General Method for Determining Absolute Configurations of Acyclic Allylic Alcohols

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Received March 29, 1982

Recently a circular dichroic exciton chirality method[1] for determining absolute configurations of cyclic allylic alcohols was reported[2] in which the alcohols are converted into benzoates. We now report that this CD method is extendable to acyclic allylic alcohols where the conformations are dynamic. This "exciton chirality" method is based on the coupled oscillator theory developed by Kuhn[3] and the polarizability theory developed by Kirkwood;[4] it has since been the subject of theoretical studies[5] and has been extended to the field of biopolymers[6-8] and inorganic complexes.[9] In the field of natural products, it was first applied by Mason[10] to calycanthine, a dimeric alkaloid.

In the case of the allylic benzoate group[11] $\pi \rightarrow \pi^*$, the ^1L_a transition interacts with the double bond $\pi \rightarrow \pi^*$ transition (allowed, 195 nm)[12] to give rise to a Cotton effect in the ^1L_a band region, the sign of which is negative for the configuration shown in Figure 3 and positive for its enantiomer. Since both transitions are polarized along the long axes of the chromophores, this finding indicates that the two transitions constitute negative and positive chiralities (Figure 1), respectively, for the benzoates shown in Figure 3 and its enantiomer.

A series of secondary acyclic allylic alcohols were resolved by the enantioselective epoxidation procedure[13] and were *p*-bromobenzoylated[14] in near quantitative yields by mixing the allylic alcohol with a slight excess of *p*-bromobenzoyl chloride and pyridine in methylene chloride for 3 h. The *p*-bromobenzoates were isolated by preparative TLC (silica gel) eluting with hexane/ether (5:1). The CD and UV spectra of (*R*)-*n*-hexylvinylcarbinol *p*-bromobenzoate (Table I, entry 1) are shown in Figure 2. In the region of the $\pi \rightarrow \pi^*$ transition around 240 nm, the

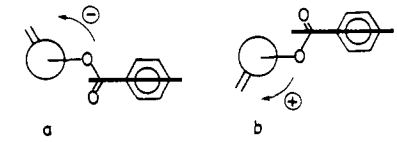

Figure 1. Exciton chirality of acyclic allylic benzoates and sign of predicted benzoate Cotton effects. The thick line deonotes the electric transition moment of the benzoate group.

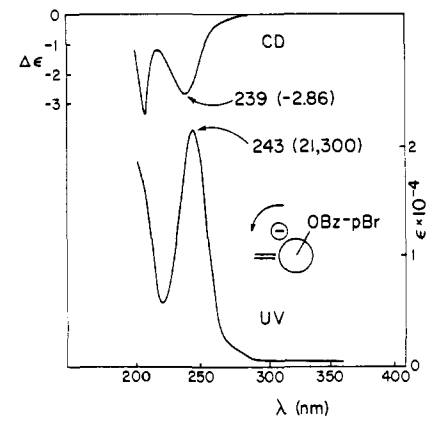

Figure 2. CD and UV spectra of (*R*)-*n*-hexylvinylcarbinol *p*-bromobenzoate (Table I, entry 1) in methanol.

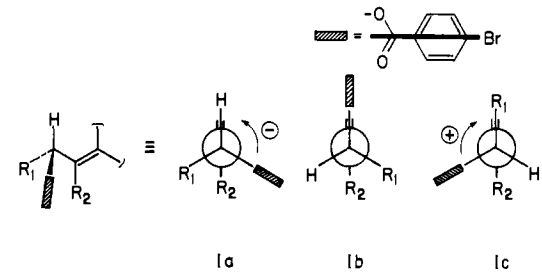

Figure 3. Limiting conformations for benzoates of secondary acyclic allylic alcohols. Signs on curved arrows show predicted signs of the Cotton effect (hatched rectangles indicate *p*-Br–C_6H_4–COO–).

CD spectrum exhibits a negative Cotton effect, the sign of which shows that the overall chirality between the benzoate and double-bond chromophores in this flexible system is negative as in Figure 1a. If the benzoate ^1L_a and the double bond $\pi \rightarrow \pi^*$ were the only two interacting transitions, the sign of the second Cotton effect of the exciton split CD curve should be opposite to that at 240 nm. However since the 200-nm region is overlaid and perturbed by other transitions,[1b,15] the sign of the shorter wavelength Cotton effect is not diagnostic.

The data for various alcohols of both the *R* and *S* series are shown in Table I. It lists compounds where the allylic double bond is mono-, 1,1-di-, 1,2-di- (both cis and trans), tri-, and tetrasubstituted; two examples of iodoalkenes are also included. It is thus found that in all cases studied, the absolute configuration shown in Figure 3 is correlated with a negative CD, while the epimeric configuration is correlated with a positive CD; the *R* and *S* designation for the configuration shown in Figure 3 may vary, but it is the enantiomer in which the benzoate substituent is on the right when the molecule is drawn with the carbinyl hydrogen and double bond eclipsed (i.e., as in Ia). This observation that the signs of the benzoate Cotton effects are dictated by the configuration of the acyclic allylic benzoates, irrespective of substitution pattern, indicates that a common preferred conformer is present. Namely, in the three limiting rotamers for the configuration shown in Figure 3, Ia should be the most favored since R_1 and benzoate are both bulkier than hydrogen.[16a] A predom-

(1) (a) Harada, N.; Nakanishi, K. *Acc. Chem. Res.* **1972**, *5*, 257. (b) Harada, N.; Nakanishi, K. "Circular Dichroic Spectroscopy—Exciton Coupling in Organic Stereochemistry"; University Science Books: Mill Valley, CA, in press.

(2) (a) Harada, N.; Iwabuchi, J.; Yokota, Y.; Uda, H.; Nakanishi, K. *J. Am. Chem. Soc.* **1981**, *103*, 5590. (b) For application to a homoallylic case see: Naya, Y.; Yoshihara, K.; Iwashita, T.; Komura, H.; Nakanishi, K. *Ibid.* **1981**, *103*, 7009.

(3) Kuhn, W. *Trans. Faraday Soc.* **1930**, *2B*, 293.

(4) Kirkwood, J. G. *J. Chem. Phys.* **1937**, *5*, 479.

(5) Schellman, J. A. *Acc. Chem. Res.* **1968**, *1*, 144. Buckingham, A. D.; Stiles, P. J. *Ibid.* **1974**, *7*, 258.

(6) Moffitt, W. *J. Chem. Phys.* **1956**, *25*, 467. Moffitt; W.; Fitt, D. D.; Kirkwood, J. G. *Proc. Natl. Acad. Sci. U.S.A.* **1957**, *43*, 723.

(7) Johnson, W. C.; Tinoco, I., Jr. *Biopolymers* **1969**, *8*, 715.

(8) Schellman, J. A.; Oriel, P. *J. Chem. Phys.* **1962**, *37*, 2114. Bayley, P. M.; Nielsen, E. B.; Schellman, J. A. *J. Phys. Chem.* **1969**, *73*, 228.

(9) Bosnich, B. *Acc. Chem. Res.* **1969**, *2*, 266.

(10) Mason, S. F. *Proc. Chem. Soc.* **1962**, 362. Mason, S. F.; Vane, G. W. *J. Chem. Soc. B* **1966**, 370.

(11) Unsubtituted, 229.5 nm; *p*-CH_3, 238.4; *p*-Cl, and *p*-CN, 240.0; *p*-Br, 244.5; *p*-OCH_3, 257.0; *p*-NO_2, 260.5; *p*-NH_2, 293.8; *p*-$N(CH_3)_2$, 311.0; cf.: Harada, N.; Nakanishi, K. *J. Am. Chem. Soc.* **1968**, *90*, 7351. Also see ref 1b.

(12) Stich, K.; Rotzler, G.; Reichstein, T. *Helv. Chim. Acta* **1959**, *42*, 1480.

(13) Martin, V. S.; Woodard, S. S.; Katsuki, Y.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 6237.

(14) Calculations and experiments[1b] show that the chirality between the double bond and allylic benzoate is still properly reflected in the Cotton effect sign of *p*-(dimethylamino)benzoates where the absorption maxima of the two chomophores differ by over 100 nm, i.e., 195 and 311 nm. The *p*-bromobenzoates were employed in the present case because the maxima at ca. 240 nm are sufficiently separated from the other shorter wavelength maxima (Figure 2).

(15) (a) Yogev, A.; Amar, D.; Mazur, Y. *Chem. Commun.* **1967**, 339. (b) Scott, A. I.; Wrixon, A. D. *Tetrahedron* **1970**, *26*, 3695; **1971**, *27*, 4787. (c) Levin, C. C.; Hoffmann, R. *J. Am. Chem. Soc.* **1972**, *94*, 3446.

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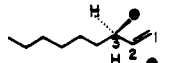
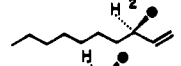
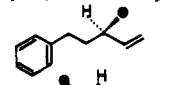
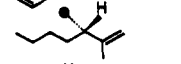
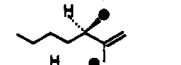
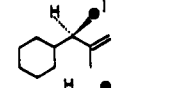
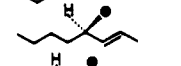
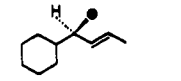
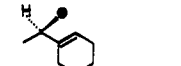
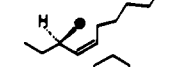
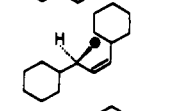
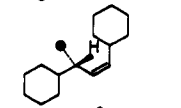
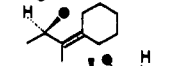
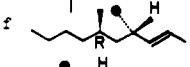
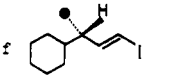
Table I. CD and NMR Coupling Constant Data of Acyclic Allylic Alcohol Benzoates[a,b]

	Compound	ee[c]	abs. config.	CD λ_{ext}, nm ($\Delta\epsilon$)	^{1}H NMR $J_{2,3}$, Hz
1.		(96%)	R	239 (-2.86)	6.3
2.		(96%)	R	237 (-2.86)	6.2
3.		(98%)	R	241 (-0.33)[d]	5.2
4.		(96%)	S	238 (+2.08)[e]	-
5.		(96%)	R	237 (-2.94)[e]	-
6.		(93%)	R	240 (-3.39)	-
7.		(96%)	R	240 (-5.08)	7.6
8.		(90%)	R	240 (-5.13)	7.6
9.		(96%)	R	240 (-2.81)	-
10.		(90%)	R	240 (-7.62)	8.5
11.		(82%)	R	238 (-8.73)	9.0
12.		(42%)	R	240 (-8.42)[e]	9.4
13.		(62%)	S	240 (+12.0)[e]	9.2
14.		(95%)	R	240 (-8.50)	-
15.[f]			S	243 (+11.24)	6.2
16.[f]			S	243 (+7.91)	6.9

[a] (•) *p*-Br-C_6H_4-COO-. [b] All CD spectra were taken in methanol with the exception of the iodo compounds, which were taken in hexane. [c] Enantiomeric excess of sample used; the CD values have been calculated for a single pure enantiomer. [d] The small $\Delta\epsilon$ value is most probably due to additional interaction between the benzoate and phenyl chomophores. [e] The discrepancies between the values for *R* and *S* enantiomers are due to experimental error(s) in the enantiomeric excess percent and/or CD measurements. [f] We are grateful to Dr. Seiji Kurozumi, Teijin Ltd., Tokyo, for gift of these compounds. The *S* configurations were assigned on various grounds: Kurozumi, et al., to be submitted for publication.

inance of rotamer Ia will give rise to a negative CD. The large J_{vic} of 5.2-9.2 Hz between the olefinic and carbinyl protons (Table I) is consistent with this analysis. As expected, the magnitude of both the Cotton effects and the $J_{2,3}$ coupling constants reach a zenith for the *Z*-type allylic benzoates shown in entries 10-14 of Table I. For these benzoates conformer Ia is virtually the only stable rotamer.[16] What is less expected is the apparent general preference for conformer Ia (over conformers Ib and Ic) exhibited by the entire family of allylic benzoates represented in Table I.

If exceptions are encountered to the rules set down in this work, one imagines they will arise in cases where both R_1 and R_2 (especially R_2) have large steric requirements.

Provided there is sufficient difference in the bulk of substituents, the present method is also applicable to acyclic *tert*-allylic alcohols, e.g., linalool, where in Figure 3, Ia, H is CH_3, R_1 is CH_2CH_2C-H=$C(CH_3)_2$, and R is H.[17]

We have thus shown that the current CD exciton method, which partly covers the empirical rules forwarded by Mills,[18] Brewster,[19] Yogev et al.,[15a] Scott and Wrixon,[15b] Harada et al.,[20] and Beecham et al.[21] is applicable to acyclic as well as cyclic allylic alcohols.

Acknowledgment. The studies were supported by NIH grants CA-11572 and GM-28384. V.M. thanks the Fundacion Juan March of Spain for a fellowship.

Registry No. 1, 81956-40-3; **2**, 81956-41-4; **3**, 81956-42-5; **4**, 81956-43-6; **5**, 81956-44-7; **6**, 81956-45-8; **7**, 81956-46-9; **8**, 81956-47-0; **9**, 81956-48-1; **10**, 81956-49-2; **11**, 81956-50-5; **12**, 81956-51-6; **13**, 81956-52-7; **14**, 81956-53-8; **15**, 81956-54-9; **16**, 81956-55-0.

Supplementary Material Available: Preparation of the three new chiral allylic alcohols (entries 3, 6, and 14 in Table I) and the determination of their absolute configurations are described (3 pages). Ordering information is given on any current masthead page.

(16) (a) Bothner-By, A. A.; Naar-Colin, C.; Gunther, H. *J. Am. Chem. Soc.* **1962**, *84*, 2748. (b) Karabatsos, G. J.; Fenoglio, D. J. "Topics in Sterochemistry"; Allinger, N. L., Elich, E. L., Eds.; Wiley-Interscience: New York, 1970; Vol. 5, p 167. (c) Bartlett, P. A. *Tetrahedron* **1980**, *36*, 3.

(17) For *tert*-alcohols the cinnamates rather than benzoates were employed to decrease steric hindrance of formation. The present method has been applied to determine the absolute configurations of *tert*-allylic moieties of the linalool type: R. Takeda, et al., submitted for publication.

(18) Mills, J. A. *J. Am. Chem. Soc.* **1952**, *74*, 4976.

(19) Brewster, J. H. *Tetrahedron* **1961**, *13*, 106. See also: Brewster, J. H. *J. Am. Chem. Soc.* **1959**, *81*, 5475, 5483, 5493.

(20) Harada, N.; Ohashi, M.; Nakanishi, K. *J. Am. Chem. Soc.* **1968**, *90*, 7349. Harada, N.; Nakanishi, K. *J. Am. Chem. Soc.* **1968**, *90*, 7351.

(21) Beecham, A. F.; Mathieson, A. M.; Johns, S. R.; Lamberton, J. A.; Sioumis, A. A.; Butterham, T. J.; Young, I. G. *Tetrahedron*, **1971**, *27*, 3725.

Absolute Stereochemistry of Palytoxin

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Received March 19, 1982

In a recent communication we reported the gross structure of palytoxin from Hawaiian *Palythoa toxica*.[1-3] This exceedingly poisonous substance is a mixture of anomeric isomers, since it possesses a labile hemiketal ring and, like fructose,[4] readily equilibrates to four anomeric forms, the major ones being, presumably, the α anomers. The subtle differences in the palytoxins from other *Palythoa* species[1] appear to be due to structural differences in the hemiketal ring. Detailed analyses of 360-, 500-, and 600-MHz ^{1}H NMR spectra of various degradation products from periodate oxidation and ozonolysis of *N*-(*p*-bromobenzoyl)palytoxin,[1,5] coupled with preliminary circular dichroism

(1) Moore, R. E.; Barolini, G. *J. Am. Chem. Soc.* **1981**, *103*, 2491.

(2) Uemura, D.; Ueda, K.; Hirata, Y.; Naoki, H.; Iwashita, T. *Tetrahedron Lett.* **1981**, *22*, 2781. These authors have concluded that palytoxin from Okinawan *Palythoa tuberculosa* has the same gross structure as that of the major component (**1B** in ref 1) in palytoxin from Hawaiian *P. toxica*.

(3) We have recently found a *Vibrio* sp. (tentative identification) in Hawaiian *P. toxica* and isolated a toxin from the cultured bacterium that is chromatographically and pharmacologically identical with palytoxin: Moore, R. E.; Helfrich, P.; Patterson, G. M. L. *Oceanus*, in press.

(4) Doddrell, D.; Allerhand, A. *J. Am. Chem. Soc.* **1971**, *93*, 2779

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