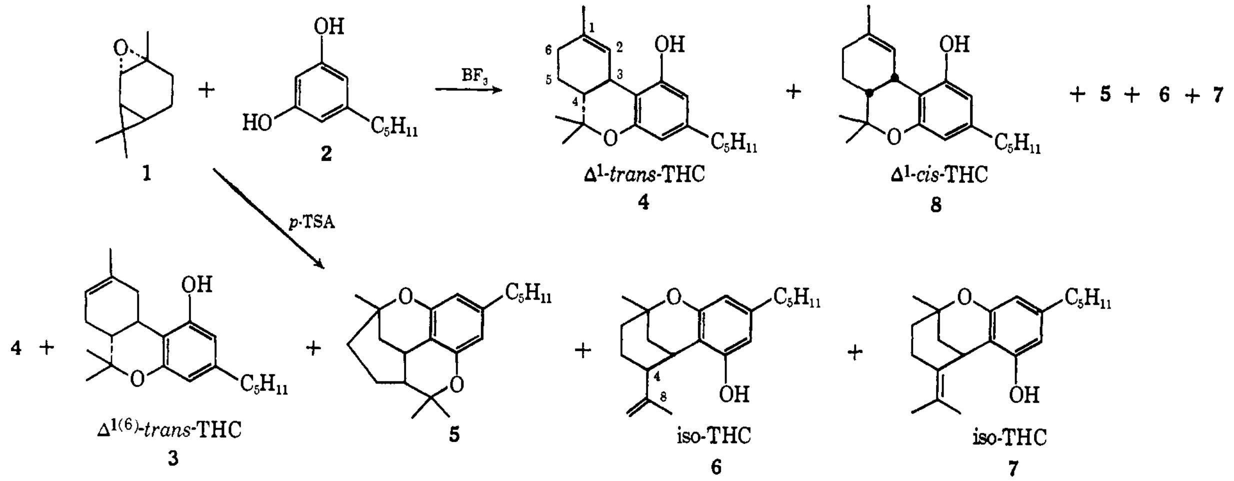
Hashish. A Stereospecific Synthesis of (−)-Δ^1- and (−)-$\Delta^{1(6)}$-Tetrahydrocannabinols[1]

Sir:

Two stereospecific syntheses of (−)-$\Delta^{1(6)}$-tetrahydrocannabinol (THC, **3**) have been reported which utilize the condensation of olivetol with either (−)-verbenol[2] or (+)-*cis*- or *trans*-*p*-mentha-2,8-dien-1-ol[3] in the presence of acids. In both cases the synthesis of (−)-Δ^1-THC (**4**) was achieved by addition and then elimination of hydrogen chloride to form **3**.

Scheme I



We wish to report an entry into cannabinoids *via* carane derivatives that provides a one-step stereospecific synthesis, leading to (−)-$\Delta^{1(6)}$-THC, and hence to (−)-Δ^1-THC. Furthermore, a slight change in the experimental conditions also provides the first one-step synthesis of Δ^1-THC (**4**) of high optical activity.

We have found that by allowing (+)-*trans*-2-carene oxide[4,5] (**1**) to react with an equimolar quantity of olivetol (**2**) in the presence of *p*-toluenesulfonic acid (0.05 mol/mol of olivetol) in benzene, a complex mixture of products was obtained. This mixture contained (glc)[6] 23% $\Delta^{1(6)}$-THC, 7% Δ^1-THC, 13% citrylidenecannabis (**5**) and Δ^8-iso-THC (**6**), 11% $\Delta^{4(8)}$-iso-THC (**7**), and 34% unreacted olivetol.[7] Careful chromatography of this mixture on silica gel and elution with 60:40 hexane–benzene, followed by chromatography on Florisil and elution with 2:98 ether–petroleum ether (bp 30–40°), gave (−)-$\Delta^{1(6)}$-THC (infrared nmr, glc, and tlc identical with those of authentic material; $[\alpha]_D$ $-245°$ ($CHCl_3$), indicating an optical purity of *ca.* 95%).[8] Since (−)-$\Delta^{1(6)}$-THC has already been converted to (−)-Δ^1-THC,[2,3] this route constitutes yet another stereospecific synthesis of (−)-**4**.

However, it was found that in the above condensation reaction, if the molar ratio of **1** was increased (1.6 mol/mol of olivetol), the major products formed were Δ^1-*trans*-THC (28%) and Δ^1-*cis*-THC (**8**) together with other products, but no $\Delta^{1(6)}$-THC was formed (Scheme I). Similar results were obtained by the addition of 1% boron trifluoride etherate in methylene chloride to an equimolar ratio of **1** and **2** in methylene chloride at room temperature. The mixture of products thus obtained was chromatographed on Florisil and eluted with 2:98 ether–petroleum ether (30–40°). A fraction, $[\alpha]_D$ $-59°$ ($CHCl_3$), contained **4** and **8** (60:40 ratio), as shown by gas chromatographic[6] and nmr analyses[9] and by conversion to $\Delta^{1(6)}$-THC and iso-THCs on treatment with *p*-toluenesulfonic acid in refluxing benzene.[1,6,10] This fraction was separated by preparative vpc (column 3.8% SE 30 on Diatoport S; gas, helium; oven temperature, 240°) to give (−)-Δ^1-THC[6] with an optical purity of >80% by comparison with the ORD curve of an authentic sample.[11] This therefore provides the first one-step synthesis of optically active Δ^1-THC.

It is interesting to note that no cannabidiol[3] was formed in any of these reactions and that the ratio of trans to cis products was *ca.* 1.2 with *p*-toluenesul-

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[1] Hashish. V. For part IV see R. K. Razdan and B. Zitko, *Tetrahedron Lett.*, 4947 (1969).

[2] R. Mechoulam, P. Braun, and Y. Gaoni, *J. Amer. Chem. Soc.*, **89**, 4552 (1967).

[3] T. Petrzilka, W. Haefliger, and C. Sikemeier, *Helv. Chim. Acta*, 52, 1102 (1969).

[4] Supplied by Glidden and Co., $[\alpha]_D$ $-45.0°$ (neat), n^{20}_D 1.4642, bp 75° (5 mm). It contains Δ^3-carene oxide as impurity (estimated as 15% by glc and nmr). It was synthesized from Δ^3-carene.

[5] B. A. Arbuzov and A. R. Vil'chinskaya, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 954 (1967); *cf. Chem. Abstr.*, **68**, 22063 (1968). For a reaction of *trans*-4-carene oxide in the presence of acids see von G. Ohloff and W. Giersch, *Helv. Chim. Acta*, **51**, 1328 (1968).

[6] The compounds were identified on the basis of relative retention times of authentic samples and by addition of authentic samples to the reaction mixture with subsequent glc.

[7] The yield of $\Delta^{1(6)}$-THC is 54% of theory, on the basis of olivetol reacted.

[8] The material after silica gel chromatography was identical with **3** except it had $[\alpha]_D$ $-212°$ ($CHCl_3$). We attribute this difficulty in obtaining optically pure **3** to our carene oxide, which was not prepared from the natural Δ^2-carene.[4] Further experiments utilizing the natural Δ^2-carene are planned to confirm this point.

[9] The nmr showed a clear separation of signals at δ ($CDCl_3$) 1.08 (s, one of the geminal methyls) and 3.18 (br, d, C-3 proton), which correspond to Δ^1-*trans*-THC, and similarly 1.26 (s) and 3.56 (br) corresponding to Δ^1-*cis*-THC. See K. E. Fahrenholtz, M. Lurie, and R. W. Kierstead, *J. Amer. Chem. Soc.*, **89**, 5934 (1967).

[10] Some **5** and **8** were also formed as expected.[1]

[11] Both ORD curves were found to be parallel in the 280–600-mμ region; $[\alpha]_D$ $-131 \pm 2°$ (cyclohexane); an authentic sample of (−)-**4** had $[\alpha]_D$ $-148 \pm 2°$.