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Exciton Coupling in Various Substituted Aryl-Phthalimide Bichromophoric Systems[1]

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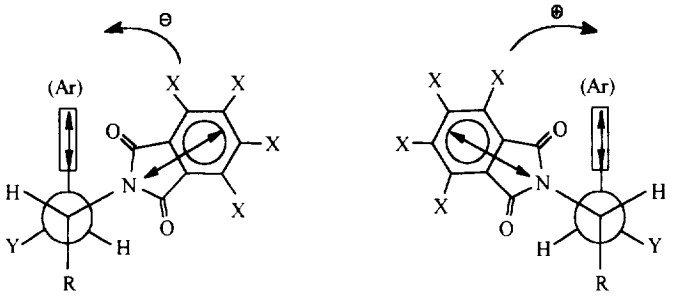
Abstract: As demonstrated in this paper, exciton Cotton effects reflecting the absolute stereochemistry of the molecule can result from coupling between the allowed transitions of phthalimide, 3,6-dichlorophthalimide, 4,5-dichlorophthalimide or 3,4,5,6-tetrachlorophthalimide and p-substituted benzene, naphthalene, benzoate or cinnamate chromophores. This significantly extends the scope of application of phthalimide chromophoric derivatives to stereochemical assignments by CD spectroscopy. The direction of the transition moments in chlorinated phthalimide chromophores are determined from linear dichroism measurements of *N*-butyl derivatives oriented in polyethylene film.

INTRODUCTION

N-Phthaloyl derivatization is one of the most frequently used methods of protection in synthesis involving compounds with primary amino group.[2,3] Its importance is amplified by the recent development of new methods of asymmetric synthesis of functionalized amines.[4] With this in mind we have recently introduced a new method of assigning the absolute configuration (or conformation) of β-phenylamines or β-hydroxyamines based on the CD exciton coupling of the electric dipole transition moments belonging to the allowed π-π* transition of the phthalimide chromophore and the ^1L_a transition of the phenyl or the π–π* transition of the benzoate chromophore.[5,6] The method is based on the effect of exciton coupling in the CD spectra of bichromophoric molecules, the so called exciton chirality method.[7] We have shown that strong, exciton - coupled type Cotton effects are obtained for β-phenylphthalimides and β-benzoyloxyphthalimides and that these Cotton effects reflect the absolute stereochemical arrangement of the two chromophores in the molecule, i. e. either absolute configuration[5] or conformation[6] (Fig. 1). The electric dipole transition moments involved in coupling are those belonging to the ^1L_a band of the phthalimide chromophore at 220 nm (ε 36000), and the ^1L_a band of the phenyl group at ca. 207 nm (ε 7000) or the π-π* charge - transfer band of the benzoate chromophore at 227 nm (ε 15000).



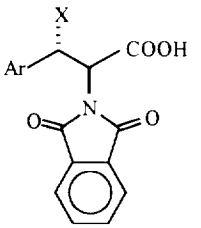
(a) (b)

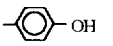
Figure 1. Negative (**a**) and positive (**b**) chirality of the bichromophoric system. For R = COOH, (**a**) represents L-aminoacid and (**b**) represents D-aminoacid configuration.

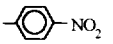
In order to extend the scope of application of the phthalimide exciton Cotton effects to stereochemical studies we have investigated the chiroptical properties of model bichromophoric systems involving the chlorinated phthalimide chromophore and/or p-substituted phenyl, naphthyl, benzoyl or cinnamoyl chromophores. In addition, the directions of the transition moments in chlorinated phthalimides were determined by linear dichroism measurements.[8]

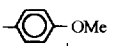
RESULTS AND DISCUSSION

The phthaloyl derivatives were prepared from the chiral β-aryl amino acids (**1-6**), chiral amines (**7**, **8**), chiral β-amino alcohols (**13**, **15**, **17**, **19**, **22**, **25**, **28**) and achiral amines (**10-12**) by standard procedures. The hydroxysubstituted phthalimides were further benzoylated to give **14**, **16**, **18**, **20**, **23**, **26** and **29** or cinnamoylated to give **21**, **24**, **27** and **30**.



1 Ar =  , X = H

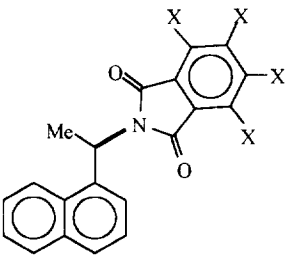
2 Ar =  , X = H

3 Ar =  , X = OH

4 Ar =  , X = H

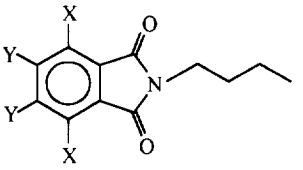
5 Ar =  , X = H

6 Ar =  , X = H

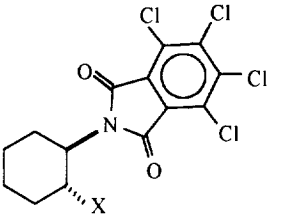


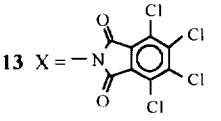
7 X = H

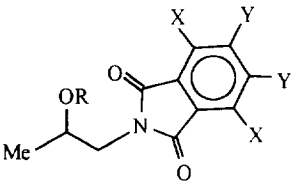
8 X = Cl



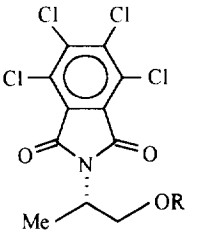
9 X = Y = H
10 X = Cl, Y = H
11 X = H, Y = Cl
12 X = Y = Cl



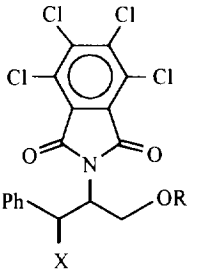
13 X = 
14 X = OBz



15 R = Y = H, X = Cl
16 R = Bz, X = Cl, Y = H
17 R = X = H, Y = Cl
18 R = Bz, X = H, Y = Cl
19 R = H, X = Y = Cl
20 R = Bz, X = Y = Cl
21 R = C(O)CH=CHPh, X = Y = Cl



22 R = H
23 R = Bz
24 R = C(O)CH=CHPh



25 R = X = H
26 R = Bz, X = H
27 R = C(O)CH=CHPh, X = H
28 R = H, X = OH
29 R = Bz, X = OH
30 R = C(O)CH=CHPh, X = OH

The CD and UV data are collected in Tables 1 and 3. The data of Table 1 demonstrate the effect of exciton coupling in *N*-phthaloyl-β-arylalanines with L-configuration shown in Fig.1 (X = Y = H, R = COOH).

Table 1. Exciton Cotton effects and UV maxima of the phthaloyl derivatives of aryl amines (solvent acetonitrile)

Compound	CD_{max}, Δε (nm)	UV_{max}, ε (nm)
1	-30.2 (225)	40 900 (218)
2	-22.9 (224)	46 300 (218)
3	-24.8 (227)	32 200 (220)
4	-103 (225); +46 (207)	85 000 (223)
5	-84.3 (226); +54.9 (214)	74 500 (225)
6	-69.3 (223); +10.3 (212)	63 200 (219)

The negative exciton Cotton effect observed in cases **1-3** reflects the spatial arrangement of the transition moments, polarized in the direction of the C-N bond (phthalimide) and the C-C_{ar} bond (p-substituted phenyl) in the extended conformation[6] shown in Fig. 1a. A similar negative exciton Cotton effect was found for *N*-phthaloylphenylalanine.[5] The presence of a β-hydroxy substituent in anti (*erythro*) configuration in **3** does not have any appreciable effect on the conformation and hence, on the amplitude of the exciton Cotton effect.[6] In the case of *N*-phthaloyl-L-naphthylalanines **4**, **5** and *N*-phthaloyl-L-tryptophan (**6**) the direction of the ^1B_b π-π* transition moment does not follow the direction of the C-C_{ar} bond. In the naphthalene ring this transition is long axis polarized while in the indole ring it is within ±15° from the direction of the pseudosymmetry axis.[9] However, the spatial relationship between the two transition moments is still as shown in Fig. 1a, for the extended conformation of the carbon chain. For example, the lowest energy conformer of **4** calculated by AM1 method[10] is shown in Fig. 2.

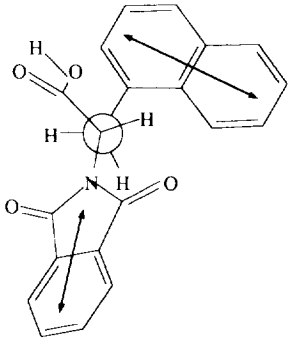


Figure 2. Calculated (AM1) lowest energy conformer of **4**.

In this conformer the two electric dipole transition moments, polarized along long axes of the naphthalene and phthalimide chromophores, form a dihedral angle of -66.8°. This nicely accounts for the observed strong negative Cotton effect of **4**. The case of the N-phthaloyl derivative of (*R*)-1-(1-naphthyl)-ethylamine (**7**) requires more detailed conformational analysis, in order to correlate the exciton Cotton effect with the absolute configuration. Unlike its phenyl analogue, which by virtue of coplanarity of the transition moments does not show any exciton Cotton effect,[5] **7** does show a strong negative exciton Cotton effect within the π-π* phthalimide and ^1B_b naphthalene absorption bands (Fig. 3).

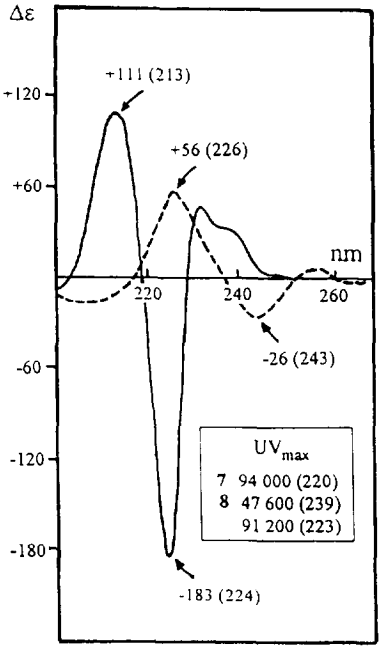
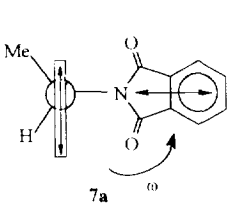


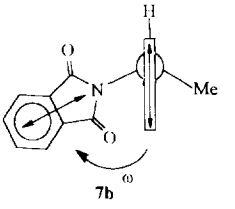
Figure 3. Negative exciton Cotton effects and UV data in acetonitrile solution:

7 ——, **8** - - - - -

This is because the transition moments in this α-aryl phthalimide bichromophoric system are noncoplanar, in low-energy conformations determined by semiempirical calculations. The two low energy conformers of 7 are shown in Fig. 4.[11]



7a



7b

	ω	ΔE (kcal/mol)	ω	ΔE (kcal/mol)
AM1	-96°	0.0	66°	3.0
PM3	-98°	0.0	76°	3.8

Figure 4. Computed low energy conformers of 7.

The negative exciton Cotton effect of 7 is thus due to the dominant contribution of conformer **7a**. Likewise, the tetrachloroderivative **8** also displays a negative exciton Cotton effect, with the negative extremum at 243 nm and the positive one at 226 nm (Fig. 3). The positions of the CD extrema correspond to the positions of UV maxima, i.e. 239 nm (tetrachlorophthalimide chromophore) and 223 nm (α–naphthyl chromophore). The amplitude of the exciton Cotton effect of **8** (A = -82) is lower compared to that of 7 (A = -294) which may be due to larger difference of excitation energy of the two chromophores in **8**.

Since the tetrachlorophthaloyl group is now emerging as a versatile protecting group for amines[12,13] we have decided to investigate its chiroptical properties in more detail. The effect of chlorine substitution on the position of the π-π^* transition band was determined by the UV measurements.

The UV spectra of the three *N*-butylphthalimides **10-12** symmetrically substituted with chlorine in the aromatic ring are shown in Fig. 5.

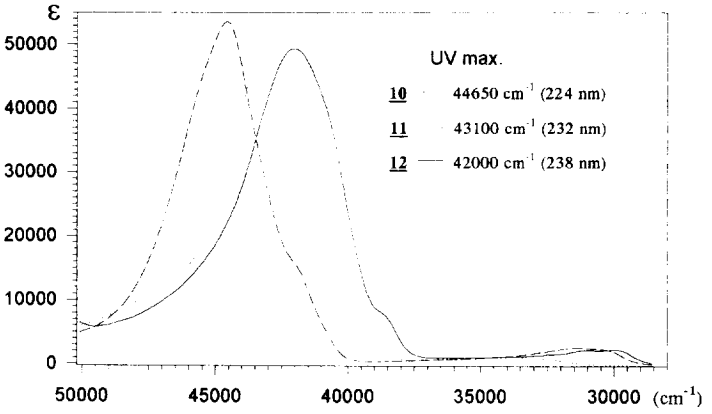


Figure 5. UV spectra of chlorine substituted *N*-butylphthalimides **10-12** (in acetonitrile).

The position of the intense π-π^* band ($\varepsilon \sim 50000$) is red-shifted with respect to the unsubstituted phthalimide **9** (λ_{max} 218 nm, in acetonitrile) by: 6 nm in **10**, 14 nm in **11** and 20 nm in **12**. It is evident that chlorine substitution in each 3,6- or 4,5- positions lowers the excitation energy of the allowed π-π^* transition, however the effect of 4,5-substitution is more pronounced (note additivity of the shifts). In order to determine the direction of polarization of the transitions in chlorinated phthalimides **10-12** we have carried LD measurements in stretched polyethylene film.

Two absorption curves, E_Z and E_Y have been recorded, with the electric vector of light polarized parallel and perpendicular to the stretching direction, respectively. An example of the LD measurement is shown in Fig. 6 for the chlorinated phthalimide **11**. Using the TEM procedure[14], we have determined the orientation factors K_i, corresponding to particular peaks in the spectra. The orientation factor provides information about the average cosine square of the angle formed between the transition moment direction and the direction of stretching. It is generally believed that the orientation in stretched films is related to the molecular shape, i.e. the orientation factor of a long axis polarized transition will be higher than the orientation factor of a transition polarized along a short axis. In the present case, since the C_{2v} symmetry of the chromophore may be assumed, only three different values of K are expected, which should sum up to unity. The largest K value will correspond to long-axis polarized π-π^* transitions, the lowest to the out-of-plane polarized transitions of n-π^* character, and the middle value to in-plane short axis polarized π-π^* transitions.

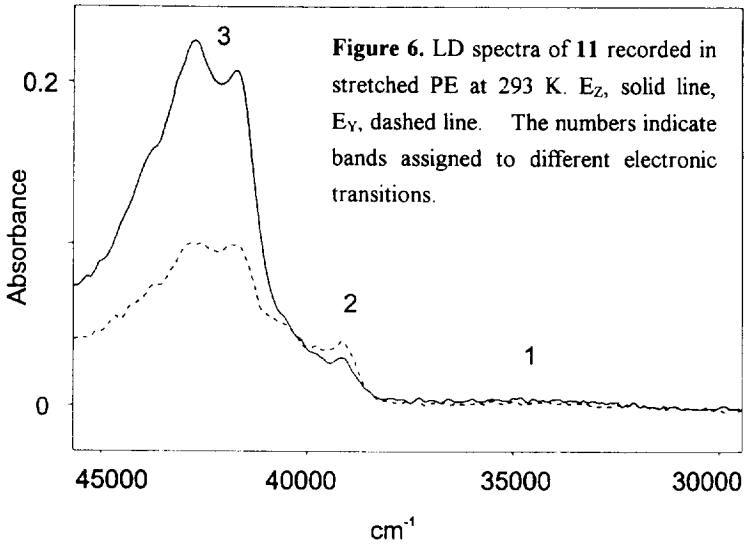


Figure 6. LD spectra of **11** recorded in stretched PE at 293 K. E_Z, solid line, E_Y, dashed line. The numbers indicate bands assigned to different electronic transitions.

Table 2. Orientation factors for **9** - **12** in stretched polyethylene at 293 K.

9		**10**		**11**		**12**	
E (10^3 cm^{-1})	K_i[a]	E (10^3 cm^{-1})	K_i[a]	E (10^3 cm^{-1})	K_i[a]	E (10^3 cm^{-1})	K_i[a]
33.4	0.41	30.5	0.40	35.0	0.55	30.0	0.40
34.4	0.41	31.5	0.40	39.0	0.30	31.0	0.40
41.6	0.32	41.5	0.40	40.5	0.30	32.0	0.40
43.3	0.32	44.0	0.40	42.0	0.55	38.0	0.30
~46.0	~0.40			43.0	0.55	41.5	0.40

[a] accuracy: ±0.02-0.05

The results for **9-12** are presented in Table 2. At least three electronic transitions can be identified in the region below 50000 cm^{-1}. A weak and broad band occurring around 33000 cm^{-1} and a strong transition with a maximum at 46000 cm^{-1} in **9** and 2000-4000 cm^{-1} lower in **10-12** have both the same and largest orientation factors. A transition located between these two, detected as a shoulder on the red edge of the strongest absorption band has a smaller K value. This is easiest to observe for the compound **11**, which, judging by its shape, should orient the best, but the results leave no doubt that the situation is similar for **9** and **12**. In compound **10**, all observed orientation factors have the same values, reflecting the disc shape of the chromophore. However, a very similar absorption pattern of **10** to that observed in **9** and **11-12** allows us to assign transition moment directions also for this molecule.

In summary, the first and third electronic bands observed for all four compounds may be assigned to long axis polarized π-π^* transitions, while the second observed band, to a short axis polarized π-π^* transition.

No n-π* transitions were detected: these should have the orientation factor values of 0.15 in **11** and 0.20 in **10**, assuming C_{2v} symmetry of the chromophore.

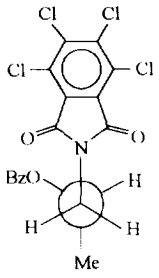
Next we have studied the exciton coupling of the chlorinated phthalimide chromophores with the benzoate or cinnamate chromophores in derivatives of chiral β-aminoalcohols. Starting with model compounds, the conformationally well-defined bis-*N,N'*-tetrachlorophthaloyl derivative of (1*R*,2*R*)-1,2-diaminocyclohexane (**13**) and the *N*-tetrachlorophthaloyl-*O*-benzoyl derivative of (1*R*,2*R*)-2-aminocyclohexanol (**14**), we observe negative exciton Cotton effects, corresponding to the UV π-π* absorption band at 237 nm (Table 3). The negative Cotton effects are due to the diequatorial conformer of **13** and **14**, as in Fig. 1a [Y = R = $(CH_2)_4$][15] and they faithfully reflect the absolute configuration of the parent molecules, as is in the case of non-chlorinated analogs.[16]

Table 3. Exciton Cotton effects and UV maxima of di- and tetrachlorophthalimides (solvent acetonitrile)

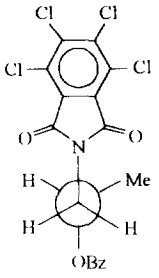
Compound	CD_{max}, Δε (nm)	UV_{max}, ε (nm)
13	-46.5 (248); +5.0 (228)	93 100 (237)
14	-28.8 (243); +17.2 (231)	53 000 (237)
16	-16.7 (231)	61 500 (224)
18	-34.0 (236); +14.8 (222)	59 400 (232)
20	-17.8 (242); +6.0 (230)	55 000 (236)
21	-10.0 (256); +14.0 (239)	22 300 (276) 53 100 (238)
23	+15.7 (241); -10.4 (228)	54 300 (236)
24	+ 7.9 (255); -11.6 (239)	22 600 (276) 53 900 (238)
25	+13.0 (243)	44 600 (238)
26	-1.5 (243); +16.0 (223)	54 000 (237)
27	-6.3 (258); +25.4 (240)	23 400 (276) 52 200 (239)
28	+2.7 (246); -1.9 (233)	40 100 (239)
29	-9.8 (245); +9.3 (232)	55 600 (238)
30	-4.5(258); +14.4 (243)	22 500 (276) 52 900 (240)

Derivatives of acyclic aminoalcohols **15-30** were studied in order to establish the utility of chlorinated phthalimides for stereochemical assignments in the presence of other chromophores.

First we note that *monochromophoric* chlorinated phthalimides (**15**, **17**, **19**, **22**) exhibit Cotton effects of low magnitude ($|\Delta\varepsilon| < 5$), in accordance with our earlier observations for phthalimides.[5] However, in the presence of a benzoate chromophore as in **16**, **18** and **20**, strong negative exciton Cotton effects arise, reflecting the absolute configuration of the molecules. It should be noted that the amplitude of the exciton Cotton effect of acyclic **20** (A = -23.8) is significantly lower than that of cyclic **14** (A = -46.0). This is due to the contribution of two conformers, **20a** and **20b**, of which **20b** gives no exciton Cotton effect.



20a



20b

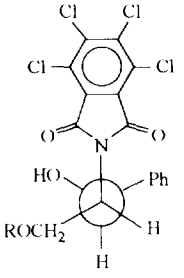
The amplitudes of the exciton Cotton effects follow the order:

chlorine substitution: 4,5 (in **18**) > none[5] > 3,4,5,6 (in **20**) > 3,6 (in **16**)

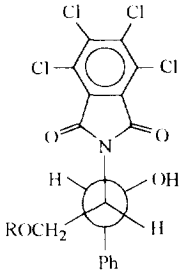
It thus appears that 4,5-disubstituted ("para"-substituted) phthalimide is the preferred chromophore for exciton coupling with other chromophores. However, the ready availability and numerous synthetic applications of 3,4,5,6-tetrachlorophthaloyl protecting group may offset the chiroptical advantage of the 4,5-dichlorophthaloyl group.

Coupling of the cinnamate and tetrachlorophthalimide chromophores, as in **21**, gives an exciton Cotton effect of very similar amplitude as that for **20**. However in **21** the lower energy CD band (at 256 nm) of the cinnamate chromophore precedes that of the tetrachlorophthalimide chromophore (at 239 nm), in contrast to the benzoate - tetrachlorophthalimide system. Furthermore, reversal of the positions of tetrachlorophthalimide chromophore and benzoate or cinnamate chromophores as in alaninol derivatives **23** and **24** has no significant effect on the amplitude of the exciton Cotton effect, when compared with the data for **20** and **21** (note, however, the sign reversal due to opposite absolute configuration).

The case of phenylalaninol derivatives (**25-30**) is more complicated. The presence of the phenyl chromophore may give rise to the tetrachlorophthalimide - phenyl coupling. This is indeed observed in the case of tetrachlorophthalimides **25** and **28**: in both cases a positive Cotton effect is observed, with low amplitude for **28** due to the contribution of two conformers, **28a** and **28b**, of which only the minor conformer **28a** contributes to the exciton Cotton effect.[6]



28a



28b

In the presence of a third, benzoate chromophore a negative exciton Cotton effect is seen for **26**, as a result of superposition of a negative Cotton effect due to the tetrachlorophthalimide/benzoate interaction and a positive Cotton effect due to the tetrachlorophthalimide/phenyl interaction, with the former dominating.[17]

In the case of **29** the net exciton Cotton effect (A = -19.1) is more negative compared to **26** due to the smaller contribution of a conformer analogous to **28b** (R = Bz).

In such complicated, trichromophoric cases substitution of the benzoate chromophore by a cinnamate chromophore, as in **27** and **30**, can simplify the interpretation of Cotton effects. Because cinnamate-tetrachlorophthalimide coupling occurs in the absorption range (240-258 nm) significantly red shifted from the ^1L_a absorption band of the phenyl chromophore, resulting negative exciton Cotton effects are predominantly due to the coupling of the cinnamate and tetrachlorophthalimide chromophores (A = -31.7 for **27** and -18.9 for **30**). Thus, the absolute configuration of an aminoalcohol can be safely determined by the tetrachlorophthalimide-cinnamate exciton coupling even in the presence of the phenyl substituent.

CONCLUSIONS

We have shown that the phthalimide chromophore can be used for stereochemical assignments (absolute configuration or conformation) in phthaloyl derivatives of aromatic amines, having p-substituted phenyl, naphtyl or indolyl chromophores. The scope of applications of the phthalimide coupling can further be extended to chlorinated phthalimides, particularly 4,5-dichloro- and 3,4,5,6-tetrachlorosubstituted derivatives. The directions of polarization of the allowed transitions in 3,6-dichloro-, 4,5-dichloro- and 3,4,5,6-tetrachlorophthalimides have been determined with the aid of LD measurements in stretched polyethylene film. The most intense π-π^* transition in these molecules is long - axis polarized, as in the case of parent phthalimide chromophore. Tetrachlorophthalimide chromophore, with absorption maximum shifted to ca. 240 nm, allows to measure exciton Cotton effect due to the interaction with the vicinal benzoate chromophore (|A| ca. 24-30 in acyclic molecules) or with the vicinal cinnamate chromophore (|A| ca. 19-24 in acyclic molecules). The cinnamate/tetrachlorophthalimide coupling is particularly useful for stereochemical assignments of molecules having additional phenyl chromophore.

EXPERIMENTAL

For general procedures see ref. 6. *N*-Phthaloyl derivatives of aminoacids were prepared according to the Nefkens method.[18] In other cases amines were refluxed with the corresponding phthaloyl anhydride in toluene or xylene with or without triethylamine,[19] the resulting *N*-phthaloyl derivative was further *O*-benzoylated or *O*-cinnamoylated,[6,20] where appropriate. N-Butylphtalimide was prepared according to literature.[21] Phthalic, 3,6-dichlorophthalic, and 3,4,5,6-tetrachlorophthalic anhydrides were commercial. 4,5-Dichlorophthalic anhydride was prepared from 4,5-dichlorophthalic acid.[22] Precursor amines, except for **3**[23] and **14**,[24] were commercial.

For LD measurements, the samples **9-12** were introduced into low-density polyethylene films from saturated chloroform solutions. The sheets were then stretched 400-600%. LD spectra were recorded on a SHIMADZU UV3100 spectrophotometer, equipped with Glan polarizers in both sample and reference beams.

***N*-Phthaloyl-L-tyrosine (1).** M.p. 162-164° (from acetone); $[\alpha]_D^{22}$ -221.7 (c 1.0, ethanol); ^{1}H NMR (acetone-d_6) δ 3.43 (dd, 1H, *J* = 14.1 and 10.8 Hz), 3.50 (dd, 1H, *J* = 14.1 and 5.8 Hz), 5.14 (dd, 1H, *J* = 10.8 and 5.8 Hz), 6.65 (m, 1H), 7.03 (m, 1H), 7.83 (m, 4H); IR (KBr) 1773, 1724, 1697 cm^{-1}.

***N*-Phthaloyl-3-(4-nitrophenyl)-L-alanine (2).** M.p. 203-5° ($CHCl_3$-hexane), lit.[25] m.p. 180-1° for L,D - 2; $[\alpha]_D^{22}$ -219.7 (c 1.0 ethanol); ^{1}H NMR ($CDCl_3$) δ 3.71 (m, 2H); 5.26 (dd, 1H, *J* = 9.3 and 7.1 Hz), 7.36 (d, 1H, *J* = 8.5 Hz), 7.76 (m, 4H), 8.07 (d, 1H, *J* = 8.5 Hz); IR (KBr) 1752, 1713 cm^{-1}.

***N*-Phthaloyl-(2*S*, 3*S*)-2-amino-3-hydroxy-3(4-methoxyphenyl)-propanoic acid (3).** M.p. 210-213° (from ethyl acetate); $[\alpha]_D^{22}$ -113.2 (c 0.64, ethanol); ^{1}H NMR (CD_3OD) δ 3.65 (s, 3H), 4.72 (d, 1H, *J* = 9.9 Hz), 5.43 (d, 1H, *J* =9.9 Hz), 6.71 (d, 2H, *J* = 8.7 Hz), 7.20 (d, 2H, *J* = 8.7 Hz), 7.70 (s, 5H); IR (KBr) 1774, 1713 cm^{-1}. Anal. Calcd for $C_{18}H_{15}NO_6$: C, 63.34; H, 4.43; N, 4.10. Found: C, 63.01; H, 4.08; N, 4.12.

***N*-Phthaloyl-3-(1-naphthyl)-L-alanine (4).** M.p. dec. > 290°; $[\alpha]_D^{20}$ -171.4 (c 0.085, methanol); ^{1}H NMR (CD_3OD) δ 3.78 (dd, 1H, *J* = 3.6 and 14.7 Hz), 4.06 (dd, 1H, J = 11.7 and 14.7 Hz), 5.24 (dd,1H, J =3.6 and 11.7 Hz), 7.0-8.2 (m 11H); IR (KBr) 1774, 1707 cm^{-1}. Anal. Calcd for $C_{21}H_{15}NO_4$: C, 73.03; H, 4.38; N,4.06. Found C, 72.62; H, 4.18; N, 3.90.

***N*-Phthaloyl-3-(2-naphthyl)-L-alanine (5).** M.p. 330-333° (dec.); $[\alpha]_D^{20}$ -167.5 (c 0.26, methanol); ^{1}H NMR (CD_3OD) δ 3.70 (m, 2H), 5.06 (m, 1H), 7.2-7.8 (m, 11H); IR (KBr) 1775, 1708 cm^{-1}. Anal. Calcd for $C_{21}H_{15}NO_4$: C, 73.03; H, 4.38; N, 4.06. Found C, 72.70; H, 4.20; N, 3.80.

***N*-Phthaloyl-L-tryptophan (6).** Viscous oil; $[\alpha]_D^{20}$ -246.4 (c 1.0, ethanol); ^{1}H NMR (acetone-d_6) δ 3.73 (dd, 1H , *J*=5.3 and 15.3 Hz), 3.82 (dd, 1H, *J* = 10.6 and 15.3 Hz), 5.32 (dd, 1H, *J* = 5.3 and 10.6 Hz), 6.90-7.85 (m, 9H), 7.75 (s, br, 1H); IR (film) 1776, 1708 cm^{-1}.

***N*-Phthaloyl-(*R*)-1-(1-naphthyl)-ethylamine (7).** M.p. 80-82° (from petroleum ether); $[\alpha]_D^{20}$ +135.0 (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.03 (d, 3H, *J* = 7.1 Hz), 6.32 (q, 1H, *J* = 7.1 Hz), 7.4-8.3 (m, 11H); IR (KBr) 1774, 1707 cm^{-1}. Anal. Calcd for $C_{20}H_{15}NO_2$: C, 79.71; H, 5.02; N, 4.65. Found C, 79.24; H, 4.80; N, 4.56.

***N*-(3',4',5',6'-Tetrachlorophthaloyl)-(*R*)-1-(1-naphthyl)-ethylamine (8).** M.p. 142-143° (from petroleum ether); $[\alpha]_D^{20}$ +121.1 (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.03 (d, 3H, *J* = 7.0 Hz), 6.33 (q, 1H, *J* = 7.0 Hz), 7.4-8.2 (m, 7H); IR (KBr) 1777, 1716 cm^{-1}. Anal. Calcd for $C_{20}H_{11}Cl_4NO_2$: C, 54.70; H, 2.53; N, 3.19. Found C, 54.25; H, 2.50; N, 3.09.

***N*-Butyl-3,6-dichlorophthalimide (10).** M.p. 125-7° (from ethyl acetate-hexane); ^{1}H NMR ($CDCl_3$) δ 0.95 (t, 3H, *J* = 7.3 Hz), 1.36 (m, 2H), 1.66 (m, 2H), 3.70 (t, 2H, *J* = 7.3 Hz), 7.56 (s, 2H); IR (KBr) 1769, 1704 cm^{-1}.

***N*-Butyl-4,5-dichlorophthalimide (11).** M.p. 78-9° (from hexane); ^{1}H NMR ($CDCl_3$) δ 0.91 (t, 3H, *J* = 7.3 Hz), 1.35 (m, 2H), 1.65 (m, 2H), 3.68 (t, 2H, *J* = 7.3 Hz), 7.92 (s, 2H); IR (KBr) 1776, 1715 cm^{-1}.

***N*-Butyl-3,4,5,6-tetrachlorophthalimide (12).** M.p. 151° (from ethanol); ^{1}H NMR ($CDCl_3$) δ 0.95 (t, 3H, *J* = 7.3 Hz), 1.37 (m, 2H), 1.66 (m, 2H), 3.71 (t, 2H, *J* = 7.3 Hz); IR (KBr) 1773, 1706 cm^{-1}.

***N,N'*-Di-(3',4',5',6'-tetrachlorophthaloyl)-(1*R*,2*R*)-diaminocyclohexane (13).** M.p. 230-4° (from n-propanol); $[\alpha]_D^{20}$ -66.0 (c 1.0 dioxane); ^{1}H NMR (dioxane-d_8) δ 1.45-1.55 (m, 3H), 1.80-1.92 (m, 3H), 2.20-2.36 (m, 2H), 4.95 (m, 2H); IR (KBr) 1776, 1728 cm^{-1}. Anal. Calcd for $C_{22}H_{10}Cl_8N_2O_4$ x C_6H_6 : C, 46.19; H, 2.20; N, 3.85. Found C, 45.58; H, 1.80; N, 3.84. This compound forms solid-state complexes with many solvents, eg benzene, toluene, dioxane, acetone, acetonitryle, as evidenced by the NMR data and broad m.p.'s.

***O*-Benzoyl-*N*-(3',4',5',6'-tetrachlorophthaloyl)-(1*R*, 2*R*)-2-aminocyclohexanol (14).** M.p. 190-3° (from ethyl acetate-hexane); $[\alpha]_D^{20}$ -92.3 (c 0.8 $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.35-1.60 (m, 3H), 1.84-1.96 (m, 3H), 2.34-2.56 (m, 2H), 4.41 (ddd, 1H, *J* = 12.7, 10.5 and 4.1 Hz), 5.56 (m, 1H), 7.34-7.41 (m, 2H), 7.45-7.54 (m, 1H), 7.85-7.91 (m, 2H); IR (KBr) 1774, 1712 cm^{-1}. Anal. Calcd for $C_{21}H_{15}Cl_4NO_4$ C, 51.77; H, 3.10; N, 2.88. Found: C, 51.66; H, 3.01; N, 2.88.

***N*-(3',6'-Dichlorophthaloyl)-(*R*)-1-amino-2-propanol (15).** M.p. 125-7° (from ethyl acetate-hexane); $[\alpha]_D^{22}$ -21.3 (c 1.0 $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.28 (d, 3H, *J* = 6.3 Hz), 2.0 (d, OH, *J* = 6.0 Hz), 3.75 (m, 2H), 4.13 (m, 1H), 7.58 (s, 2H); IR (KBr) 1775, 1718 cm^{-1}.

***O*-Benzoyl-*N*-(3',6'-dichlorophthaloyl)-(*R*)-1-amino-2-propanol (16).** M.p. 147-9° (from ethyl acetate-hexane); $[\alpha]_D^{22}$ -87.0 (c 1.0 $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.45 (δ, 3H, *J* = 6.3 Hz), 3.88 (dd, 1H, *J* = 14.2 and 3.3 Hz), 4.07 (dd, 1H, *J* = 14.2 and 8.2 Hz), 5.41 (m, 1H), 7.4-7.6 (m, 3H), 7.54 (s, 2H), 8.00 (m, 2H); IR (KBr) 1778, 1713 cm^{-1}. Anal. Calcd for $C_{18}H_{13}Cl_2NO_4$: C, 57.15; H, 3.47; N, 3.70. Found: C, 56.87; H, 3.65; N, 3.50.

***N*-(4',5'-Dichlorophthaloyl)-(*R*)-1-amino-2-propanol (17).** M.p. 142-3° (from ethyl acetate-hexane); $[\alpha]_D^{22}$ -27.6 (c 1.0 $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.27 (d, 3H, *J* = 6.3 Hz), 2.1 (bs, OH), 3.70 (dd, 1H, *J* = 14.0 and 7.0 Hz), 3.76 (dd, 1H, *J* = 14.0 and 4.5 Hz), 4.10 (m, 1H), 7.94 (s, 2H); IR (KBr) 1775, 1703 cm^{-1}.

***O*-Benzoyl-*N*-(4',5'-dichlorophthaloyl)-(*R*)-1-amino-2-propanol (18).** M.p. 118-120° (from ethyl acetate-hexane); $[\alpha]_D^{22}$ -108.7 (c 0.8 $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.43 (δ, 3H, *J* = 6.4 Hz), 3.87 (dd, 1H, *J* = 14.2 and 3.2 Hz), 4.04 (dd, 1H, *J* = 14.2 and 8.2 Hz), 5.42 (m, 1H), 7.38-7.45 (m, 2H), 7.50-7.57 (m, 1H), 7.90 (s, 2H), 7.94-7.98 (m, 2H); IR (KBr) 1786, 1731, 1716 cm^{-1}. Anal. Calcd for $C_{18}H_{13}Cl_2NO_4$: C, 57.15; H, 3.47; N, 3.70. Found C, 56.94; H, 3.14; N, 3.62.

***N*-(3',4',5',6'-Tetrachlorophthaloyl)-(*R*)-1-amino-2-propanol (19).** M.p. 182-4° (from methanol); $[\alpha]_D^{22}$ -22.4 (c 1.0 $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.28 (d, 3H, *J* = 6.3 Hz), 2.0 (bs, OH), 3.74 (d, 2H, *J* = 5.8 Hz), 4.13 (m, 1H); IR (KBr) 1771, 1700 cm^{-1}.

***O*-Benzoyl-*N*-(3',4',5',6'-tetrachlorophthaloyl)-(*R*)-1-amino-2-propanol (20).** M.p. 136-8° (from ethyl acetate-hexane); $[\alpha]_D^{22}$ -85.5 (c 1.0 $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.45 (d, 3H, *J* = 6.4 Hz), 3.89 (dd, 1H, *J* = 14.2 and 3.3 Hz), 4.08 (dd, 1H, *J* = 14.2 and 8.3 Hz), 5.41 (m, 1H), 7.38-7.45 (m, 2H), 7.51-7.58 (m, 1H), 7.94-8.00 (m, 2H); IR (KBr) 1777, 1710 cm^{-1}. Anal. Calcd for $C_{18}H_{11}Cl_4NO_4$: C, 48.35; H, 2.48; N, 3.13. Found: C, 48.24; H, 2.53; N, 3.21.

***O*-Cinnamoyl-*N*-(3',4',5',6'-tetrachlorophthaloyl)-(*R*)-1-amino-2-propanol (21).** M.p. 163-5° (from ethyl acetate); $[\alpha]_D^{22}$ -137.2 (c 1.0 $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.39 (d, 3H, *J* = 6.4 Hz), 3.84 (dd, 1H, *J* = 14.2 and 3.4 Hz), 3.98 (dd, 1H, *J* = 14.2 and 7.9 Hz), 5.33 (m, 1H), 6.33 (d, 1H, *J* = 16.0 Hz), 7.35-7.40 (m, 3H), 7.47-7.53 (m, 2H), 7.60 (d, 1H, *J* = 16.0 Hz); IR (KBr) 1777, 1723, 1635 cm^{-1}. Anal. Calcd for $C_{20}H_{13}Cl_4NO_4$: C, 50.77; H, 2.77; N, 2.96. Found: C, 50.60; H, 2.41; N, 2.99.

***N*-(3',4',5',6'-Tetrachlorophthaloyl)-(*S*)-2-amino-1-propanol (22).** M.p. 232-4° (from dioxane); $[\alpha]_D^{22}$ +34.2 (c 0.7 dioxane); ^1H NMR (dioxane-d_8) δ 1.36 (d, 3H, *J* = 7.0 Hz), 3.64 (dd, 1H, *J* = 11.0 and 5.6 Hz), 3.91 (dd, 1H, *J* = 10.8 and 9.9 Hz), 4.38 (m, 1H); IR (KBr) 1772, 1706 cm^{-1}.

***O*-Benzoyl-*N*-(3',4',5',6'-tetrachlorophthaloyl)-(*S*)-2-amino-1-propanol (23).** M.p. 184-6° (from ethyl acetate), $[\alpha]_D^{22}$ +48.2 (c 1.0 $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.62 (d, 3H, *J* = 6.9 Hz), 4.55 (dd, 1H, *J* = 10.8 and 4.2 Hz), 4.79 (dd, 1H, *J* = 10.8 and 9.5 Hz), 4.83 (m, 1H), 7.37-7.45 (m, 2H), 7.50-7.60 (m, 1H), 7.90-7.97 (m, 2H); IR (KBr) 1772, 1707 cm^{-1}. Anal. Calcd for $C_{18}H_{11}Cl_4NO_4$: C, 48.35; H, 2.48; N, 3.13. Found: C, 48.21; H, 2.65; N, 3.11.

***O*-Cinnamoyl-*N*-(3',4',5',6'-tetrachlorophthaloyl)-(*S*)-2-amino-1-propanol (24).** M.p. 193.5-195° (from ethyl acetate), $[\alpha]_D^{22}$ +115.4 (c 1.0 $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.55 (d, 3H, *J* = 6.9 Hz), 4.46 (dd, 1H, *J* = 10.8 and 4.1 Hz), 4.66 (dd, 1H, *J* = 10.8 and 9.6 Hz), 4.72 (m, 1H), 6.33 (d, 1H, *J* = 16.0 Hz), 7.34-7.39 (m, 3H), 7.45-7.50 (m, 2H), 7.62 (d, 1H, *J* = 16.0 Hz); IR (KBr) 1773, 1707 cm^{-1}. Anal. Calcd for $C_{20}H_{13}Cl_4NO_4$: C, 50.77; H, 2.77; N, 2.96. Found: C, 50.67; H, 2.43; N, 3.10.

***N*-(3',4',5',6'-Tetrachlorophthaloyl)-(*R*)-3-phenyl-2-amino-1-propanol (25).** M.p. 158-160° (from ethyl acetate-hexane), $[\alpha]_D^{22}$ +100.4 (c 1.0 $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.17 (dd, OH, *J* = 8.2 and 4.0 Hz), 3.12-3.26 (m, 2H), 3.93 (dt, 1H, *J* = 11.7 and 4.0 Hz), 4.12 (dt, 1H, *J* = 11.7 and 8.2 Hz), 4.68 (ddd, 1H, *J* = 12.0, 8.2 and 4.0 Hz), 7.15-7.30 (m, 5H); IR (KBr) 1777, 1718 cm^{-1}. Anal. Calcd for $C_{17}H_{11}Cl_4NO_3$: C, 48.71; H, 2.65; N, 3.34. Found: C, 48.58; H, 2.20; N, 3.32.

***O*-Benzoyl-*N*-(3',4',5',6'-tetrachlorophthaloyl)-(*R*)-3-phenyl-2-amino-1-propanol (26).** M.p. 148-9° (from ethyl acetate-hexane). $[\alpha]_D^{22}$ +48.3 (c 1.0 $CHCl_3$); ^1H NMR ($CDCl_3$) δ 3.30 (dd, 1H, *J* = 14.0 and 6.7 Hz), 3.42 (dd, 1H, *J* = 14.0 and 9.8 Hz), 4.60 (dd, 1H, *J* = 11.4 and 4.1 Hz), 4.86 (dd, 1H, *J* = 11.4 and 9.3 Hz), 5.00 (m, 1H), 7.16-7.30 (m, 5H), 7.35-7.43 (m, 2H), 7.50-7.57 (m, 1H), 7.88-7.93 (m, 2H); IR (KBr) 1776, 1732, 1716 cm^{-1}. Anal. Calcd for $C_{24}H_{15}Cl_4NO_3$: C, 55.09; H, 2.89; N, 2.68. Found: C, 54.96; H, 2.54; N, 2.84.

***O*-Cinnamoyl-*N*-(3',4',5',6'-tetrachlorophthaloyl)-(*R*)-3-phenyl-2-amino-1-propanol (27).** M.p. 118-120° (from ethyl acetate-hexane). $[\alpha]_D^{22}$ -10.4 (c 1.0 $CHCl_3$); ^1H NMR ($CDCl_3$) δ 3.24 (dd, 1H, *J* = 14.0 and 6.6 Hz), 3.36 (dd, 1H, *J* = 14.0 and 9.8 Hz), 4.53 (dd, 1H, *J* = 11.4 and 4.3 Hz), 4.75 (dd, 1H, *J* = 11.4 and 9.5 Hz), 4.91 (m, 1H), 6.32 (d, 1H, *J* = 16.0 Hz), 7.15-7.29 (m, 5H), 7.33-7.39 (m, 3H), 7.43-7.50 (m, 2H), 7.61 (d, 1H, *J* = 16.0 Hz); IR (KBr) 1777, 1714, 1637 cm^{-1}. Anal. Calcd for $C_{26}H_{17}Cl_4NO_4$: C, 56.86; H, 3.13; N, 2.55. Found: C, 56.68; H, 3.25; N, 2.56.

***N*-(3',4',5',6'-Tetrachlorophthaloyl)-(1*S*,2*S*)-2-amino-1-phenyl-1,3-propanodiol (28).** M.p. 190-3° (from methanol). $[\alpha]_D^{22}$ +47.6 (c 1.0 $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.38 (bs, OH), 2.97 (d, OH, *J* = 6.0 Hz), 3.82 (dd, 1H, *J* = 12.1 and 3.8 Hz), 3.97 (m, 1H), 4.71 (dt, 1H, *J* = 8.0 and 4.0 Hz), 5.31 (dd, 1H, *J* = 8.0 and 6.0 Hz), 7.3-7.5 (m, 5H); IR (KBr) 1778, 1720 cm^{-1}. Anal. Calcd for $C_{17}H_{11}Cl_4NO_4$: C, 46.92; H, 2.55; N, 3.22. Found: C, 46.97; H, 2.47; N, 3.16.

1-*O*-Benzoyl-*N*-(3',4',5',6'-tetrachlorophthaloyl)-(1*S*,2*S*)-2-amino-1-phenyl-1,3-propanodiol (29). M.p. 151-4° (from methanol). $[\alpha]_D^{22}$ +3.6 (c 0.6 $CHCl_3$); ^1H NMR ($CDCl_3$) δ 3.0 (d, OH, *J* = 6.4 Hz), 4.42 (dd, 1H, *J* = 11.8 and 4.0 Hz), 4.79 (dd, 1H, *J* = 11.8 and 9.2 Hz), 5.02 (m, 1H), 5.44 (dd, 1H, *J* = 8.3 and 6.4 Hz), 7.28-7.55 (m, 8H), 7.82-7.87 (m, 2H); IR (KBr) 1780, 1730, 1715 cm^{-1}. Anal. Calcd for $C_{24}H_{15}Cl_4NO_5$: C, 53.46; H, 2.80; N, 2.60. Found: C, 53.15; H, 2.51; N, 2.53.

1-*O*-Cinnamoyl-*N*-(3',4',5',6'-tetrachlorophthaloyl)-(1*S*,2*S*)-2-amino-1-phenyl-1,3-propanodiol (30). M.p. 130-6° (from methanol). $[\alpha]_D^{22}$ -45.3 (c 1.0 $CHCl_3$); ^1H NMR ($CDCl_3$) δ 3.01 (d, OH, *J* = 6.5 Hz), 4.34 (dd, 1H, *J* = 11.9 and 3.9 Hz), 4.71 (dd, 1H, *J* = 11.9 and 9.4 Hz), 4.95 (m, 1H), 5.37 (dd, 1H, *J* = 8.1 and 6.5 Hz), 6.27 (d, 1H, *J* = 16.0 Hz), 7.31-7.48 (m, 10H), 7.55 (d, 1H, *J* = 16.0 Hz); IR (KBr) 1777, 1714, 1632 cm^{-1}. Anal. Calcd for $C_{26}H_{17}Cl_4NO_5$: C, 55.25; H, 3.03; N, 2.48. Found: C, 54.85; H, 2.97; N, 2.43.

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