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Helicity Induction in a Bichromophore: A Sensitive and Practical Chiroptical Method for Absolute Configuration Determination of Aliphatic Alcohols

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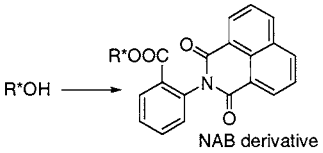
ABSTRACT



A practical method for the determination of the absolute configuration of aliphatic secondary alcohols, based on the circular dichroism of the readily available *N*-(1,8-naphthaloyl)-2-aminobenzoyl (NAB) derivative, is presented. The origin of the induced Cotton effects is traced by ab initio calculations to the dominant helicity of the NAB π-electron system.

Current stereochemical studies employ two methods for the absolute configuration determination: either the X-ray diffraction method (Flack parameter)[1] or the circular dichroism (CD) method. In the latter case, exciton-coupled circular dichroism (ECCD)[2] is of particular value, as it allows the determination of absolute configuration on a microscale, often without the need to perform tedious theoretical model calculations. The method requires the presence of two chromophores with the allowed $\pi-\pi^*$ transitions; these can be introduced, when necessary, through suitable derivatization of diols, amino alcohols, hydroxy acids, etc. with a chromophoric derivative, the typical representative being the benzoate group. Alcohols are among the most abundant chiral compounds of synthetic and natural origin. If the absolute configuration of a chiral nonchromophoric alcohol is to be determined by the ECCD method, a bichromophoric molecule has to be attached to the hydroxy group. Derivatives of this type bearing axially chiral 2,2′-binaphthalene-3,3′-dicarboxylic acid[3] or 5,5′-dinitrodiphenic acid[4] have been recently introduced by Hosoi, Ohta, and co-workers. Harada and co-workers used for this purpose esters of di(1-naphthyl)-acetic acid.[5] An entirely different approach was demonstrated by Nakanishi, Berova, and co-workers[6] and relies on chiral recognition by a CD-sensitive dimeric zinc porphyrin host. The guest molecule forms a complex with the zinc porphyrin host in solution, but the chiral alcohol (or amine) has to be derivatized with an achiral carrier molecule.

The field of chromophoric derivatives of monoalcohols has not matured yet and new derivatives with broad sensitivity to the structural variations of the alcohol molecule and a convenience of preparation are needed. We reasoned that the bichromophore, consisting of the benzoate substituted in the *ortho* position with the naphthalimide group (the NAB

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(1) Flack, H. D. *Acta Crystallogr*. **1983**, *A39*, 879−881.

(2) (a) Harada, N.; Nakanishi, K. *Circular Dichroic Spectroscopy−Exciton Coupling in Organic Stereochemistry*; University Science Books: Mill Valley, CA, 1983. (b) Nakanishi, K.; Berova, N. In *Circular Dichroism−Principles and Applications*; Berova, N., Nakanishi, K., Woody, R. W., Eds.; Wiley-VCH: New York, 2000; pp 337−382.

(3) Hosoi, S.; Kamiya, M.; Ohta, T. *Org. Lett.* **2001**, *3*, 3659−3662.

(4) Hosoi, S.; Kamiya, M.; Kiuchi, F.; Ohta, T. *Tetrahedron Lett.* **2001**, *42*, 6315−6317.

(5) Ishiya, F.; Ehara, H.; Yoshida, N.; Goto, H.; Monde, K.; Harada, N. *40th Symposium on the Chemistry of Natural Products*, symposium papers, 1998; pp 85−90.

(6) (a) Kurtán, T.; Nesnas, N.; Li, Y.-Q.; Huang, X.; Nakanishi, K.; Berova, N. *J. Am. Chem. Soc*. **2001**, *123*, 5962−5973. (b) Kurtán, T.; Nesnas, N.; Koehn, F. E.; Li, Y.-Q.; Nakanishi, K.; Berova, N. *J. Am. Chem. Soc*. **2001**, *123*, 5974−5982.

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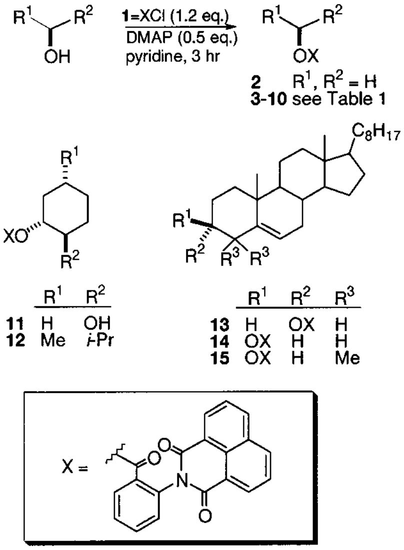
Scheme 1



chromophore), will act as a sensor of the alcohol chirality, by conformationally induced Cotton effects within its $\pi-\pi^*$ absorption bands.

N-(1,8-Naphthaloyl)-2-aminobenzoates of primary and secondary alcohols (**2**−**15**) are readily available from NAB chloride (**1**) (Scheme 1).

The UV spectra of the NAB derivatives display two intense maxima at 332 nm (ϵ 13500−14000) and at 232 nm (ϵ 45000−50000) in acetonitrile solution. These absorption maxima are clearly associated with the $\pi-\pi^*$ transitions of the 1,8-naphthalimide chromophore;[7] the benzoate absorption is apparently hidden under the envelope of the absorption bands between 240 and 200 nm. The 232 nm band is CD active: in the CD spectra of derivatives **3**−**15** (Table 1) there are observed two opposite-sign Cotton effects (see also Figure 4), one at 240 ± 5 nm, associated with the long-axis polarized $\pi-\pi^*$ transition in the naphthalene ring of the 1,8-naphthalimide chromophore, and the other at below 226 nm and presumably due to the benzoate $\pi-\pi^*$ charge-transfer transition. The signs of these Cotton effects are solvent-independent.

These Cotton effects form a couplet, the sign of which is clearly related to the difference in size of the R^1 and R^2 substituents, i.e., to the absolute configuration at the carbinol atom (Figure 1).

Table 1. CD Data for NAB Derivatives **3**−**15** in Acetonitrile Solution

	R^1	R^2	$\Delta\epsilon$ (nm)
3	Me	Et	+5.7 (240), −2.4 (226)
4	Me	CH_2COOEt	+7.0 (243), −5.6 (226)
5	Me	COOEt	+4.8 (235)[a]
6	Me	(*S*)-$CH_2CH(OH)Me$	+12.5 (240), −4.3 (222)
7	Me	(*S*)-CH(OH)Me	+7.0 (243), −1.9 (220)
8	CH_2Ph	COOMe	−5.5 (240), +3.5 (216)
9	CH_2COOMe	COOMe	−1.8 (244), +4.3 (224)
10	(*S*)-CH(OH)-COOMe	COOMe	−7.9 (241), +10.9 (213)
11			−6.1 (243), +1.4 (224)
12			−22.8 (239), +6.0 (225)
13			−11.0 (242), +2.7 (225)
14			+4.0 (235)[a]
15			+18.3 (238), −13.2 (204)

[a] No distinct second Cotton effect observed.

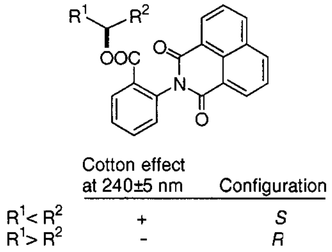


Figure 1. Correlation between the size of R^1, R^2 (absolute configuration) and the sign of the NAB Cotton effect.

The size of R^1, R^2 according to the CD data increases in the order Me < COOR < CH_2R < CH(OH)R < CHRR′, which does not exactly follow the differences in conformational energies of substituents in monosubstituted cyclohexanes. It is of importance to note that the NAB chromophore has high sensitivity to relatively small differences in substituent size. The chromophore differentiates two homologous substituents, the methyl and the ethyl group in **3**. Comparable sensitivity in chirogenesis was reported for a supramolecular system based on a complex formation between chiral amines and the ethane-bridged bis(zincporphyrin).[8] Noteworthy also is the sensitivity of the NAB chromophore to γ-substitution in the cyclohexane skeleton. Thus, NAB derivatives of cholesterol **14** and 3-epicholesterol **13** differ in the sign and magnitude of the Cotton effects. The structural differences between R^1 and R^2 groups in these molecules appear between substituents at C1 and C5. The Cotton effects of **13** are stronger, as the axial C3−O bond brings the NAB chromophore closer to the two stereodifferentiating C1 and C5 groups, compared to the equatorial C3−O bond in **14**. Finally, the strongest Cotton effects (*A* ca. 30) are observed for two NAB derivatives significantly differentiated in the size of substituents in the β position: **12** (CH_2 vs CH*i*-Pr) and **15** (CH_2 vs CMe_2). The sensitivity range ($\Delta\epsilon/\epsilon$) for the series of NAB derivatives **3**−**15** is 1×10^{-4} to 6×10^{-4}, i.e., well within the range easily measured by commercial dichrographs.

To provide an insight into the induction of optical activity of the NAB chromophore we carried out extensive conformational modeling of the chromophore as well as semiem-

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(7) Gawroński, J.; Gawrońska, K.; Skowronek, P.; Holmén, A. *J. Org. Chem.* **1999**, *64*, 234−241.

(8) Borovkov, V. V.; Lintuluoto, J. M.; Inoue, Y. *J. Am. Chem. Soc.* **2001**, *123*, 2979−2989.

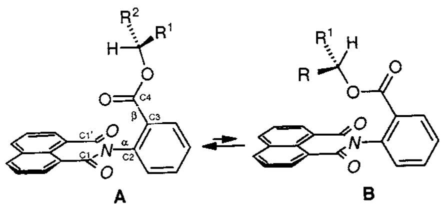

Figure 2. Extended (**A**) and folded (**B**) conformers of the NAB chromophore.

pirical and ab initio computation of rotational strength of the chiral conformers of **2**.

Conformation of the NAB moiety is described by the two torsion angles[9] α (C1or C1′−N−C2−C3) and *β* (C2−C3−C4═O), Figure 2. Angle α determines nonplanarity of the phenyl and the imide ring system and is within the range 0, ±90°. Angle *β* determines nonplanarity of the benzoyl group, and it changes between 0° for the extended (**A**) conformer and 180° for the folded (**B**) conformer.

The conformers of **2** were fully optimized by the DFT b3lyp/3-31g(d) method. At the b3lyp/6-31g/(d) level nonplanar conformers **A** and **B** were obtained as the energy minima. The minimum-energy conformer **A** was found for $\alpha = 80°$, $\beta = 10°$; the energy of the molecule raised significantly for $|\alpha| < 75°$ and $|\beta| > 20°$ (Figure 3). Folded conformers **B** are of higher energy, but their energy profile as a function of α and *β* (not shown) is quite similar: a minimum obtained for $|\alpha| = 85°$, $\beta = 180°$ is 0.66 kcal·mol^{-1} above the conformer **A** energy minimum (the energy difference between **B** and **A** conformers rises with the size of the alkyl ester group). An important conclusion emerged from the computational study: the angles α and *β* are correlated, i.e., they have the same sign for conformers **A** and opposite sign for conformers **B**. Other combinations lead to a sharp increase of the energy of **2**.

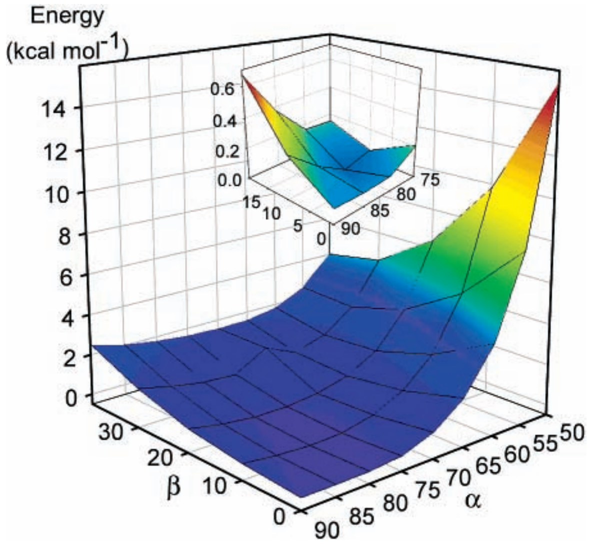

Figure 3. Molecular energy of the extended (**A**) conformer of **2** as a function of angles α and *β*. Insert shows the energy minimum ($\alpha = 80°$, $\beta = 10°$).

Analysis of the X-ray diffraction of crystals **3**[10] provides additional insight into the structure of the real NAB molecules. Compound **3** crystallizes in the space group *P*1 with four independent molecules in the asymmetric unit. This result is apparently due to molecular flexability of **3**. The four molecules of **3** in the crystal are in the extended A conformation and differ in the conformation of the (*S*)-2-butyl chain as well as in the helicity (torsion angles α, *β*) of the NAB chromophore (Table 2).

Table 2. Torsion Angles (deg) α and *β* of NAB Chromophore in Four Independent Molecules of **3** in Crystal

(*S*)-2-butyl chain conformation	α	*β*
trans	−75.3	−41.6
gauche (−)	−73.7	−29.6
gauche (+)	+71.1	+44.2
gauche (+)	+79.7	+34.4

The NAB chromophores form either an *M* helix (negative α and *β* values) or a *P* helix (positive α and *β*), from the carbonyl group of the benzoate to the carbonyl group of the imide, but there is no preference toward one or the other in the crystal of **3**.

The excited states of the NAB chromophore have been initially computed by the ZINDO method for a number of chromophore geometries in **2**, systematically varying magnitudes of angles α and *β*. Variations of the oscillator strength (*f*) and of the electronic transition energies were observed, but the salient features, i.e., the presence of an allowed transition at 300−350 nm and a set of strongly allowed transitions at below 250 nm, were present in all of the computed spectra. The spectrum computed by the ZINDO and the ab initio CIS/6-31g(d)[11] methods for $\alpha = 70°$, $\beta = 10°$ is shown in Figure 4.

The computed pattern of the most intense transitions correlates reasonably well with the experimental UV spectrum of the NAB chromophore. The computed rotational strengths of the transitions for $\alpha = 70°$, $\beta = 10°$ are in good agreement with the CD spectrum of **12**. The allowed transition at 350 nm does not show significant rotational strength. On the other hand, the 240 nm transition displays a large negative rotational strength for a *P*-helical NAB chromophore, just as is observed in the CD spectrum of **12** (Figure 4). According to computations, variations of angle *β* between 0° and 40° had little effect on *R*; negative *R* values

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[9] Additional conformational parameter is the spatial relation of the carbinol C−H bond to the benzoyl C═O bond; this is invariably *syn*, as in Figure 2.

[10] Rychlewska, U. Unpublished data; e-mail: urszular@amu.edu.pl.

[11] The computed wavelengths of the transitions were multiplied by a factor 1.35 to account for electron correlation.

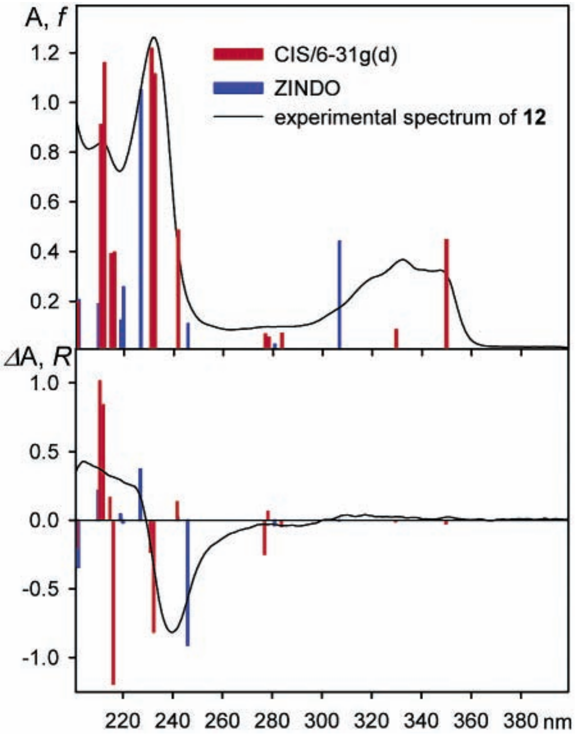

Figure 4. Computed oscillator strengths *f* (upper panel, vertical bars) and rotational strengths *R* (lower panel, vertical bars) for the electronic transitions of the NAB chromophore in **2** ($\alpha = 70°$, $\beta = 10°$). Overlaid are the UV and CD spectra of **12**.

were computed for all α values between 90° and 60° (Figure 5). The computed rotational strength of the shorter-wavelength transitions (below 230 nm) were positive, again in agreement with the signs of the Cotton effects of **12** below 230 nm.

The computations provide a model of induction of optical activity of the NAB chromophore. For $R^2 > R^1$ in an extended **A** conformation (Figure 2) angle α is negative as a result of the interaction between R^2 and the nearest carbonyl group of the 1,8-naphthalimide chromophore. To release the strain due to the imide C═O/benzoyl C═O group interaction, the latter is rotated in the direction of negative angle *β*, resulting in the NAB chromophore of dominant *M* helicity.

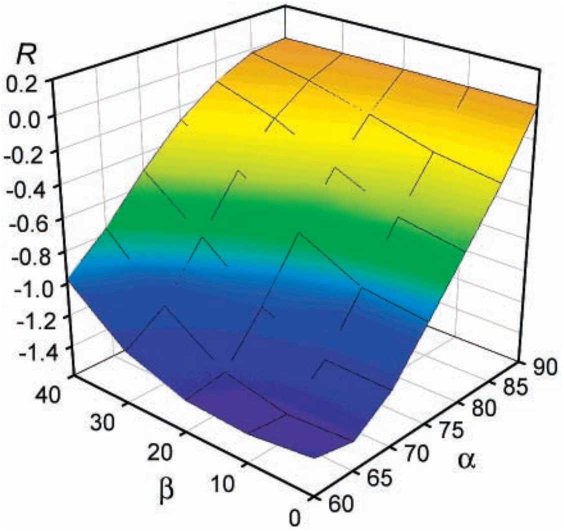

Figure 5. ZINDO method computed rotational strength *R* of the 240 nm transition of the NAB chromophore in **2** as a function of angles α and *β*.

Accordingly, the Cotton effect at around 240 nm is positive, as observed experimentally for the alcohol of the *S* configuration (Figure 1).

In summary, we have developed a sensitive and practical method for determination of the absolute configuration of aliphatic secondary alcohols. The method is based on the induced helicity of the NAB chromophore, which in turn determines the sign of the observed Cotton effects in the 250−200 nm range. The NAB derivatives are readily obtained from the cheap commercial substrates.

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Supporting Information Available: Experimental procedure for the preparation of NAB derivatives and characterization of compounds, details of computation procedures, and numerical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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