

Chromatographic Enantiomer Separation, Circular Dichroism Spectrum, and Absolute Configuration of the 7-Methoxycoumarin *syn* Head-to-Tail Dimer

Tihamér Hargitai,^a Per Reinholdsson,^a and Jan Sandström,^{b,*}

^aDivision of Chemical Engineering 2, Chemical Center, Lund Institute of Science and Technology, P.O. Box 124, S-221 00 Lund, Sweden and ^bDivision of Organic Chemistry 3, Chemical Center, University of Lund, P.O. Box 124, S-221 00 Lund, Sweden

Hargitai, T., Reinholdsson, P. and Sandström, J., 1991. Chromatographic Enantiomer Separation, Circular Dichroism Spectrum, and Absolute Configuration of the 7-Methoxycoumarin *syn* Head-to-tail Dimer. – Acta Chem. Scand. 45: 1076–1079.

The 7-methoxycoumarin *syn*, head-to-tail dimer with C_2 symmetry has been resolved into enantiomers by repeated column chromatography on a chiral stationary phase (CSP) consisting of poly[ethyl (*S*)-2(acryloylamino)-3-phenylpropionate] immobilized in the pores of macroporous poly(trimethylolpropyl trimethacrylate), TRIM, with hexane-dioxane (1:1, v/v) as the mobile phase. The CD spectra of the pure enantiomers have been recorded, and a theoretical CD spectrum has been calculated based on the geometry from a published X-ray crystallographic study and on transition moments and transition charge densities from the UV spectrum and from CNDO/S calculations. Good agreement between the calculated CD spectrum and that of one of the enantiomers permits the assignment of the absolute configuration of the latter.

Three chiral photodimers, the *syn*, head-to-tail indolo[1,7-*ab*][1]benzazepine and coumarin dimers and the *anti*, head-to-head coumarin dimer, all with C_2 symmetry, have recently been resolved by chromatography, and their absolute configurations have been predicted by calculation of the CD spectra of the enantiomers by a semiempirical method.¹ The prediction for the *anti* coumarin dimer is in agreement with the result of a recent X-ray crystallographic study,² and since the same chromophores in a different spatial arrangement are responsible for the CD spectrum of the *syn* dimer, and the agreement between experimental and calculated CD spectra was quite satisfactory for both compounds, the prediction for the *syn* dimer was also considered credible.

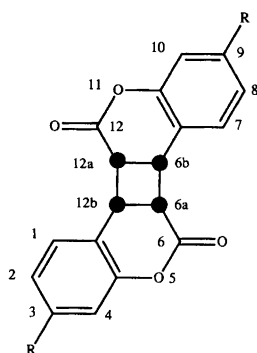
In the previous work,¹ it was found that the coumarin dimers could not be resolved by chromatography on triacetlylcellulose, which requires methanol or ethanol as the

mobile phase. In these media, opening of the lactone rings occurred, and several optically active bands appeared in the chromatogram. Instead, the resolution was performed by chromatography on a column with bulk poly[ethyl (*S*)-2-(acryloylamino)-3-phenylpropionate] (*S*-PAA) as the chiral stationary phase (CSP).

A new CSP has now been developed, consisting of (*S*)-PAA immobilized in the pore system of macroporous particles of poly-[1-methacryloyloxy-2,2-bis(methacryloyloxy-methyl)butane], trivial name poly(trimethylolpropane trimethacrylate), TRIM. The preparation and functionalization of the TRIM particles will be described elsewhere.^{3,4} It was found worthwhile to test the capacity of this new CSP to resolve coumarin dimers, and at the same time it was desirable to test the model for calculating the CD spectra by a study of an analogous dimer in which the polarizations and strengths of the main transitions were modified by substitution. For these purposes, the *syn*, head-to-tail dimers of coumarin (**1a**) and 7-methoxycoumarin (**1b**) were selected.

Experimental

The chromatographic equipment consisted of a Beckman 110 B pump (Beckman Instrument Inc., Altex Division, San Ramon, USA), a LKB 2158 UNICORD SD ultraviolet detector (LKB-Produkter AB, Bromma, Sweden) and a BBC SE 120 dual channel potentiometric recorder (Brown Boveri Goerz Metrawatt, Vienna, Austria). The samples were injected with a Rheodyne 7120 injector (Rheodyne Inc., Cotati, California, USA), equipped with a 100 μ l or a 300 μ l loop. The separation of the coumarin dimers **1a** and



1 a, R = H

1 b, R = OCH₃

1b was performed on a 250×4.6 mm stainless steel column packed with 10 μm TRIM particles functionalized with 55 weight % of (*S*)-PAA. The particles were slurry-packed into the column with the Beckman pump at a flow rate of 2 ml min⁻¹. Hexane–dioxane (1:1, v/v) was used as the slurry-packing solvent and also as the mobile phase in the separation. A solution of 4 mg dimer per ml of solvent was injected by the 300 μl loop. Enantiomerically pure (+)- and (-)-forms were collected in the first and last parts of the eluate. After eight repeated injections, 5–6 mg of each antipode were collected for CD spectroscopy.

The CD spectra were recorded with a JASCO Model J-500 A spectropolarimeter, and the UV spectra with a Cary Model 2290 spectrophotometer.

The CNDO/S calculations were performed with the program described by Guimon *et al.*,⁵ with configuration interaction between the 99 lowest singly excited configurations. The two-centre Coulomb integrals were calculated according to Nishimoto and Mataga.⁶ As a model for the chromophores in **1b** 3-formyloxy-4-methylanisole **2** was used, with a geometry taken from a fragment of **1b** with hydrogen atoms finishing the broken bonds.

The calculations of rotational strengths were performed as described in Ref. 1.

Results and discussion

The use of *S*-PAA functionalized TRIM particles as a CSP gave better resolution of **1a** than *S*-PAA alone, and the resolution of **1b** on the new CSP was even better, giving only moderately overlapping bands in the chromatogram [Fig. 1(a)]. Fractions taken in the first and last parts of the eluate gave enantiomerically pure material, as shown by reinjection [Fig. 1(b)] and by comparison of the CD spectra, which were perfect mirror images.

The first eluted enantiomer showed a positive rotation, and its CD spectrum [Table 1, Fig. 2(a), solvent acetonitrile] consisted of a positive band system between 260 and 305 nm (band 1), a stronger negative band at 246.5 nm (band 2), a positive band at 221 nm (band 3) and a negative

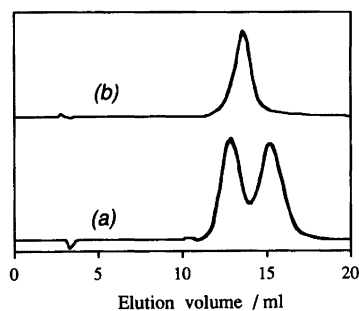


Fig. 1. (a) Chromatogram of **1b** with hexane–dioxane (1:1, v/v) as the mobile phase. (b) Chromatogram of a fraction taken at an early stage of the elution.

Table 1. UV and CD spectra of **1b** in acetonitrile.

	λ_{\max}/nm (ϵ or $\Delta\epsilon$)
UV	287 (3070), 279 (3230), 205sh ^a (41 000), 196 (49 600)
CD ^b	291 (+2.80), ^c 280sh (+2.65), ^c 267.5 (+4.48), ^c 246.5 (-13.3), ^d 221 (+24.1), ^e 195.5 (-15.0) ^f

^ash = shoulder. ^bFirst eluted enantiomer. ^cTogether band 1. ^dBand 2. ^eBand 3. ^fBand 4.

band at 195.5 nm (band 4). The UV spectrum (Table 1, Fig. 3) showed a band with fine structure around 280 nm, a shoulder at 205 nm, and an intense maximum at 196 nm. The three rather strong bands in the CD spectrum between 187 and 260 nm (bands 2, 3 and 4) seem to result from overlap of two similar symmetric couplets with opposite signs, a positive one centred at 205 nm and a negative one at 235 nm. The CD spectrum of **1a** could be satisfactorily explained by interactions between three transitions, the ¹L_a and ¹L_b transitions in the benzene chromophore⁷ and the n → π* transition in the lactone carbonyl group.¹ The 7-methoxy group in **1b** can be expected to cause batho-

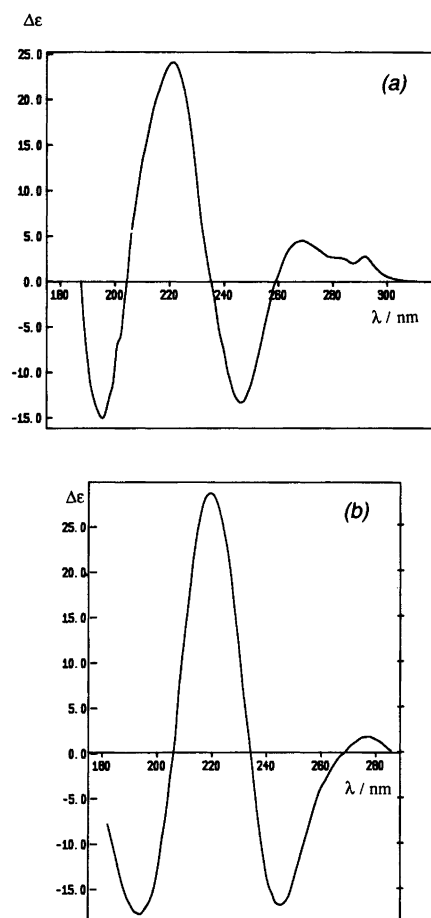


Fig. 2. (a) CD spectrum of (+)-**1b** in acetonitrile. (b) Calculated CD spectrum for (6a*R*, 6b*S*, 12a*R*, 12b*S*)-**1b**.

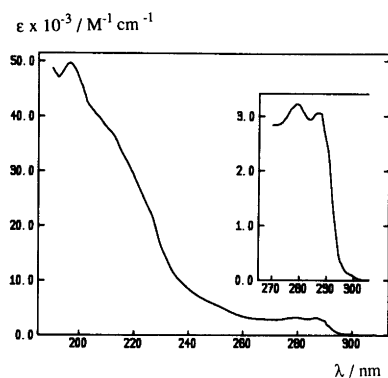


Fig. 3. UV spectrum of (±)-**1b** in acetonitrile.

chromic shifts of both the 1L_a and the 1B transitions, which is also supported by CNDO/S calculations (Table 2). The intensity of the UV band at 196 nm ($\epsilon = 49600$) indicates that it is caused by a ${}^1A \rightarrow {}^1B$ type transition.⁷ Thus a reasonable interpretation of the CD spectrum is that band 1 is due to the 1L_b transitions and band 2 is the negative long-wavelength lobe of a negative couplet caused by interaction between the 1L_a transitions in the two chromophores. Band 3 is composed of the short-wavelength positive lobe of the 1L_a couplet and the long-wavelength lobe of a positive 1B_b couplet, and band 4 is the short-wavelength lobe of the latter couplet.

The geometry of **1b** is known from an X-ray crystallographic study.⁸ The atomic coordinates given⁹ correspond to the 6aR,6bS,12aR,12bS configuration. We have used this geometry to calculate the rotational strengths and the CD spectrum of **1b**, using the semiempirical matrix technique developed by Schellman and coworkers.^{10,11} The input required is transition energies, strengths and directions of electric transition moments and the corresponding transition charge densities for $\pi \rightarrow \pi^*$ transitions, and strengths and directions of magnetic transition moments, quadrupolar transition charges and static charges for $n \rightarrow \pi^*$ transitions. The latter are taken from the calculations for **1a**,¹ but the data for the 1L_b and 1L_a transitions are strongly affected by the 7-methoxy group.

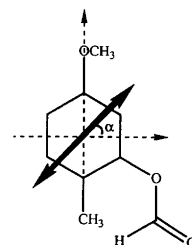
The initial transition moment for the 1L_b transitions was

Table 2. Calculated transition data (CNDO/S) for 3-formyloxy-4-methylanisole (**2**) with geometry as for **1b**.

Transition wavelength/nm	f^a	$\alpha^{b/\circ}$	Assignment
337.8	0.0000		$n \rightarrow \pi^*$
287.6	0.0128	-24.9	1L_b
233.6	0.0622	+56.4	1L_a
206.8	0.5842	-45.3	1B_b
200.8	0.3309	+54.3	1B_a
198.3	0.0105	-71.2	
191.5	0.0055	+44.1	
184.6	0.0009	-24.1	

^aOscillator strength. ^bDirection as shown for **2**.

derived by use of the spectroscopic moment technique.^{12,13} The moments for the O=C-O-, CH-, and CH₃O- groups were given values corresponding to those for the acetoxy (+10),¹⁴ methyl (+6),¹⁴ and methoxy (+30 ± 3)¹⁵ groups, all in units of (cm mol l⁻¹)⁻¹. Vector addition of these moments¹³ leads to a direction close to that given in Table 3 ($\alpha = +13.5^\circ$).



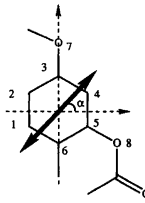
2

No spectroscopic moments have been derived for 1L_a and 1B transitions, but directions broadly parallel to the axis through the CH₃O-C_{Ar} bond are reasonable for the 1L_a and 1B_a transitions, and a direction approximately perpendicular to this axis is predicted for the 1B_b transition.

In a study of the polarized UV spectra of a number of di- and poly-substituted benzene derivatives, Sagiv¹⁴ found the 1B_a and 1B_b transitions to be nearly degenerate in the majority of the compounds studied, the exceptions being 1,4-dimethoxybenzene and methyl 4-methoxybenzoate. For **1b** degeneracy does not seem to apply, since the UV spectrum (Fig. 3) indicates the presence of a strong band on the short-wavelength side of the 196 nm band, and the CNDO/S calculations predict the 1B_a transition to have higher energy than the 1B_b transition (Table 2). It was not possible to obtain agreement between experimental and calculated CD spectra when two strong and nearly perpendicular B-type transitions were located close together at ca. 200 nm. On the other hand (*vide infra*), good agreement for both UV and CD spectra was found with a 1B_b transition near 200 nm and a 1B_a transition at 180 nm, but not when the transition wavelengths were reversed.

The appearance of the CD spectrum requires the 1L_b transition and the 1L_a and 1B_b couplets to have alternating signs, + - + or - + -. The 1L_b transitions in dimers in general acquire the larger part of their rotational strength by interaction with the stronger transitions at higher energies in the opposite chromophore, but their mutual interaction is often too weak to give notable couplet splittings. Calculations were performed with $\alpha({}^1L_a)$ and $\alpha({}^1B_a)$ varied in steps of 15° in the interval +45° to +135°, and with $\alpha({}^1L_b)$ and $\alpha({}^1B_b)$ varied similarly in the interval -45° to +45°. In the first screening, calculations were performed for the 49 combinations, in which the 'a' transitions have the same α value and likewise the 'b' transitions. In the next step, the most promising combinations were selected, and the four α values were varied individually in steps of 5° until the best fit with the experimental curve was obtained.

Table 3. Input data for the calculation of the CD spectrum of **1b**.^a

	Transition and direction ($\alpha/^\circ$)	Energy/ 10^3 cm^{-1}	Δ/nm^b	Transition moment/D
	1L_b (+15.0)	35.50	10.0	1.500
	1L_a (+110.0)	42.50	15.0	2.700
	1B_b (-15.0)	47.60	17.0	4.817
	1B_a (+110.0)	55.55	17.0	3.559 ^c
Transition charges ^d				
Atom	Transition			
	1L_b	1L_a	1B_b	1B_a
1	-0.0534	+0.2792	-0.1520	+0.0982
2	-0.0980	-0.2394	-0.1736	-0.1160
3	+0.0012	+0.3344	-0.0908	-0.0558
4	+0.0606	-0.2980	+0.0984	-0.1968
5	+0.0384	+0.2668	+0.1998	+0.0842
6	+0.0238	-0.3822	+0.0054	+0.0354
7	-0.0114	-0.0436	+0.0872	+0.1390
8	+0.0388	+0.0828	+0.0256	+0.0120

^aData for the $n \rightarrow \pi^*$ transition are taken from Ref. 1. ^bBandwidth at $\Delta\epsilon_{\text{max}}/e$. ^cFrom the CNDO/S calculation.

The best values for the transition charges corresponding to a given α value were derived with the Lagrangian multiplier technique.^{11,16} With the chosen geometry, the sign sequence $+, -, +$ could be obtained, but not the $-, +, -$ sequence (but several non-alternating ones). The best theoretical spectrum [Fig. 2(b)] was obtained with the input data given in Table 3.

Inclusion of the $n \rightarrow \pi^*$ transition leads to a positive contribution to band 3 and a negative one to band 2 corresponding to a maximum of $\pm 1.5 \Delta\epsilon$ units, but not to the appearance of a separate $n \rightarrow \pi^*$ band or shoulder.

The good agreement between calculated and experimental CD spectra, including five different transitions in each chromophore, gives credence to the assignment to the first-eluted enantiomer of **1b**, (+)-**1b**, of the absolute configuration 6a*R*,6b*S*,12a*R*,2b*S*. It is worth noting that the first-eluted enantiomer of **1a**, (-)-**1a**, has the opposite absolute configuration.

The CD spectra of (+)-**1a** and (+)-**1b** show several similarities, such as positive 1L_b bands and a positive couplet at ca. 200 nm. However in **1a** this couplet is mainly due to the 1L_a transition, and in **1b** to the 1B_b transition, while the 1L_a transition in **1b** gives rise to an oppositely signed couplet. This is a caveat against assigning absolute configurations on the basis of similarities in the CD spectra without a careful analysis of the energies and directions of the transition moments.

Acknowledgements. We are grateful to Docent Roland Isaksson for much good advice, to Professor Kailasam Venkatesan, Bangalore, for supplying us with a sample of the

7-methoxycoumarin dimer **1b**, and to the Natural Science Research Council and the Knut and Alice Wallenberg Foundation for financial support through grants to J. S.

References

- Hallberg, A., Isaksson, R., Martin, A. R. and Sandström, J. *J. Am. Chem. Soc.* **111** (1989) 4387.
- Saigo, K., Yonezawa, N., Sekimoto, K., Hasegawa, M., Ueno, K. and Nakanishi, H. *Bull. Chem. Soc. Jpn.* **58** (1985) 1000; **60** (1989) 2704.
- Hargitai, T., Reinholdsson, P., Törnell, B. and Isaksson, R. *J. Chromatogr.* **540** (1991) 145.
- Reinholdsson, P., Hargitai, T., Isaksson, R. and Törnell, B. *Unpublished results*.
- Guimon, C., Gonbeau, D. and Pfister-Guillouzo, G. *Tetrahedron* **29** (1973) 3395.
- Nishimoto, K. and Mataga, N. *Z. Phys. Chem.* **12** (1957) 335.
- Platt, R. J. *J. Chem. Phys.* **17** (1949) 484.
- Ramasubbu, N., Guru Row, T. N., Venkatesan, K., Ramamurthy, V. and Rao, C. N. R. *J. Chem. Soc., Chem. Commun.* (1982) 178.
- Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, England.
- Bayley, P. M., Nielsen, E. B. and Schellman, J. A. *J. Phys. Chem.* **73** (1969) 228.
- Rizzo, V. and Schellman, J. A. *Biopolymers* **23** (1984) 435.
- Platt, J. R. *J. Chem. Phys.* **19** (1951) 263.
- Stevenson, P. E. *J. Chem. Educ.* **41** (1964) 234 and references therein.
- Sagiv, J. *Tetrahedron* **33** (1977) 2303.
- Sagiv, J. *Tetrahedron* **33** (1977) 2315.
- Nilsson, I., Berg, U. and Sandström, J. *Acta Chem. Scand., Ser. B* **40** (1986) 625.

Received March 4, 1991.