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4,5-Dimethoxyphthalimide and 6,7-Dimethoxy-2,3-naphthalimide - Two New Chromophoric Derivatives for the Amino Group

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Abstract: We have developed new chromophoric derivatives for the amino group: 4,5-dimethoxyphthalimide and 6,7-dimethoxy-2,3-naphthalimide, particularly suitable for CD applications. These highly fluorescent imides show very strong Cotton effects due to exciton coupling which are red-shifted with respect to the parent phthalimide and 2,3-naphthalimide chromophores. No significant Cotton effects other than those due to the transition with the electric dipole transition moment colinear with the C_2-axis of the chromophore were observed.

Keywords: electronic spectra, circular dichroism, imides.

Recently we have demonstrated that the phthalimide group, widely used as a protected form of the amino group, is also useful as a chromophoric derivative of the amino group.[1,2] The phthalimide chromophore is particularly well-suited for CD studies directed towards the determination of absolute configuration based on exciton coupling - either degenerate or non-degenerate - and employing the strong, π-π^* transition of the phthalimide. This transition is located at 219 nm and is polarized along the C_2-axis of the chromophore - an important feature, making the stereochemical applications independent of any conformational equilibria of the phthalimide group. Di- and tetrachlorinated derivatives of phthalimide[3] as well as 2,3-naphthalimides[4] were also used in the CD studies based on exciton coupling.

Despite the successful use of the phthalimide chromophore for structural studies[5,6] we felt that the CD spectra may sometimes be misinterpreted due to the presence of another π-π^* transition at ca. 240 nm, polarized perpendicularly to the C_2-axis. This transition, although much weaker than the principal one, produces significant exciton Cotton effect which is of *opposite sign* to the principal one at 220 nm in non-degenerate couplings, such as coupling between the phthalimide and the benzoate chromophores.

We envisaged that by substituting the phthalimide chromophore with two electron-donating substituents (amino, hydroxy or methoxy groups) in the 4 and 5 positions to preserve the C_2-symmetry, we will not only shift the principal band λ_{max} bathochromically but also make the transition polarized orthogonally less visible due to the increased intensity of the principal band.

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Inspection of the data on λ_{max} of 4- and 4,5- substituted phthalimides[7,8] clearly demonstrated that the red shift due to the amino group ($\Delta\lambda$ + 48 nm) is larger that than for the hydroxy group ($\Delta\lambda$ +18 nm) but for practical reasons (ease of preparation and stability) the 4,5-dimethoxy derivative (λ_{max} 247 nm)[9] is the preferred choice. 4-Substituted phthalimides on their own recently found diverse applications.[10]

4,5-Dimethoxyphthalimides are available by the thermal condensation of amines with 4,5-dimethoxyphthalic anhydride (*m*-hemipinic anhydride)[11] by the conventional methods used for the preparation of phthalimides. The related 6,7-dimethoxy-2,3-naphthalimides are likewise accessible from the corresponding amine and 6,7-dimethoxy-2,3-naphthalic anhydride.[12]

N-Methylimides **1a**[9] and **1b** show UV maxima (Figure 1) which are red-shifted from the UV maxima of *N*-methylphthalimide[13] and *N*-methyl-2,3-naphthalimide, respectively, by 27 nm and 30 nm. Imide **1a** displays characteristic blue fluorescence (λ_{em} 455 nm in acetonitrile), imide **1b** is also highly fluorescent (λ_{em} 424 nm in acetonitrile).

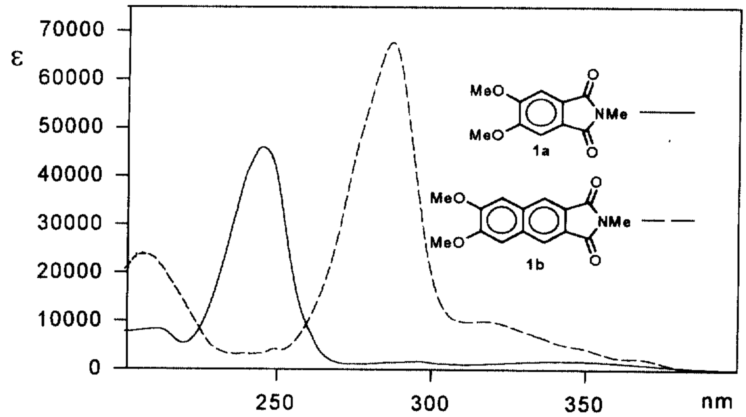
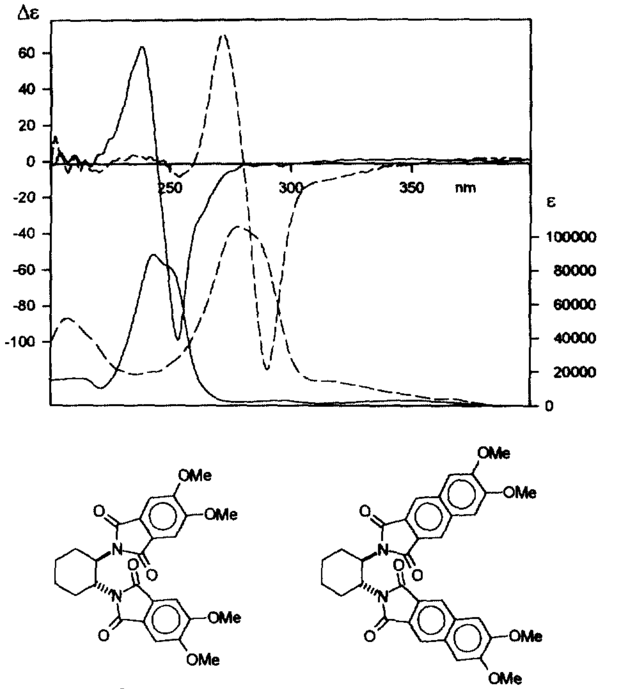


Figure 1. UV maxima in acetonitrile

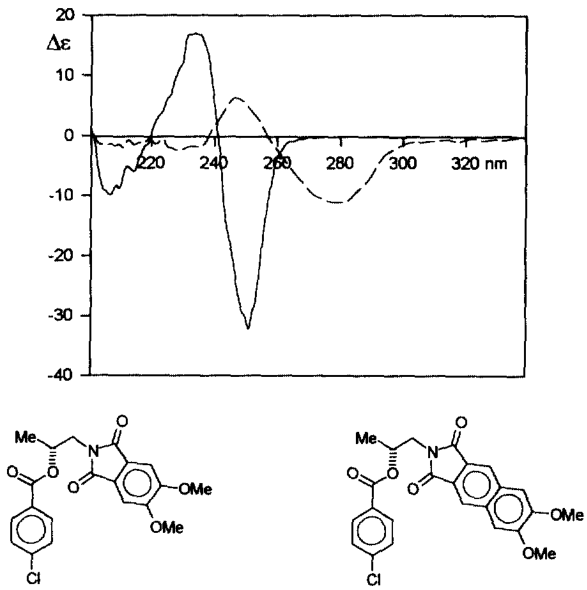
Chiral bis-imides **2a** and **2b**[14] display typical strong, negative exciton Cotton effects reflecting the negative chirality of the long-axis polarized degenerate bichromophoric system (Figure 2). There is no ambiguity in assigning the exciton Cotton effect to the long-axis polarized π-π^* transition. Accordingly, their UV spectra show typical broadened shapes with partially split maxima, due to the skew geometry of the interacting electric dipole transition moments.

Likewise, non-degenerate coupling cases represented by the benzoate-imide derivative **3a** and **3b** follow the pattern, producing clean negative exciton Cotton effects due to the coupling of the π-π^* substituted benzoate transition (polarized approximately in the direction of the C-O axis) and the π-π^* imide transition (polarized colinearly with the C-N axis) and reflecting the negative chirality of the bichromophoric system in the preferred C-C bond extended conformation.[1,2] (Figure 3).



2a **2b**

Figure 2. CD and UV spectra of **2a** (——) and **2b** (- - -) in acetonitrile



3a **3b**

Figure 3. CD spectra of **3a** (——) and **3b** (- - -) in acetonitrile

We have thus demonstrated here that both 4,5-dimethoxyphthalimide and 6,7-dimethoxy-2,3-naphthalimide chromophores can be used for unequivocal stereochemical assignments based on exciton coupling, producing exciton Cotton effects due to the long axis polarized transitions at ca 245 nm and 285 nm, respectively. Because of the ease of preparation and cleaner reactivity of 4,5-dimethoxyphthalic anhydride as compared to 6,7-dimethoxy-2,3-naphthalic anhydride, 4,5-dimethoxyphthalimides are the preferred chromophoric derivatives of chiral amines.

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7. Fabian, W. *Z. Naturforsch.* **1980**, *35A*: 865. The red shift is much smaller for the 3-substituted phthalimides.
8. The effect of two substituents in 4 and 5 positions on λ_{max} of the phthalimide chromophore is non-additive, probably due to the steric interactions of the two substituents (J. Gawroński, unpublished data; see also: White, E. H.; Matsuo, K. *J. Org. Chem.* **1967**, *32*: 1921).
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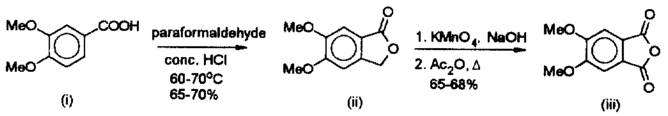
11. 4,5-Dimethoxyphthalic anhydride (iii) is readily available from veratric acid (i) in a three-step sequence involving the intermediate lactone *m*-meconine (ii):



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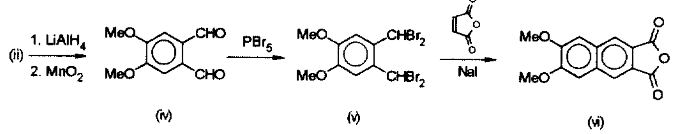

13. (a) Wintgens, V.; Valat, P.; Kossanyi, J.; Biczok, L.; Demeter, A.; Bérces, T. *J. Chem. Soc. Faraday Trans.* **1994**, *90*: 411. (b) Rigaudy, J.; Sparfel, D. *Tetrahedron* **1978**, *34*: 2263.
14. All new products have been fully characterized by spectroscopic methods. Some data: **2a**, m.p. 276-278°C, $[\alpha]_D^{20}$ -174 (c = 0.9, $CHCl_3$), λ_{max} 244 nm (ε 89100); **2b**, m.p. 380°C (dec.), $[\alpha]_D^{20}$ -350 (c = 0.5, $CHCl_3$), λ_{max} 278 nm (ε 105800); **3a**, m. p. 195-196°C, $[\alpha]_D^{20}$ -123 (c = 0.9, $CHCl_3$); **3b**, m. p. 229-233°C, $[\alpha]_D^{20}$-120 (c = 0.08, $CHCl_3$).