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A superior molecular bichromophore for the determination of absolute configuration of primary amines

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Abstract—Readily available molecular bichromophore, *N*-(1,8-naphthaloyl)-3-amino-2-naphthoic acid (NAN), is used to derivatize primary amines. NAN-amides show superior sensitivity in the determination of absolute configuration of amines from the sign of the induced exciton Cotton effect. The sign of the Cotton effect is determined by the preferred helicity of the NAN chromophore, which is dependent on the relative size of the substituents at the chiral $R^1R^2C^*HN$ carbon atom.

Chiral molecules with just one functional group, such as amino or hydroxy group, attached to a stereogenic center are common among compounds of natural or synthetic origin. Determination of the absolute configuration requires the use of either X-ray diffraction technique or a chiroptical method, such as electronic circular dichroism or vibrational circular dichroism. Electronic circular dichroism is a commonly used technique, providing that the molecule under study has a suitable chromophore(s) to develop a Cotton effect(s) in the accessible UV–vis range. Exciton coupled circular dichroism (ECCD)[1] is a powerful method with well-developed theoretical background, allowing us to study the stereostructures of molecules without the necessity to use advanced MO computations to obtain theoretical CD spectra for comparison with the experimental ones. This method requires the presence of two or more chromophores on the molecule, whose electric dipole transition moments interact to produce exciton-split Cotton effects. However, in the case of monofunctional molecules, the necessary condition of having at least a two-chromophoric system can only be fulfilled by the attachment of a *bichromophore* to a single functional group. A number of bichromophoric molecules have recently been introduced to derivatize chiral alcohols or amines.[2] These include covalent derivatives of di(1-naphthyl)acetic acid,[3] 2,2′-binaphthalene-3,3′-dicarboxylic acid,[4] and 5,5′-dinitrodiphenic acid.[5] Non-covalent bonding of chiral substrates to achiral dimeric zinc porphyrin host constitutes another approach of great potential.[6] However, chiral recognition (chirogenesis) with dimeric porphyrin hosts may be complicated by the known tendency of porphyrins for aggregation.[7]

We have recently introduced a practical method for the determination of the absolute configuration of aliphatic alcohols with the use of the readily available *N*-(1,8-naphthaloyl)-2-aminobenzoyl (NAB) derivative.[8] In this derivative, an example of which is shown in Scheme 1C, the exciton Cotton effect is induced by nonplanarity of the two chromophores, *ortho*-substituted benzoate and 1,8-naphthalimide. The direction of the twist depends on the difference in size of the two substituents R^1 and R^2 in chiral alcohol $R^1CH(OH)R^2$. The exciton Cotton effect is generated through the interaction of the electric dipole transition moments of the allowed π–π^* transitions in the 1,8-naphthalimide chromophore (λ_{max} at 232 nm) and in the substituted benzoate chromophore (estimated (λ_{max} at 225 nm); the directions of the transition moments are shown in Scheme 1C.

There are three basic criteria that a bichromophoric derivative should meet: (a) ready availability of the derivatizing agent, (b) easy and high-yield derivatizing procedure, (c) high sensitivity (high $\Delta\varepsilon/\varepsilon$ ratio) of the CD measurement, to allow working with small amounts of the analyte. While NAB derivatives of the alcohols seem to meet all the three criteria, there is still room for improvement. Some of our earlier attempts resulted in biphenyl (Scheme 1A) and *N*-phthaloyl-2-aminobenzoyl (Scheme 1B) chromophores. The biphenyl chromophore in the phosphite derivative[9] of (−)-menthol A only gave

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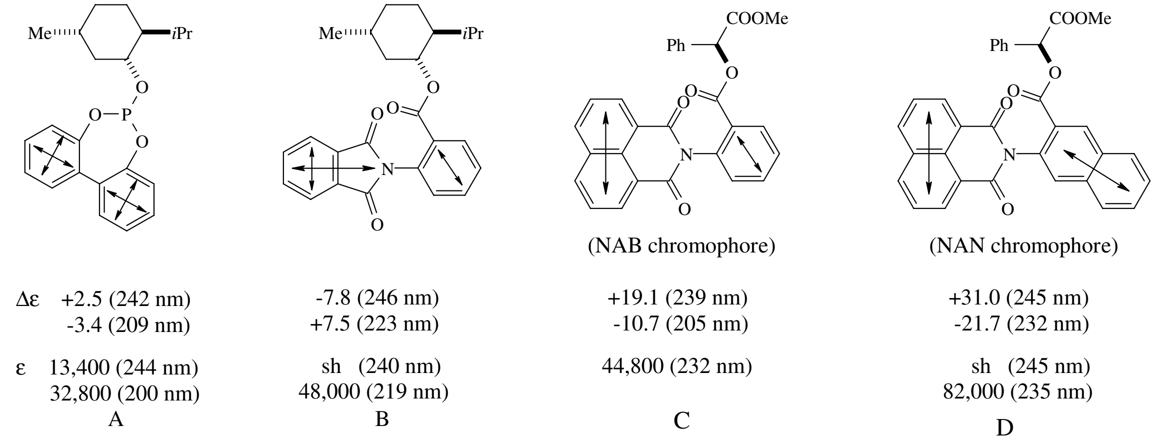


Scheme 1. Development of bichromophores for CD structural studies.

weak Cotton effects within the long-wavelength (band K, long-axis polarized) and short-wavelength (short-axis polarized) transitions, apparently due to the lack of an effective conformational transmission from the chiral alcohol moiety to the skew sense of the biphenyl chromophore. *N*-Phthaloyl-2-aminobenzoyl chromophore has been recently used in decarboxylative photocyclization reactions.[10] Derivative B of (−)-menthol generated sizable Cotton effects due to phthalimide–benzoate coupling. The amplitude of the exciton Cotton effect ($A = -15.3$) was, however, lower than the amplitude of the exciton Cotton effect of the NAB derivative of (−)-menthol ($A = -28.8$).[8] This is because the intense, long-axis polarized π–π* transition of the phthalimide chromophore is CD inactive in chromophore B, since the corresponding transition moment is coplanar with the benzoate transition moment, regardless of the chromophore conformation. Instead, the weaker short-axis polarized transition of the phthalimide chromophore at ca. 240 nm is CD active and responsible for the generated exciton Cotton effect. Thus, for the two chromophores, *N*-phthaloyl-2-aminobenzoate and *N*-(1,8-naphthaloyl)-2-aminobenzoate (NAB) with a comparable UV absorption in the region 220–230 nm, the latter provides better sensitivity, measured as the $\Delta\varepsilon/\varepsilon$ ratio.

We reasoned that a bichromophore having an even better chiral sensitivity than NAB could be obtained by substituting the benzoate on NAB by the 2-naphthoate chromophore (Scheme 1D). This would provide a bichromophoric system NAN, consisting of two naphthalene units, which would give strong absorption at nearly the same wavelength, that is, at around 230 nm; a condition optimal for effective exciton coupling. Indeed, a much stronger exciton Cotton effect ($A = 52.7$) was observed in the case of *N*-(1,8-naphthaloyl)-3-amino-2-naphthoate, NAN derivative of (*S*)-methyl cinnamate (Scheme 1D), compared to the NAB derivative ($A = 29.8$) (Scheme 1C).

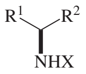
Like the NAB derivatives, NAN analogues are obtained from the corresponding acid, in this case *N*-(1,8-naphthaloyl)-3-amino-2-naphthoic acid,[11] which in turn is readily prepared from commercial 3-amino-2-naphthoic acid and 1,8-naphthoic anhydride by thermal condensation in dimethylformamide (yield 77%). The acid reacts sluggishly with secondary alcohols in the presence of DCC and DMAP but analogous reaction with amines can be carried out efficiently in CH_2Cl_2–DMF (9:1) solution. Therefore NAN derivatization is best suited for amines; a number of such derivatives **1b**–**5b**, as well as related NAB **1a**–**5a** derivatives, were prepared and their CD/UV data compared in Table 1.

It can be seen that the signs of the Cotton effects of the NAB and NAN derivatives of the corresponding chiral amines are the same, reflecting similar mechanism of chirogenesis. However the amplitudes of the exciton Cotton effects of the NAN derivatives are 2.5–4 times higher than analogous NAB derivatives, providing a higher chiral sensitivity with regard to the absorption of the chromophores.

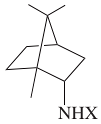
Since the signs of the exciton Cotton effects of NAB derivatives of structurally analogous amines and alcohols are the same, for example, compare the data for (+)-bornylamine derivative **5a** (Table 1) and for (+)-borneol NAB derivative (not shown), $\Delta\varepsilon = +5.4$ (244 nm) and −5.6 (225 nm), the chirogenesis (induction of optical activity) of NAB and NAN chromophores is assumed to be similar, as depicted in Figure 1.

As in the case of the NAB chromophore,[8] positive exciton Cotton effect is due to the dominant extended conformation A of *M* helicity, where the two torsion angles α and β are negative. Angle α is the measure of non-coplanarity of the naphthalimide and the naphthalene ring systems, whereas angle β shows the degree of nonplanarity of the naphthoyl group. *M* helicity arises when $R^2 > R^1$, since the interaction of R^2 with the nearest carbonyl group of the naphthalimide chromophore results in a strain due to the imide C=O and naphthoyl C=O group interaction. The strain is released by rotation of the latter in the direction of a negative angle β. Thus, *M* helicity conformer of the NAN chromophore leads to a positive exciton Cotton effect, as observed experimentally for cases **1** (Et>Me), **2** (CH_2OH>Me), and **5** (CR^3>CH_2R). On the other hand, *P* helicity conformer of the NAN chromophore displays a negative exciton Cotton effect, as can be seen in the

Table 1. Selected CD and UV data for derivatives of amines (solvent acetonitrile)



1 R^1 = Me, R^2 = Et
2 R^1 = Me, R^2 = CH_2OH
3 R^1 = Cy, R^2 = Me
4 R^1 = Ph, R^2 = Me



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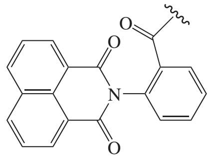
a X =



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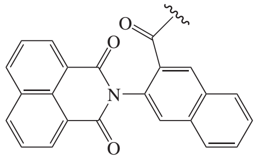

Compound	NAB derivative (**a**)		NAN derivative (**b**)	
	Δε (nm)	ε (nm)	Δε (nm)	ε (nm)
1	+0.9 (240) −1.2 (217)	42,000 (231)	+5.2 (236) −3.4 (220)	99,500 (230)
2	+2.2 (237) −2.3 (215)	41,000 (231)	+8.5 (239) −7.7 (222)	99,200 (229)
3	−7.6 (236) +3.7 (219)	44,400 (231)	−20.6 (237) +15.5 (220)	98,700 (228)
4	−12.2 (237) +14.3 (220)	42,700 (232)	−46.6 (238) +41.9 (216)	100,500 (230)
5	+6.4 (237) −5.5 (214)	43,100 (232)	+26.1 (239) −26.3 (220)	99,800 (228)

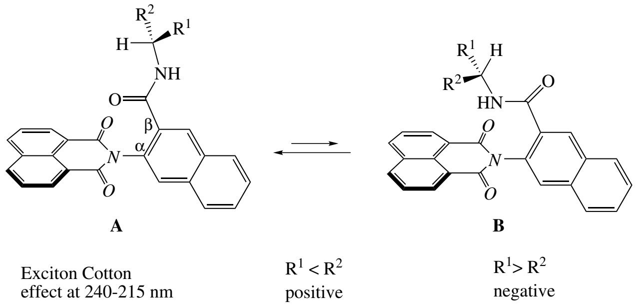

Figure 1. Extended (A) and folded (B) conformers of the NAN chromophore in amide derivatives and correlation of the sign of the exciton Cotton effect.

cases of **3** (Cy>Me) and **4** (Ph>Me). Although the largest Cotton effects are obtained for molecules with a large difference in size of R^1 and R^2 **3**–**5**, NAN chromophore is able to differentiate with good sensitivity R^1 and R^2 groups of similar size, as in **1** and **2**. Furthermore, the presence of an additional chromophore, the phenyl group in **4**, does not seem to contribute significantly to the exciton coupling of the two transitions in the naphthalene rings of NAN.

A significant solvent effect on the CD spectra of NAN derivatives (Fig. 2) was observed. Whereas in the acetonitrile and methanol solution, the CD spectra of **4** remained nearly identical; in dioxane solution the amplitude of the exciton Cotton effect was reduced by 50%. This reduction can be accounted for by the effect of intramolecular (amide)N–H···(imide)C=O attractive dipole interaction, stabilizing folded conformer B. Molecular modeling of **4** at AM1 level shows that lowest energy conformer B assumes *M* helicity ($\alpha = -3°$, $\beta = -61°$), which is opposite to *P* helicity induced in conformer A. This can lead to partial canceling of the observed exciton Cotton effect. Due to this effect, the use of a polar solvent for CD measurements with the NAN derivatives of amines is justified and recommended.

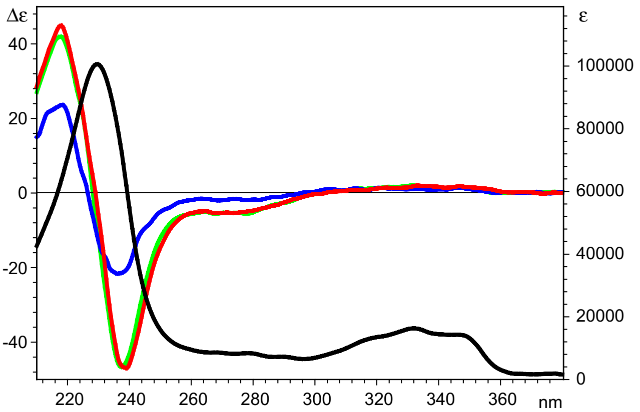

Figure 2. CD spectra of **4** in methanol (full line), acetonitrile (broken line), and dioxane (dotted line). Due to similarity only one UV trace (in acetonitrile) is shown (gray line).

Figure 2 shows that there are two other CD active spectral regions. A Cotton effect in the 300–360 nm region is due to the π–π* transition in 1,8-naphthalimide chromophore,[12] polarized along the local C_2 axis of the chromophore and hence having a positive sign, that is, opposite to the exciton Cotton effect at around 230 nm. Another Cotton effect in the region 260–300 nm is negative and apparently due to a transition (not identified) within the 2-naphthaloyl chromophore. These Cotton effects are weak, but since they originate from the transitions of low oscillator strength they can be conveniently used for stereochemical correlations.

In summary we have developed a CD active bichromophore NAN for the determination of the absolute configuration of amines. This derivative is readily obtained from commercial substrates and shows superior sensitivity when compared to the previously introduced NAB chromophore.

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