

## The Exciton Chirality Method and Its Application to Configurational and Conformational Studies of Natural Products

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Many rules correlating the signs of Cotton effects with absolute configurations have been proposed, the most widely known being the octant rule for ketones.<sup>1</sup> Although most of these rules deal with the Cotton effect of a single chromophore, spatial interactions between two or more chromophores also give rise to Cotton effects. Such interactions have been studied in the field of biopolymers<sup>2,3</sup> and inorganic complexes,<sup>4</sup> and they also have been the subject of theoretical treatments.<sup>5,6</sup> However, except for some isolated cases,<sup>6-9</sup> this type of Cotton effect has not been used for general structural studies of natural products.

Recently we have been investigating a method to deduce the chiralities of optically active glycols and aromatic alcohols utilizing such Cotton effects and have succeeded in determining absolute configurations or conformations of a variety of complex natural products. We present in this Account a summary of this method, including a brief account of theoretical results.<sup>10</sup>

In order to deduce the absolute configurations of cyclic secondary alcohols, Brewster's benzoate rule,<sup>11</sup> which covers Freudenberg's phthalate rule<sup>12</sup> and Mills' rule,<sup>13</sup> is widely employed together with chemical methods<sup>14</sup> such as those developed by Prelog,<sup>15</sup> Cram,<sup>16</sup> and more recently by Horeau,<sup>17</sup> and their respective coworkers.

On the other hand, it was found that the Cotton effect of benzoates due to the  $\pi \rightarrow \pi^*$  intramolecular charge-transfer transition at *ca.* 225 nm enabled one to

deduce absolute configurations of a variety of cyclic *sec*-hydroxyl groups ("benzoate sector rule").<sup>18,19</sup> This benzoate sector rule has since been extended to the "dibenzoate chirality rule,"<sup>20</sup> which correlates the chirality of glycols with signs of the intense and split  $\pi \rightarrow \pi^*$  Cotton effects of their dibenzoates. We now propose to call this the exciton chirality method.

The exciton chirality method is not confirmed to 1,2-glycols, but may also include phenolic hydroxyl groups;<sup>21</sup> subsequently, it was found to be applicable

(1) W. Moffitt, R. B. Woodward, A. Moscowitz, W. Klyne, and C. Djerassi, *J. Amer. Chem. Soc.*, **83**, 4013 (1961); for a recent monograph on CD and ORD see: P. Crabbé, "ORD and CD in Chemistry and Biochemistry," Academic Press, New York, London, 1972.

(2) I. Tinoco, Jr., *Advan. Chem. Phys.*, **4**, 113 (1962); I. Tinoco, Jr., and C. A. Bush, *Biopolym. Symp.*, **1**, 235 (1964); I. Tinoco, Jr., *Radiat. Res.*, **20**, 133 (1963).

(3) See D. W. Urry in "Spectroscopic Approaches to Biomolecular Conformation," D. W. Urry, Ed., American Medical Association, Chicago, Ill., 1970, Chapter III.

(4) B. Bosnich, *Accounts Chem. Res.*, **2**, 266 (1969).

(5) J. A. Schellman, *ibid.*, **1**, 144 (1968).

(6) R. Grinter and S. F. Mason, *Trans. Faraday Soc.*, **60**, 274 (1964).

(7) L. S. Forster, A. Moscowitz, J. G. Berger, and K. Mislow, *J. Amer. Chem. Soc.*, **84**, 4353 (1962).

(8) S. F. Mason, *J. Chem. Soc. B*, 370 (1966); S. F. Mason, K. Schofield, R. J. Wells, J. S. Whitehurst, and G. W. Vane, *Tetrahedron Lett.*, 137 (1967); G. Gottarelli, S. F. Mason, and G. Torre, *J. Chem. Soc. B*, 1349 (1970).

(9) O. E. Weigang, Jr., and M. J. Nugent, *J. Amer. Chem. Soc.*, **91**, 4555, 4556 (1969).

(10) N. Harada, S. Suzuki, H. Uda, and K. Nakanishi, *ibid.*, **93**, 5577 (1971).

(11) J. H. Brewster, *Tetrahedron*, **13**, 106 (1961); *J. Amer. Chem. Soc.*, **81**, 5475, 5483, 5493 (1959).

(12) K. Freudenberg, "Stereochemie," Deuticke, Leipzig, 1933, p 696.

(13) J. A. Mills, *J. Chem. Soc.*, 4976 (1952). Also see A. I. Scott and A. D. Wrixon, *Tetrahedron*, **27**, 4787 (1971).

(14) For a summary see: R. Bentley, "Molecular Asymmetry in Biology," Academic Press, New York, N. Y., 1969.

(15) V. Prelog and H. L. Meier, *Helv. Chim. Acta*, **36**, 308 (1953).

(16) D. J. Cram and F. D. Greene, *J. Amer. Chem. Soc.*, **75**, 6005 (1953); D. J. Cram and K. R. Kopecky, *ibid.*, **81**, 2748 (1959).

(17) A. Horeau, *Tetrahedron Lett.*, 506 (1961); 965 (1962); A. Horeau and H. B. Kagan, *Tetrahedron*, **20**, 2431 (1964).

(18) N. Harada, M. Ohashi, and K. Nakanishi, *J. Amer. Chem. Soc.*, **90**, 7349 (1968).

(19) N. Harada and K. Nakanishi, *ibid.*, **90**, 7351 (1968).

(20) N. Harada and K. Nakanishi, *ibid.*, **91**, 3989 (1969).

(21) N. Harada and K. Nakanishi, *Chem. Commun.*, 310 (1970).

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to triol benzoates prepared from sugars<sup>22</sup> and to steroids which are not necessarily 1,2,3-triols.<sup>23</sup> More significantly, the same treatment can be extended to the chiral interaction between chromophores other than the benzoates,<sup>24,25</sup> and apparently even to complexes formed *in situ* between  $\alpha$ -glycols and Pr(DPM)<sub>3</sub>.<sup>26</sup>

Cotton effects of organic compounds may be conveniently classified into three types<sup>27</sup> by considering the symmetry properties and nature of the chromophores and their transitions: (1) Cotton effects arising from inherently symmetric chromophores which are asymmetrically perturbed (ketones,<sup>1</sup>  $\beta,\gamma$ -unsaturated ketones, double bonds,<sup>28</sup> benzoates, aromatic compounds, etc.); (2) Cotton effects arising from inherently dissymmetric chromophores (conjugated dienes,  $\alpha,\beta$ -unsaturated ketones, hexahelicene, etc.); (3) Cotton effects due to dipole-dipole interactions between more than two chromophores, the orbitals of which do not mutually overlap, *e.g.*, 1,1'-bianthryl,<sup>6</sup> certain alkaloids,<sup>8</sup> biopolymers, and types of compounds discussed in this article.

The amplitudes of Cotton effects of type 1 are the smallest, while those of type 3 are the largest. Theoretical treatments are also different. Type 1 requires calculation of the small perturbation term arising from asymmetric substituents; type 2 Cotton effects can be calculated solely from the wave function of the chromophore, but it is difficult to determine the absolute sign of the Cotton effect in a nonempirical manner.<sup>29</sup> In contrast, treatment of type 3 Cotton effects is much simpler, and, moreover, the absolute sign, *i.e.*, absolute configuration, can be calculated nonempirically by application of the molecular exciton theory.<sup>2,8,30</sup>

### The Exciton Chirality Method

The benzoate chromophore shows three  $\pi \rightarrow \pi^*$  transitions in the ultraviolet region: 280 nm ( $\epsilon$  1000)  $^1A_{1g} \rightarrow ^1B_{2u}$  ( $^1L_b$ ), 230 nm ( $\epsilon$  14,000) intramolecular charge-transfer transition, and 195 nm ( $\epsilon$  40,000)  $^1A_{1g} \rightarrow ^1B_{1u}$  ( $^1L_a$ ). In these transitions, the first and second absorption bands have the transition moments along the short and long axis of the benzoate chromophore,<sup>31</sup> respectively.

(22) N. Harada, H. Sato, and K. Nakanishi, *Chem. Commun.*, 1691 (1970).

(23) M. Koreeda, N. Harada, and K. Nakanishi, *ibid.*, 548 (1969).

(24) N. Harada, K. Nakanishi, and S. Tatsuoka, *J. Amer. Chem. Soc.*, **91**, 5896 (1969).

(25) S. Marumo, N. Harada, K. Nakanishi, and T. Nishida, *Chem. Commun.*, 1693 (1970).

(26) K. Nakanishi and J. Dillon, *J. Amer. Chem. Soc.*, **93**, 4058 (1971).

(27) Customarily the optically active chromophores have been classified into two extreme types (A. Moscowitz, *Advan. Chem. Phys.*, **4**, 67 (1962)), namely, (i) inherently dissymmetric chromophores, and (ii) inherently symmetric chromophores which are asymmetrically perturbed.

(28) A. I. Scott and A. D. Wrixon, *Tetrahedron*, **26**, 3695 (1970).

(29) For example, there are limiting cases which cannot be treated by the diene helicity rule: U. Weiss, H. Ziffer, and E. Charney, *ibid.*, **26**, 3127 (1970). Allylic axial chirality contributions have been considered for such cases: A. W. Burgstahler and R. C. Barkhurst, *J. Amer. Chem. Soc.*, **92**, 7601 (1970); A. Yogeve, D. Amar, and Y. Mazur, *Chem. Commun.*, 339 (1967).

(30) A. S. Davydov, "Theory of Molecular Excitons," M. Kasha and M. Oppenheimer, Jr., Translators, McGraw-Hill, New York, N. Y., 1962.

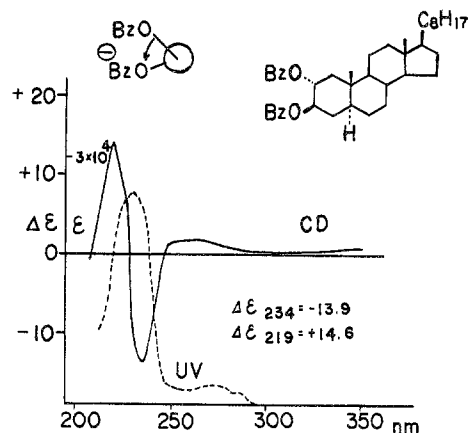


Figure 1. CD and uv spectra of  $2\alpha,3\beta$ -dibenzoyloxy- $5\alpha$ -cholestane in ethanol-dioxane (9:1).

In glycol dibenzoates having interacting chromophores, the intramolecular charge-transfer band gives rise to two strong Cotton effects of the same amplitude but of opposite signs at 233 nm (first Cotton effect) and 219 nm (second Cotton effect). This is exemplified by the CD spectrum of  $2\alpha,3\beta$ -dibenzoyloxy- $5\alpha$ -cholestane (Figure 1), which resembles an ORD curve.

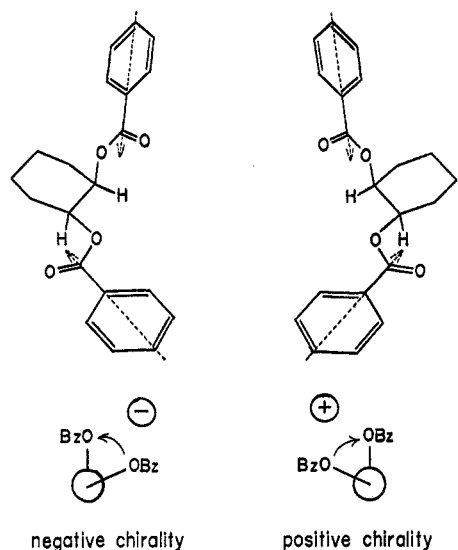
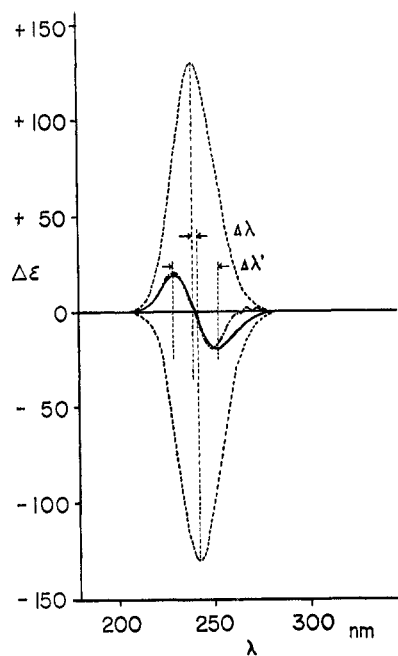
The resulting splitting indicates that the two Cotton effects are mainly due to a dipole-dipole interaction between the electric transition moments of the intramolecular charge-transfer band of two benzoate chromophores, and that the Cotton effects are separated from each other by a Davydov splitting ( $\Delta\lambda$ ).<sup>30</sup>

As shown in the following theoretical discussion, the coupling type Cotton effects depend on the chirality between two electric dipole transition moments. Since the 230-nm intramolecular charge-transfer transition of benzoates is mainly directed along the long axis,<sup>31</sup> the electric transition moment is approximately parallel to the alcoholic C-O bond, irrespective of the rotational conformation around the C-O bond.

If chiralities between two benzoate groups which reflect the chiralities between two electric transition moments, to a first approximation, are defined as being positive or negative, respectively, according to whether the rotation is in the sense of a right- or left-handed screw (Figure 2) (clockwise or counterclockwise twist), then the sign of the first Cotton effect around 233 nm is in accordance with the chirality ("dibenzoate chirality rule").<sup>20</sup>

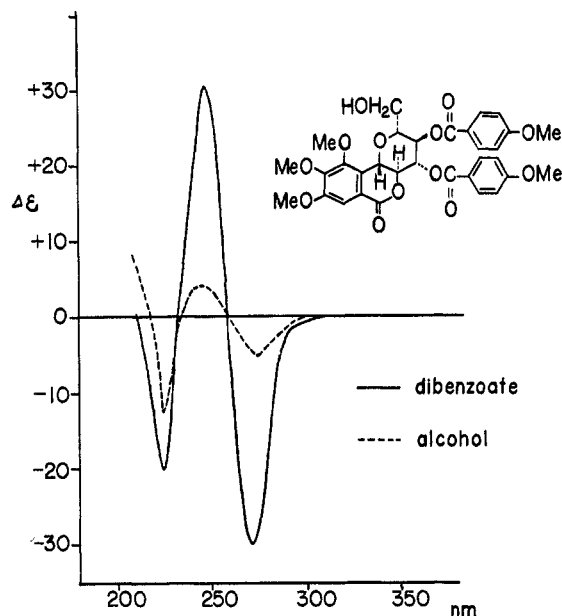
$2\alpha,3\beta$ -Dibenzoyloxy- $5\alpha$ -cholestane (Figure 1) has a negative chirality, and the sign of the first CD Cotton effect is also negative ( $\Delta\epsilon_{234} = -13.9$ ,  $\Delta\epsilon_{219} = +14.6$ ). Figure 3 shows the observed CD spectrum of  $3\beta,4\beta$ -bis(*p*-chlorobenzoyloxy)cholest-5-ene, the pattern of which is again typical for Cotton effects separated by a Davydov splitting (compare with ideal summation curves) and shows a red shift due to the *p*-chloro substituents. The compound has a negative chirality as depicted in the left half of Figure 2, and the signs of Cotton effects are in agreement with this skewness.

(31) J. Tanaka, *Bull. Chem. Soc. Jap.*, **36**, 833 (1963).

Figure 2. Chiralities of  $\alpha$ -glycol dibenzoates.Figure 3. Cholest-5-ene  $3\beta,4\beta$ -bis(*p*-chlorobenzoate). (----) The two-component CD curves, (—) summation curve, and (· · · · ·) observed curve.  $\Delta\lambda$  (Davydov splitting)  $487\text{ cm}^{-1}$ ;  $\Delta\lambda'$  (apparent splitting) calcd  $3812\text{ cm}^{-1}$  and obsd  $3182\text{ cm}^{-1}$ .

The CD spectrum also shows fine structure consisting of three peaks (Figure 3) corresponding to the 280-nm vibrational structure in the uv spectrum. This Cotton effect is very small, which indicates that the dipole-dipole coupling between the 280-nm transitions is not as effective as that between charge-transfer transitions. The small amplitude is also a result of the smaller electric transition moment of the 280-nm band ( $\epsilon \sim 1000$ ); the exciton splitting due to electric dipole-electric dipole coupling is thus characteristic of strong  $\pi \rightarrow \pi^*$  transitions.<sup>32</sup>

(32) In addition to the electric dipole-electric dipole coupling mechanism, there are Cotton effects due to magnetic dipole-electric dipole or magnetic dipole-magnetic dipole coupling mechanisms; see ref 2.

Figure 4. CD spectra of dimethylbergenin and its bis(*p*-methoxybenzoate) in ethanol (the phenolic group para to the lactone is the one methylated in the original bergenin).

The dibenzoate Cotton effect is one of the strongest encountered in common molecules, and, in addition, the peak and trough of the apparent Cotton effects for unsubstituted benzoates are fixed at *ca.* 233 nm (first) or 219 nm (second). These are the two aspects which make the present method conveniently suited for determining the absolute configurations or chiralities of glycols. Other chromophores usually do not interfere because of the difference in position and intensity of the Cotton effects. However, *if necessary, the dibenzoate Cotton effects can be shifted by introducing suitable para substituents.*

Thus, dimethylbergenin<sup>33</sup> (Figure 4) exhibits a negative Cotton effect arising from the gallate chromophore at 224 nm, which would overlap with the Cotton effects of unsubstituted benzoates. On the other hand, extrema of the bis(*p*-methoxybenzoate) (Table I, entry 1) are not only located at 270 and 247 nm, where there would be no overlap, but also have very strong amplitudes and therefore they can be clearly distinguished from the twist-gallate Cotton effect at 224 nm.

The facts that in para-substituted benzoates the extrema are located at longer wavelengths and are more intense, as exemplified by a comparison between Figures 1 and 4, show that for practical purposes it is more advantageous to employ para-substituted benzoates, *e.g.*, *p*-chloro or *p*-methoxyl. Indeed, a linear relation has been found to hold between amplitudes of Cotton effects and uv  $\epsilon$  values in a series of steroidal para-substituted 1,4-dibenzoates.<sup>10</sup>

A typical example of a complex molecule is the derivative of ponasterone A (A/B cis steroid) in which steroidal 7-en-6-one Cotton effects ( $\Delta\epsilon_{327} = +1.8$ ,  $\Delta\epsilon_{248} = -3.9$ ) are much weaker than those of

(33) T. Ito, N. Harada, and K. Nakanishi, *Agr. Biol. Chem.*, **35**, 797 (1971).

**Table I**  
CD Cotton Effects of Dibenzoates

Entry	Compound	Chirality	$\Delta\epsilon$ (nm) <sup>a</sup>		Solvent <sup>b</sup>
			1st	2nd	
1	Dimethylbergenin bis( <i>p</i> -methoxybenzoate) (Figure 4)	(-)	-29.9 (270)	+30.8 (247)	E
2	Estriol 3-methyl ether 16 $\alpha$ ,17 $\beta$ -bis( <i>p</i> -chlorobenzoate) <sup>c</sup>	(-)	-21.9 (246)	+21.1 (231)	E
3	17-Epiestriol 3,16 $\alpha$ ,17 $\alpha$ -tris( <i>p</i> -chlorobenzoate) <sup>c</sup>	(+)	+14.9 (247)	-8.2 (232)	E-D
4	Illudin S derivative, bis( <i>p</i> -chlorobenzoate) ( <b>2</b> )	(-)	-18.2 (248)	+12.6 (229)	E
5	Cholest-5-ene 3 $\beta$ ,4 $\beta$ -di- $\beta$ -naphthoate	(-)	-182.4 (242)	+156.9 (229)	E-D

<sup>a</sup> CD spectra were measured using a Jasco ORD/UV-5 spectropolarimeter with CD attachment. <sup>b</sup> E, ethanol; E-D, ethanol-dioxane (9:1). <sup>c</sup> Samples received from Dr. T. Wada, Teikoku Hormone Co.

the dibenzoate ( $\Delta\epsilon_{235} = -14.5$ ,  $\Delta\epsilon_{218} = +15.9$ ),<sup>20</sup> and therefore the Cotton effects due to the 2 $\beta$ ,3 $\beta$ -dibenzoate moiety are clearly observed (*cf.* figure in ref 23). The present method has also been used to ascertain the 2 $\alpha$ ,3 $\alpha$ -glycol group in ponasterone B.<sup>34</sup> In tetrahydrotaxinine 9,10-dibenzoate (Figure 3 in ref 20) the enone group shows an abnormally strong  $\pi \rightarrow \pi^*$  Cotton effect, but the dibenzoate Cotton effects are again clearly measurable.<sup>20</sup> The absolute configuration of rishitin, an antifungal antibiotic isolated from infected potato tubers,<sup>35</sup> was determined on the basis of this method.<sup>20,36</sup>

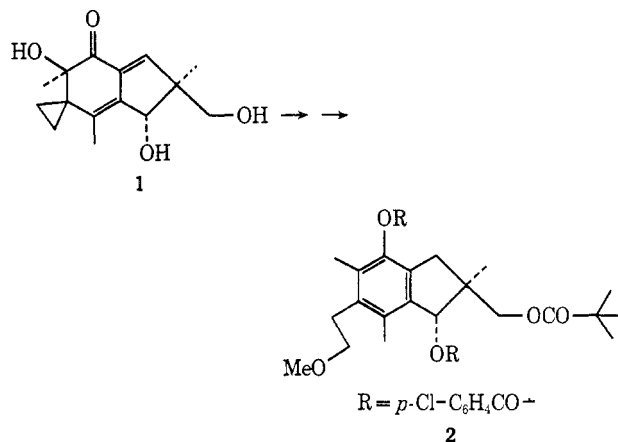
Conformations of the five-membered ring in methyl  $\beta$ -D-ribose 2,3-dibenzoate and its  $\alpha$  epimer can be defined unambiguously from the chiralities.<sup>20</sup>

17-Epiestriol tribenzoate (16 $\alpha$ ,17 $\alpha$ ) exhibits a positive first Cotton effect (entry 3),<sup>37</sup> while the methyl ether of estriol dibenzoate (16 $\alpha$ ,17 $\beta$ ), having a dihedral angle larger than 90°, shows a negative first Cotton effect (entry 2), both signs of which are in accordance with prediction.<sup>20</sup>

The coupling between two benzoate chromophores to give split Cotton effects is not confined to 1,2-glycol systems. Thus, in the 5 $\alpha$ -cholestane-3 $\beta$ ,6 $\beta$ -diol derivative (1,4-dibenzoate) the Cotton effect sign is in agreement with prediction (*p*-chlorobenzoate,  $\Delta\epsilon_{246} = -16.4$ ,  $\Delta\epsilon_{231} = +12.1$ ).<sup>20</sup> The glycol may also include primary alcohols; *e.g.*, the sign of terpenoid dibenzoate derivatives agreed with the chirality predicted from the preferred conformation of the 1,3-dibenzoate moiety (see Table I in ref 20).

The present method has been applied to the phenol **2** (Table I, entry 4) derived from the antitumor antibiotic, illudin S.<sup>21</sup> As the CD extrema of dibenzoate **2** was typical for bis(*p*-chlorobenzoates) it was clear that the nuclear benzene ring was not conjugated to the phenolic *p*-chlorobenzoate; a straightforward application of the dibenzoate chirality method then led to absolute configuration **1**.

3 $\beta$ ,4 $\beta$ -Di- $\beta$ -naphthoyloxycholest-5-ene (entry 5) gives two extremely strong Cotton effects due to the dipole-



dipole coupling at the  ${}^1A_{1g} \rightarrow {}^1B_{3u}$  transition ( $\Delta\epsilon_{242} = -182.4$ ,  $\Delta\epsilon_{229} = +156.9$ ). Although this band has a long axis transition moment, its direction is not parallel to that of the alcoholic C-O bond. Therefore, the exciton chirality method is not strictly applicable to the  $\beta$ -naphthoyloxy system, but it is obvious that chromophores giving rise to exciton split Cotton effects of the magnitude of  $\beta$ -naphthoyloxy groups would be most useful for a variety of purposes.

### Theoretical Aspects

According to molecular exciton theory,<sup>30</sup> the electric transition ( $o \rightarrow a$ ) of two interacting chromophores  $i$  and  $j$  splits into two states ( $\alpha$  and  $\beta$  states), namely

$$E^\alpha = E_a - V$$

$$\Psi_a^\alpha = (1/\sqrt{2})(\Phi_{ia}\Phi_{jo} - \Phi_{io}\Phi_{ja}) \quad (1)$$

$$E^\beta = E_a + V$$

$$\Psi_a^\beta = (1/\sqrt{2})(\Phi_{ia}\Phi_{jo} + \Phi_{io}\Phi_{ja}) \quad (2)$$

where  $V$  is the interaction energy and is considered to be mainly a dipole-dipole interaction. The rotational

$$V_{ij} = \frac{\mathbf{u}_{ioa} \cdot \mathbf{u}_{joa}}{R_{ij}^3} - 3 \frac{(\mathbf{u}_{ioa} \cdot \mathbf{R}_{ij})(\mathbf{u}_{joa} \cdot \mathbf{R}_{ij})}{R_{ij}^5} \quad (3)$$

strength of such a system can be approximated as in eq 4,<sup>2,5</sup> where the upper and lower signs correspond to the

$$R_{ao} = \mp [(1/2)\pi\tilde{\nu}_a\mathbf{R}_{ij}](\mathbf{u}_{ioa}\mathbf{u}_{joa}) \quad (4)$$

$\beta$  and  $\alpha$  states, respectively. Figure 5 shows one mode of two interacting electric transition moments (in phase), which indicates that the absolute sign of the Cotton effect at longer wavelength calculated according to eq 4 is in accordance with the sign of chirality.

(34) M. Koreeda and K. Nakanishi, *Chem. Commun.*, 351 (1970).

(35) N. Katsui, A. Murai, M. Takasugi, K. Imaizumi, T. Masamune, and K. Tomiyama, *ibid.*, 43 (1968).

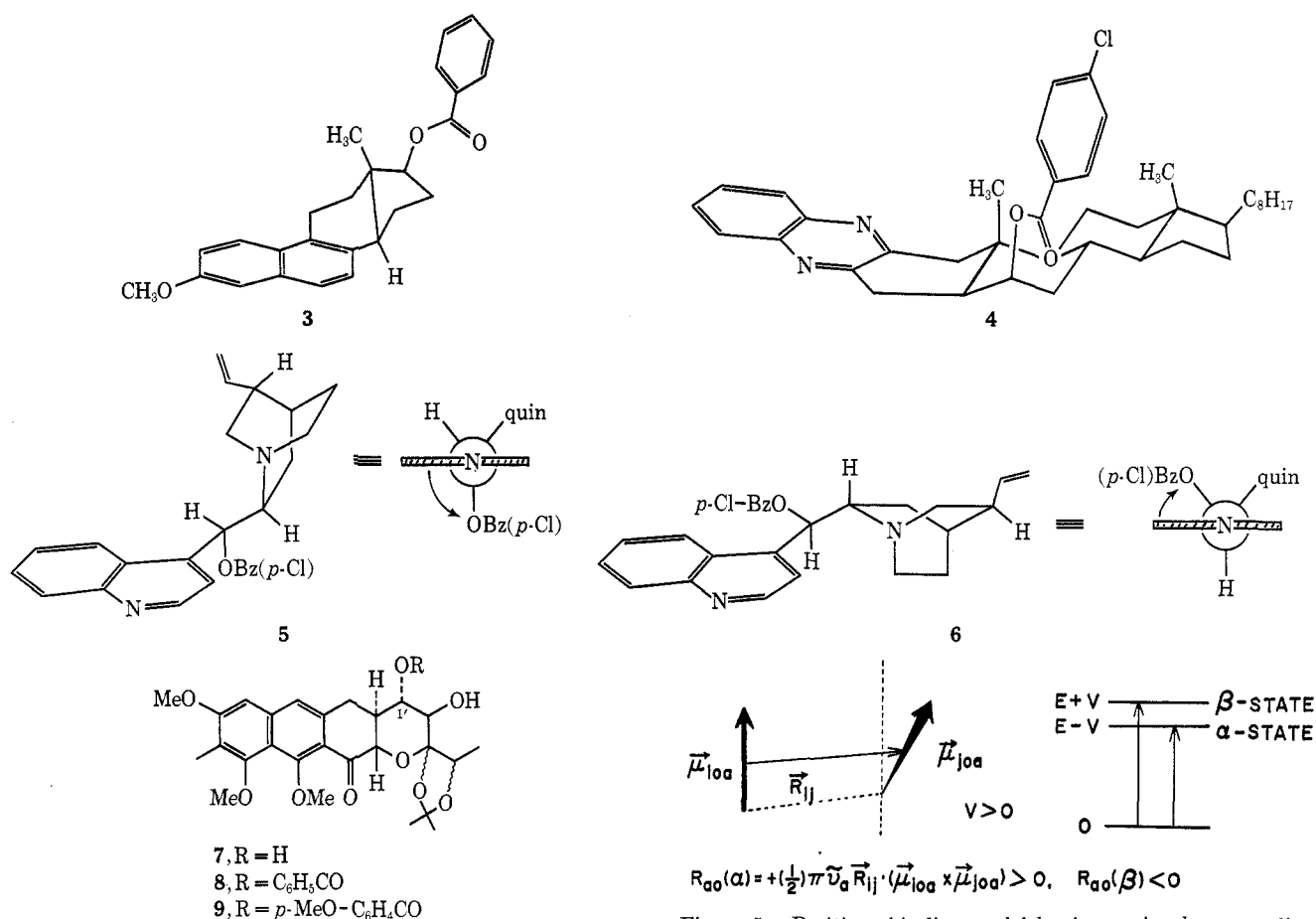
(36) The same absolute configuration was independently derived from the CD spectrum of its cuprammonium complex: S. T. K. Bukhari and R. D. Guthrie, *J. Chem. Soc. C*, 1072 (1969).

(37) Interaction of the ring A phenolic benzoate group with the ring D benzoates need not be considered as seen from the fact that no split Cotton effect is observed in estradiol 3,17 $\beta$ -bis(*p*-chlorobenzoate).

Table II  
CD Cotton Effects of Aromatic Alcohols and Their Benzoates

Entry	Compound	Chirality	$\Delta\epsilon$ (nm)		Solvent <sup>a</sup>
			1st	2nd	
1a	17 $\beta$ -Dihydroequilenin 3-methyl ether <sup>b</sup>		+14.8 (226)		E
b	17-Benzoate (3)	(+)	+34.0 (235)	-14.3 (220)	E
2a	Quinoxaline derivative of 6 $\beta$ -hydroxy-5 $\alpha$ -cholestane-2,3-dione		+8.0 (251)	-10.9 (238)	E
b	6-Acetate		+6.6 (247)	+2.3 (232)	E
c	6- <i>p</i> -Chlorobenzoate (4)	(-)	-23.6 (243)	+24.6 (231)	E
3a	Cinchonine		+8.1 (232)		HCl
b	9- <i>p</i> -Chlorobenzoate (5)	(-)	-19.1 (241)	+2.4 (231)	HCl
4a	Cinchonidine		-17.0 (236)		HCl
b	9- <i>p</i> -Chlorobenzoate (6)	(+)	+15.9 (244)	-2.2 (231)	HCl
5a	Chromomycinone derivative (7)		-8.5 (269)	+5.1 (223)	E
b	1'-Benzoate (8)	(-)	-19.9 (270)	+16.8 (230)	E
c	1'- <i>p</i> -Methoxybenzoate (9)	(-)	-70.6 (271)	+34.0 (250)	E

<sup>a</sup> E, ethanol; aqueous 0.1 N HCl. <sup>b</sup> Sample received from Dr. P. Crabbé, Syntex S. A.



The same treatment holds for the other mode (out of phase).

The calculation of the split Cotton effect of 3 $\beta$ ,4 $\beta$ -bis-(*p*-chlorobenzyloxy)cholest-5-ene gave the CD summation curve shown in Figure 3. This figure also shows a comparison of the calculated CD curve with the observed spectrum (the positive Cotton effect at 280 nm was not considered in the theoretical treatment). The excellent agreement in position and intensity shows that the dipole-dipole coupling mechanism can be applied to these systems in a facile and satisfactory manner.<sup>10</sup>

### The Aromatic Chirality Method

The nonempirically calculated absolute signs of

Figure 5. Positive chirality model having an in-phase coupling mode of interacting electric transition moments. This shows that the absolute sign of the first Cotton effect can be nonempirically calculated. Exactly the same treatment holds for an out-of-phase coupling mode.

Cotton effects resulting from interacting benzoate chromophores agree with the chirality of the two aromatic groups.<sup>6,20</sup> It was thus expected that the treatment employed in the case of interacting benzoate groups could be extended to other groups as well. This was confirmed by the CD data of 17 $\beta$ -dihydroequilenin 3-methyl ether 17-benzoate (entry 1b in Table II). The free 17 $\beta$ -ol (entry 1a) exhibits two weak Cotton effects centered at 330, 280 nm, and a strong Cotton effect at 226 nm corresponding to the uv maxima of the  $\beta$ -methoxynaphthalene group, none

of which can be interpreted to make any sense. In the spectrum of the 17 $\beta$ -benzoate (entry 1b), the 226-nm band is strongly coupled with the benzoate transition at 230 nm, and consequently the CD spectrum has strong Cotton effects at 235 and 220 nm (Figure 1 in ref 24). In this case, the 230-nm absorption of the  $\beta$ -methoxynaphthalene chromophore is easily assigned to the  $^1A \rightarrow ^1B_b$  transition (long axis) of the naphthalene chromophore, by comparison with uv spectra of pertinent  $\beta$ -substituted naphthalene (Figure 2 in ref 24).<sup>38</sup> Significantly, the positive sign of the Cotton effect is in agreement with the chirality between the long axis of the naphthalene moiety and the benzoate group (or, to a first approximation, direction of the C<sub>17</sub>-O bond; see 3).

The two other transitions,  $^1A \rightarrow ^1L_a$  (short) at 280 nm and  $^1A \rightarrow ^1L_b$  (long) at 330 nm, were not affected by the dipole-dipole coupling with the benzoate groups because the bands are located far from the 230-nm benzoate transition and because their electric transition moments are relatively small; the rotational strength which is proportional to the electric transition moment is thus also small.

Exactly the same phenomenon is encountered in the quinoxaline derivative of 6 $\beta$ -*p*-chlorobenzoyloxy-5 $\alpha$ -cholestane-2,3-dione (entry 2c); the uv spectrum of the alcohol (entry 2a) is typical for an  $\alpha$ -substituted naphthalene chromophore where the two longer wavelength bands,  $^1A \rightarrow ^1L_a$  (short) and  $^1A \rightarrow ^1L_b$  (long) transitions, mutually overlap. The shorter wavelength band at 239 nm, which is assignable to a  $^1A \rightarrow ^1B_b$  (long) transition by comparison with other naphthalenoid spectra, strongly interacts with the *p*-chlorobenzoate intramolecular charge-transfer band at 240 nm to give a negative first Cotton effect in accordance with the predicted negative chirality (4).

Cinchonine (entry 3a) and cinchonidine (entry 4a) represent interesting and unique examples as the *sec*-hydroxyl groups are acyclic. The two alkaloids have opposing configurations at two chiral centers, and it was only after considerable confusion that the absolute configurations were finally established. As tabulated in Table II (entries 4b and 3b) the first Cotton effect signs are opposed; in each case the sign agrees with the chirality between the long axis of the quinoline and *p*-chlorobenzoate chromophores adopting the preferred conformation (see 5 and 6).

The method was next applied to chromomycin A<sub>3</sub> belonging to the chromomycin and olivomycin groups of antitumor antibiotics. The CD curve of the glycol 7 (entry 5a) derived from the aglycone, chromomycinone, consists of weak negative and positive Cotton effects, while that of the benzoate 8 (entry 5b) is typical for coupled Cotton effects centered at the uv peaks of the two chromophores, 270 and 230 nm ( $\Delta\epsilon_{270} = -19.9$ ,  $\Delta\epsilon_{230} = +16.8$ ). This clearly shows that the Cotton effects of the benzoate originate from the dipole-

dipole interaction between the electric transition moments of the benzoate chromophore (230 nm ( $\epsilon$  14,000), long axis) and naphthalenoid chromophore (270 nm ( $\epsilon$  57,200), long axis). The negative sign of the first Cotton effect led to assigning an  $\alpha$  configuration for the 1'-oxygen function, and this established the absolute configuration of the antibiotic.<sup>24,39</sup>

This deduction is also supported by the fact that the Davydov-split Cotton effects of the *p*-methoxybenzoate 9 have greatly enhanced amplitudes ( $\Delta\epsilon_{271} = -70.6$ ,  $\Delta\epsilon_{250} = +34.0$ ). This indicated that the long axis transition of the *p*-methoxybenzoate chromophore (256 nm ( $\epsilon$  18,000)) couples much more efficiently with the corresponding naphthalenoid band (270 nm) because of their closer maxima. The absolute configurations of the antibiotics cervicarcin<sup>25</sup> and chelocardin<sup>40</sup> (tetracycline) have also been determined from the exciton split CD curves; in the latter case interaction between a naphthalenoid chromophore and a cross-conjugated  $\beta$ -triketone was utilized.

Recently we have found that the so-called nmr shift reagents, Pr(DPM)<sub>3</sub> and Eu(DPM)<sub>3</sub>, interact with 1,2-glycols in dry carbon tetrachloride, chloroform, etc. (1:1 mixture), to give split-type Cotton effects centered at 305 nm, the sign of which agrees with the glycol chirality.<sup>26</sup> Although the origins of these split-type extrema are as yet not clear, it is conceivable that they do arise from an exciton splitting since the 1:1 mixture of reagent and substrate has a uv shoulder at this wavelength,  $\epsilon$  15,000. In any event it is a convenient method as no derivation is required<sup>41</sup> and because of its applicability to tertiary alcoholic groups as well (*e.g.*, steroidal 5 $\alpha$ ,6 $\alpha$ -diol). Extension of the Pr(DPM)<sub>3</sub> method to acyclic  $\alpha$ -glycols has enabled us to determine the absolute configuration of the insect juvenile hormone.<sup>42</sup>

Split-type Cotton effects are also encountered in alkaloids which already have two interacting chromophores within the molecule<sup>8</sup> such as *o*-dimethoxybenzene and methylenedioxybenzene groups, and this had led to the determination of absolute configurations of calycanthine,<sup>8</sup> pavine,<sup>8</sup> isopavine,<sup>43</sup> rhocadine,<sup>43</sup> and spirobenzylisoquinoline alkaloids.<sup>43</sup>

### Extension to Tribenzoate System

A tribenzoate having interacting chromophores shows Cotton effects arising from intramolecular

(38) H. H. Jaffe and M. Orchin, "Theory and Application of Ultraviolet Spectroscopy," Wiley, New York, N. Y., 1962.

(39) The same configuration has been derived independently by chemical correlations: Yu. A. Berlin, M. N. Kolosov, and L. A. Piotrovich, *Tetrahedron Lett.*, 1329 (1970).

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(41) Chiralities of  $\alpha$ -glycols and  $\alpha$ -amino alcohols can also be determined without derivatization by the cuprammonium method: S. T. Bukhari, R. D. Guthrie, A. I. Scott, and A. D. Wrixon, *Chem. Commun.*, 1580 (1968); *Tetrahedron*, **26**, 3653 (1970).

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(43) M. Shamma, J. L. Moniot, W. K. Chan, and K. Nakanishi, *Tetrahedron Lett.*, 3425, 4207 (1971); M. Shamma, J. L. Moniot, R. H. F. Manske, W. K. Chan, and K. Nakanishi, *Chem. Commun.*, 310 (1972).

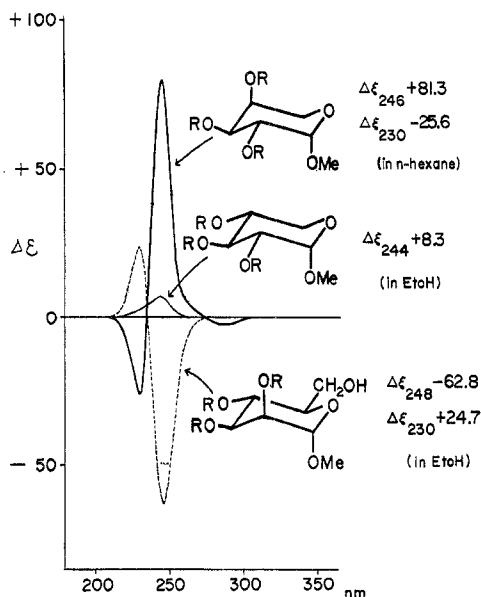


Figure 6. CD spectra of tris(*p*-chlorobenzoates) of sugars. (—) Methyl  $\alpha$ -L-arabinoside 2,3,4-tris(*p*-chlorobenzoate); (---) methyl  $\alpha$ -D-xyloside 2,3,4-tris(*p*-chlorobenzoate); (.....) methyl  $\alpha$ -D-mannoside 2,3,4-tris(*p*-chlorobenzoate) (R = *p*-ClC<sub>6</sub>H<sub>4</sub>CO).

charge-transfer bands.<sup>22,23</sup> In the case of cyclic 1,2,3-triol tribenzoates in which the chiralities between the 1,2-, 2,3-, and 1,3-hydroxyl groups are all negative or positive, two extremely strong Cotton effects of opposite signs are observed and its first Cotton effect sign again agrees with the chirality. For example, methyl  $\alpha$ -L-arabinoside 2,3,4-tri-*p*-chlorobenzoate (Figure 6) with all positive chiralities exhibits a positive first Cotton effect ( $\Delta\epsilon_{246} = +81.3$ ) and a negative second Cotton effect ( $\Delta\epsilon_{230} = -25.6$ ). In contrast, the CD spectrum of methyl  $\alpha$ -D-mannoside 2,3,4-tris(*p*-chlorobenzoate) having all negative chiralities shows negative first and positive second Cotton effects, respectively, which are approximately mirror images of those of methyl  $\alpha$ -L-arabinoside 2,3,4-tris(*p*-chlorobenzoate) (Figure 6).<sup>22</sup>

Similar results are obtained with the 1,2,3-tris(*p*-chlorobenzoate) of kogagenin which has a more rigid steroid ring system:  $\Delta\epsilon_{247} = +85.6$ ,  $\Delta\epsilon_{230} = -36.6$ .<sup>22</sup> The signs are in agreement with the 1 $\beta$ ,2 $\beta$ ,3 $\alpha$ -hydroxyl arrangements (A/B *cis*).

In contrast to the examples cited, the benzoate of a

symmetric triol moiety such as that encountered in methyl  $\alpha$ -D-xyloside 2,3,4-tris(*p*-chlorobenzoate) (Figure 6) shows no clear-cut split Cotton effects. Instead only one small Cotton effect is seen because the rotatory power of three interacting benzoate groups with opposite chiralities cancel out. The method is widely applicable to other sugars, and the mentioned interpretations are supported by theoretical calculations.<sup>10</sup>

The interaction still operates between more remote benzoate groups, as was seen for the tribenzoate of metagenin ( $\Delta\epsilon_{237} = -24.4$ ,  $\Delta\epsilon_{220} = +20.0$ ), an A/B *cis* steroid with 11 $\alpha$ ,2 $\beta$ ,3 $\beta$ -hydroxyl groups. Similarly enhanced CD amplitudes for the phytoecdysone derivative, ajugasterone C 20,22-acetonide 2,3,11-tribenzoate ( $\Delta\epsilon_{237} = -30$ ,  $\Delta\epsilon_{222} = +34$ ), led to an  $\alpha$  configuration for the 11-hydroxyl.<sup>23</sup>

To summarize, the exciton chirality method depends on measurements of split CD Cotton effects resulting from interaction between two or more chromophores, for which the directions of interacting transitions are known. The sign of the longer wavelength CD extremum is then in agreement with the sense of handedness of the interacting transition moments. The interaction is not confined to adjacent chromophores, but operates between more distant groups as well. If necessary, the Cotton effect wavelengths can also be shifted to avoid confusion by usage of substituted chromophores.

If the substrate already has one chromophore which can be used in the chirality method, the chromophoric interaction or Cotton effect amplitudes can be greatly enhanced by proper choice of the second chromophore to be introduced. Results of the present method are also in agreement with nonempirical calculations. Moreover, a similar treatment can apparently be applied to 1:1 mixtures of  $\alpha$ -glycols and Pr(DPM)<sub>3</sub>, etc.

The method provides a versatile and powerful method for determining the absolute configuration or conformations of natural products, and should be applicable to many other systems.

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