Pergamon

Tetrahedron: *Asymmetry* 10 (1999) 4585–4590

TETRAHEDRON:
ASYMMETRY

Absolute configuration of α-phthalimido carboxylic acid derivatives from circular dichroism spectra

P. Skowronek * and J. Gawroński

Department of Chemistry, Adam Mickiewicz University, Poznań, Poland

Received 28 October 1999; accepted 18 November 1999

Abstract

It is demonstrated that the Cotton effects due to the 220 nm phthalimide π–π* transition observed for a series of derivatives of α-phthalimidocarboxylic acids unequivocally reflect the amino acid absolute configuration. This method is based on the exciton coupling of the allowed transitions of the phthalimide and the carboxylic acid derivative chromophores.

1. Introduction

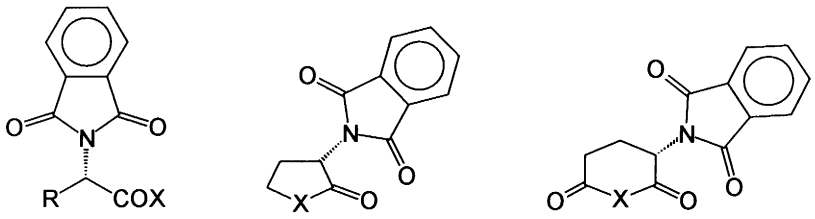
Optically active α-aminocarboxylic acids play an important role in organic chemistry and biochemistry and determination of their configuration is a crucial part of their asymmetric synthesis. However, in the literature there are only few examples of using CD spectra of α-amino acid chromophoric derivatives for determining absolute configuration. Although the carboxyl chromophore (and its derivatives) did not find many applications in the exciton coupling method, mainly due to the high energy of the π–π* transition placed below 190 nm, examples of the CD spectra of *N*-salicylidene[1] and *N*-(4-bromobenzoyl)[2] derivatives of α-amino acids show that exciton coupling with the carboxyl chromophore can be effective. The phthaloyl group is one of the most frequently used protecting groups in amino acid chemistry, but surprisingly to date this derivative has not been used for the determination of the absolute configuration of α-amino acids. Recently we have demonstrated that the phthaloyl group is an excellent chromophoric derivative for the non-empirical determination of the absolute configuration of diamines, aminoalcohols, and arylamines, based on the exciton coupling mechanism.[3,4]

* Corresponding author.

0957-4166/99/$ - see front matter
PII: S0957-4166(99)00521-2

2. Results and discussion

In this report we show that *N*-phthaloyl α-amino acids and their derivatives exhibit Cotton effects at ca. 220 nm, i.e. at the maximum absorption for the π–π* transition of the phthalimide chromophore, whose sign unequivocally reflects the absolute configuration of the α-amino acids or its derivative. Both acyclic **1a**–**1g** and cyclic **2a**–**2c**, **3a**, **3b** derivatives of *S* configuration (i.e. belonging to the L configurational series) are characterized by a negative Cotton effect at 220 nm (Scheme 1).†



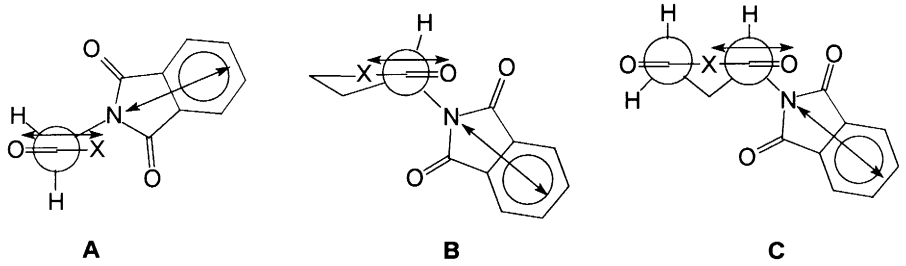
	R	X	Δε
1a	Me	OH	-12.0
1b	i-Pr	OH	-15.9
1c	i-Bu	OH	-12.7
1d	Me	OMe	-10.3
1e	i-Pr	OMe	-11.0
1f	i-Bu	OMe	-11.8
1g	CH_2SMe	OMe	-10.0

	X	Δε
2a	O	-4.0
2b	NH	-4.9
2c	S	-3.0*

	X	Δε
3a	O	-7.8
3b	NH	-7.1

Scheme 1.

The negative π–π* transition Cotton effect of α-phthalimido carboxylic acid and derivatives results from the excited state interaction of the electric dipole transition moments of the phthalimide (polarized along the C_2 axis of the chromophore)[3,4] and the carboxylic chromophore (Scheme 2).



A **B** **C**

Scheme 2. Minimum energy conformations of α-phthalimido carboxylic acid derivatives

In the case of acyclic amino acid derivatives, molecular mechanics calculations suggest that conformation **A** is preferred. The preferred conformation of acyclic compounds **1a**–**1g** is similar to that found for α-amino acids[5] and for α-hydroxyacids both in solution[5] and in the solid state,[6] as well as for α-phenylacids.[7] Minimum energy conformations of the cyclic compounds **2a**–**2c** were determined as **B** and for **3a**,**3b** as **C** by molecular mechanics calculations and proved by measurement of the $^3J_{H\alpha,H\beta}$ coupling constants (**2a**: 9.3, 10.7; **2b**: 9.9, 9.9; **2c**: 7.0, 13.0; **3a**: 5.8, 7.0; **3b**: 5.3, 12.7 Hz). These data correspond well with the conformation reported for derivatives of homoserine lactone[8,9] and for substituted glutaric anhydride and glutarimides.[10–13]

† The CD spectrum of the thiolactone **2c** is more complicated due to the contribution of the thiolactone σ–π* transition at around 235 nm. Nevertheless, a negative Cotton effect at ca. 230 nm ($\Delta\varepsilon$ −3.0) was found by subtracting the CD spectrum of L-homocysteine thiolactone hydrochloride from the CD spectrum of **2c**.

The negative helicity of the two-dipole system results in a negative Cotton effect at 220–225 nm (the other part of the couplet is expected to appear below 200 nm, i.e. where the carboxylic acid derivative π–π* absorption band is located). Calculation of the sign of the rotational strength[14] for the long wavelength chromophore as a function of the dihedral angle N–C*–C(O)–X gives negative rotational strength for all negative values of the dihedral angle (Fig. 1). This result is in agreement with the sign of the experimental Cotton effects for the phthalimide chromophore at 220–225 nm in derivatives **1**–**3**.

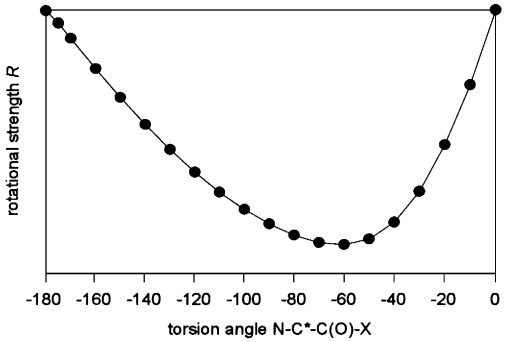


Fig. 1. Calculated rotational strength of the phthalimide 220 nm transition as a function of the N–C*–C(O)–X angle

The CD spectra of *N*-phthaloyl amino acids are affected by the solvent; however in all cases studied a negative Cotton effect at 220–225 nm was consistently observed (Fig. 2).

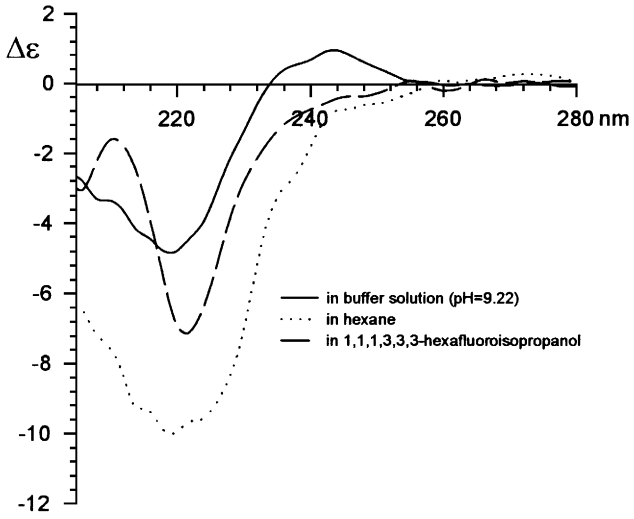


Fig. 2. CD spectra of *N*-phthaloyl-l-alanine **1a** in various solvents

In the case of the solution in borate buffer (pH 9.2) the amino acid derivative is ionized; the carboxylate ion transition, occurring at a longer wavelength than that of the carboxylic acid, gives rise to a weak Cotton effect at ca. 245 nm (Fig. 2). This Cotton effect is apparently due to the coupling of the carboxylate transition dipole to the dipole of the 240 nm phthalimide transition, polarized perpendicularly to the chromophore C_2 axis.[3,4]

3. Conclusion

In summary, we have shown that the absolute configuration of an α-amino acid or its derivative can be readily determined from the CD spectrum of its *N*-phthaloyl derivative. The sign of long-wavelength

Cotton effect at 220 nm directly reflects the helicity of the bichromophoric system, i.e. for a negative sign of Cotton effect the absolute configuration of the *N*-phthaloyl-α-amino acid or its derivative is *S*. This statement is straightforward and insensitive to additional non-chromophoric substituents for rigid cyclic derivatives of *N*-phthaloyl-α-amino acids as well as for acyclic *N*-phthaloyl-α-amino acids or its esters. In doubtful cases a conformational analysis is necessary to establish the correct helicity of bichromophoric systems. Further applications are now under development.

4. Experimental

IR spectra were recorded with a FT IR Bruker IFS 113v spectrophotometer. ^{1}H NMR were recorded on a Varian EM-360 spectrometer in $CDCl_3$ solutions unless noted otherwise. CD spectra were taken with a Jobin-Yvon III dichrograph in acetonitrile solutions. Optical rotations were measured with a Perkin–Elmer 243B polarimeter. The enantiomeric purity of the compounds **1a**–**c** was better than 92%, as determined by HPLC analysis on a DAICEL OD-H 250/4 column. Melting points are uncorrected.

4.1. N-*Phthaloyl*-L-*amino acids*

The title compounds were synthesized according to literature procedures.[15,16]

4.1.1. N-*Phthaloyl*-L-*alanine* ***1a***

M.p. 148–149°C (lit. 144–146°C[15]); $[\alpha]_D$ −25.7, c=10, EtOH (lit. $[\alpha]_D$ −24.2, c=3, EtOH[15]).

4.2. N-*Phthaloyl*-L-*valine and* N-*phthaloyl*-L-*leucine*

The title compounds were synthesized by melting 1 equiv. of the amino acid with 1 equiv. of phthalic anhydride at 140°C. Crude *N*-phthaloylamino acids were purified by crystallization from cyclohexane.

4.2.1. N-*Phthaloyl*-L-*valine* ***1b***

M.p. 110–112°C (lit. 114–115°C[16]); $[\alpha]_D$ −71.7, c=1.46, EtOH (lit. $[\alpha]_D$ −68.5, EtOH[16]).

4.2.2. N-*Phthaloyl*-L-*leucine* ***1c***

M.p. 118–120°C (lit. 118–119°C[16]); $[\alpha]_D$ −24.2, c=3, EtOH (lit. $[\alpha]_D$ −22.1, EtOH[16]).

4.3. N-*Phthaloyl*-L-*amino acid methyl esters*

The title compounds were prepared from *N*-phthaloyl-L-amino acid chlorides.[17] Acid chlorides were used without purification. Methyl esters were obtained from acid chlorides by dissolving in methanol at 0°C. Products were purified by column chromatography on silica gel.

4.3.1. N-*Phthaloyl*-L-*alanine methyl ester*[18] ***1d***

Yield 87%; m.p. 33–34°C; $[\alpha]_D$ −17.1, c=1, MeOH; ^{1}H NMR δ 1.7 (d, J=7.4 Hz, 3H), 3.75 (s, 3H), 4.98 (q, J=7.4 Hz, 1H), 7.2–7.8 (m, 4H); IR (KBr) 2957, 1708, 1748, 1714, 1391, 1245, 1147, 1072, 883, 718, 530 cm^{-1}.

4.3.2. N-*Phthaloyl*-L-*valine methyl ester* ***1e***

Yield 89%; oil; $[\alpha]_D$ −69.3, c=1, MeOH (lit. $[\alpha]_D$ −66.7, c=1.2, MeOH[19]); ^{1}H NMR δ 0.9 (d, J=6.8 Hz, 3H), 1.15 (d, J=6.7 Hz, 3H), 2.76 (m, 1H), 3.7 (s, 3H), 4.5 (d, J=8.4 Hz, 1H), 7.7–7.9 (m, 4H); IR (film) 2963, 1769, 1714, 1467, 1383, 1354, 1332, 1073, 719 cm^{-1}.

4.3.3. N-*Phthaloyl*-L-*leucine methyl ester* ***1f***

Yield 95%; oil; $[\alpha]_D$ −30.2, c=1, MeOH (lit. $[\alpha]_D$ −20.8, c=5.6, $CHCl_3$[20]); ^{1}H NMR δ 0.93 (d, J=6.4 Hz, 3H), 0.96 (d, J=5.9 Hz, 3H), 1.5 (m, 1H), 1.96 (ddd, J=4.4, 10, 14.1 Hz, 1H), 2.3 (ddd, J=4.1, 11.6, 14.2 Hz, 1H), 3.37 (s, 3H), 5.0 (dd, J=4.4, 11.5 Hz, 1H), 7.7–7.9 (m, 4H); IR (film) 2958, 2872, 1776, 1746, 1715, 1387, 1255, 720, 530 cm^{-1}.

4.3.4. N-*Phthaloyl*-L-*cysteine methyl ester* ***1g***

Obtained by treatment of *N*-phthaloyl-L-cysteine with excess diazomethane in methanol solution, oil; $[\alpha]_D$ −105.5, c=1, $CHCl_3$; ^{1}H NMR δ 2.11 (s, 3H), 3.35 (d, J=7.6 Hz, 2H), 3.77 (s, 3H), 5.04 (t, J=8.0 Hz, 1H), 7.82 (m, 4H); IR (film) 1770, 1715, 1385, 1245, 1100, 715 cm^{-1}.

*4.3.5. (*S*)*-N-*Phthaloyl-α-amino-γ-butyrolactone* ***2a***

N-Carboethoxyphthalimide (87 mg, 0.4 mmol) was dissolved in DMF (1 ml) and α-amino-γ-butyrolactone hydrochloride (55 mg, 0.4 mmol) and Et_3N (40 mg, 0.4 mmol) were added. The mixture was stirred for 4 h at room temperature. Half of the solvent was evaporated in vacuo and water (1 ml) was added to give 55 mg (62%) of **2a**, m.p. 181–182°C; $[\alpha]_D$ −29.2, c=1, $CHCl_3$ (lit. $[\alpha]_D$ −39.5, c=1, MeCN[21]); ^{1}H NMR δ 2.6 (m, 1H), 2.8 (m, 1H), 4.4 (m, 1H), 4.6 (dt, J=2.2, 9.0 Hz, 1H), 5.1 (dd, 9.0, 10.0 Hz, 1H), 7.7–7.9 (m, 4H); IR (KBr) 3473, 2991, 2924, 1788, 1773, 1713, 1469, 1403, 1387, 1230, 1204, 1124, 1089, 1033, 1015, 1007, 895, 798, 717, 531 cm^{-1}.

*4.3.6. (*S*)*-N-*Phthaloyl-α-amino-γ-butyrolactam* ***2b***

L-2,4-Diaminobutyric acid dihydrochloride (195 mg, 1.02 mmol) and HMDS (4 ml) were refluxed in acetonitrile (5 ml) for 72 h.[22] The solvents were evaporated and the residue was dissolved in $CHCl_3$. After filtration the clear solution was evaporated to give 89 mg of crystalline α-amino-γ-butyrolactam (yield 88%).

To the lactam (39 mg, 0.39 mmol) in DMF (0.5 ml) *N*-carboethoxyphthalimide (85 mg, 0.39 mmol) was added and the solution was stirred for 4 h at room temperature. Half of solvent was evaporated and water (1 ml) was added to give 61 mg (68%) of **2b**, m.p. 192–194°C; $[\alpha]_D$ −56.2, c=0.445, $CHCl_3$; ^{1}H NMR δ 2.56 (m, 2H), 3.5 (q, J=7.9, 9.3 Hz, 1H), 3.6 (t, J=7.9 Hz, 1H), 4.95 (t, J=9.9 Hz, 1H), 6.9 (s, 1H), 7.7–7.9 (m, 4H); IR (KBr) 3431, 3353, 2929, 1773, 1704, 1466, 1425, 1395, 1292, 1265, 1192, 1135, 1044, 1027, 898, 802, 722, 640, 562, 525 cm^{-1}.

Racemic form of the compound **2b** was reported.[23]

*4.3.7. (*S*)*-N-*Phthaloyl-α-amino-γ-butyrothiolactone* ***2c***

N-Phthaloyl-L-methionine[21,24] (72 mg, 0.48 mmol) was dissolved in CH_2Cl_2 (3 ml) and $SOCl_2$ (3 ml) was added. After 2 h of refluxing, the solution was evaporated to dryness. Crude acid chloride was dissolved in CS_2 (10 ml) and after addition of 3 equivalents $SnCl_4$ in CS_2 (10 ml) the solution was refluxed with stirring for 4 h.[25] Afterwards ice (0.5 g) and 2N HCl (4 ml) were added to the solution. The product was extracted with benzene and purified by column chromatography; **2c** was obtained as an oil, yield 48 mg (40%); $[\alpha]_D$ −56, c=1, $CHCl_3$ (lit. $[\alpha]_D$ −4.5, c=0.85, $CHCl_3$[26]); ^{1}H NMR δ 2.6 (m, 1H), 2.9 (m, 1H), 3.5 (m, 2H), 5.0 (dd, J=7.2, 13.0 Hz, 1H), 7.76–7.87 (m, 4H); IR (KBr) 3040, 2900, 1720, 1680, 1380, 1100, 710 cm^{-1}.

4.3.8. N-*Phthaloyl*-L-*glutamic acid anhydride* ***3a***

To *N*-phthaloyl-L-glutamic acid[27] (40 mg, 0.14 mmol) in THF (1 ml) DCC (33 mg, 0.16 mmol) in THF (1 ml) was added. After removal of dicyclohexylurea by filtration the anhydride **3b** crystallized, yield 26 mg (71%); m.p. 190–193°C (lit. 200–202°C[28]); $[\alpha]_D$ −36.4, c=1, dioxane (lit. $[\alpha]_D$ −47.0, c=1, dioxane[28]); ^{1}H NMR (acetone-d_6) 2.3 (ddd, J=3.0, 5.7, 13.1 Hz, 1H), 2.8 (ddd, J=5.0, 13.1, 13.1 Hz, 1H), 3.15 (ddd, J=3.0, 5.0, 17.8 Hz, 1H), 3.3 (ddd, J=5.7, 13.1, 17.8 Hz, 1H), 5.45 (dd, J=5.8, 7.0 Hz, 1H), 7.9 (s, 4H).

*4.3.9. (*S*)*-N-*Phthaloyl-α-aminoglutarimide (thalidomide* ***3b****)*

This compound was obtained according to the recorded procedure,[29] m.p. 268–270°C; $[\alpha]_D$ −54.4, c=1, DMF (lit. −64.2, c=1, DMF[29]).

Acknowledgements

This work was supported by the Committee for Scientific Research (KBN), grant no. 3T09A/08/10.

References

1. Smith, H. S. *Chem. Rev.* **1983**, *83*, 359–377.
2. Molinski, T. F.; Ireland, C. M. *J. Org. Chem.* **1988**, *53*, 2103–2105.
3. Kaźmierczak, F.; Gawrońska, K.; Rychlewska, U.; Gawroński, J. *Tetrahedron: Asymmetry* **1994**, *5*, 527–530.
4. Gawroński, J.; Kaźmierczak, F.; Gawrońska, K.; Rychlewska, U.; Nordén, B.; Holmén, A. *J. Am. Chem. Soc.* **1998**, *120*, 12083–12091.
5. Craig, J. C.; Pereira Jr., W. E. *Tetrahedron* **1970**, *26*, 3457–3460.
6. Gawroński, J.; Gawrońska, K.; Skowronek, P.; Rychlewska, U.; Warżajtis, B.; Rychlewski, J.; Hoffman, M.; Szarecka, A. *Tetrahedron* **1997**, *53*, 6113–6144.
7. Klyne, W.; Scopes, P. M.; Thomas, R. N.; Dahn H. *Helv. Chim. Acta* **1971**, *54*, 2420–2430.
8. Son, J.-K.; Kalvin, D.; Woodart, R. W. *Tetrahedron Lett.* **1988**, *29*, 4045–4048.
9. Meguro, H.; Konno, T.; Tuzimura, K. *Tetrahedron Lett.* **1972**, 3165–3168.
10. Połoński, T. *J. Chem. Soc., Perkin Trans. 1* **1988**, 639–648.
11. Allen, F. H.; Trotter, J. *J. Chem. Soc. (B)* **1971**, 1073–1075.
12. Caira, M. R.; Botha S. A.; Falangan D. R. *J. Chem. Crystallography* **1994**, *24*, 95–99.
13. Reepmayer, J. C.; Rhodes, M. O.; Cox, D. C.; Silverton, J. V. *J. Chem. Soc., Perkin Trans. 2* **1994**, 2063–2067.
14. Rodger, A.; Nordén, B. *Circular Dichroism and Linear Dichroism*; Oxford University Press: Oxford, 1997; pp. 66–89.
15. Bose, A.; Greer, F.; Price, C. *J. Org. Chem.* **1958**, *23*, 1335–1338.
16. Fling, M.; Minard, F. N.; Fox, S. W. *J. Am. Chem. Soc.* **1947**, *69*, 2466–2468.
17. Juaristi, E.; Beck, A. K.; Hansen, J.; Matt, T.; Mukhopadhyay, T. *Synthesis* **1993**, 1271–1290.
18. Griesbeck, A. G.; Mauder, H.; Mueller, I. *Chem. Ber.* **1992**, *125*, 2467–2476.
19. Griesbeck, A. G.; Mauder, H. *Angew. Chem.* **1992,** *104*, 97–99.
20. Marshall, J. A.; Garofalo, A. W. *J. Org. Chem*. **1993**, *58*, 3675–3680.
21. Griesbeck, A. G.; Hirt, J. *Liebigs Ann. Chem.* **1995**, 1957–1961.
22. Pellegata, R.; Pinza, M.; Pifferi, G. *Synthesis* **1987**, 614–616.
23. Reppe, W. *Liebigs Ann. Chem.* **1955**, *596*, 158–188.
24. Guttmann, S.; Boissannas, R. A. *Helv. Chim. Acta* **1958**, *41*, 1852–1867.
25. Fleš, D.; Markovac-Prpic, A.; Tomasic, V. *J. Am. Chem. Soc.* **1958**, *80*, 4654–4655.
26. Dehmlow, E. V.; Westerheide, R. *Synthesis* **1993**, 1225–1226.
27. Nefkens, G. H. L. *Rec. Trav. Chim. Pay-Bas* **1960**, *79*, 688–698.
28. Echavarren, A. M.; Castano, A. M. *Tetrahedron* **1995**, *51*, 2369–2378.
29. Reepmayer, J. C. *Chirality* **1996**, *8*, 11–17.