

Studies of Chiral Indoles. Part III.* The Absolute Configuration of 1-(1-Phenylethyl)indole

Ingemar Nilsson,[§] Ulf Berg and Jan Sandström

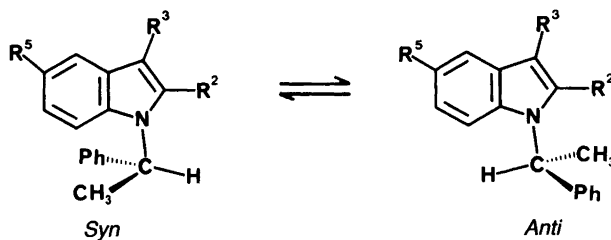
Division of Organic Chemistry 3, Chemical Center, University of Lund, P.O. Box 124, S-221 00 Lund, Sweden

Nilsson, I., Berg, U. and Sandström, J., 1987. Studies of Chiral Indoles. Part III. The Absolute Configuration of 1-(1-Phenylethyl)indole. – Acta Chem. Scand., Ser. B 41: 261–266.

In a previous study, the absolute configuration of 1-(1-phenylethyl)indole was derived by analysis of its temperature-dependent CD spectrum and by theoretical calculation of the rotational strengths of the $\pi \rightarrow \pi^*$ transitions in the three conformations which result from molecular mechanics calculations. According to the analysis, the title compound and its 2-methyl analogue with the same configuration have opposite signs of all strong CD bands at ambient temperature and below. This assignment has now been proven correct by unambiguous synthesis of (*S*)-1-(1-phenylethyl)-5-methoxyindole. The conformational situation for this compound and its 5-H analogue is very similar, as are their CD spectra except for a bathochromic effect of the 5-MeO group on the indole 1L_b transition.

In a recent publication¹ concerning the utility of temperature-dependent circular dichroism spectra as a tool for conformational analysis, we have assigned absolute configurations to a number of 1- and 3-(1-phenylethyl)indoles. These compounds adopt two conformations, denoted *syn* and *anti* (Scheme 1). The absolute configurations

were in some cases established unambiguously by stereospecific synthesis (**4**) or by comparison of CD spectra of pairs of compounds with similar conformational equilibria (**3** and **4**) for which the absolute configuration of one compound (**4**) was known. In another case (**1**), the absolute configuration was derived by analysis of the temperature



- 1: $R^2 = R^3 = R^5 = H$
2: $R^2 = R^3 = H, R^5 = OCH_3$
3: $R^3 = R^5 = H, R^2 = CH_3$
4: $R^2 = R^3 = CH_3, R^5 = OCH_3$

Scheme 1.

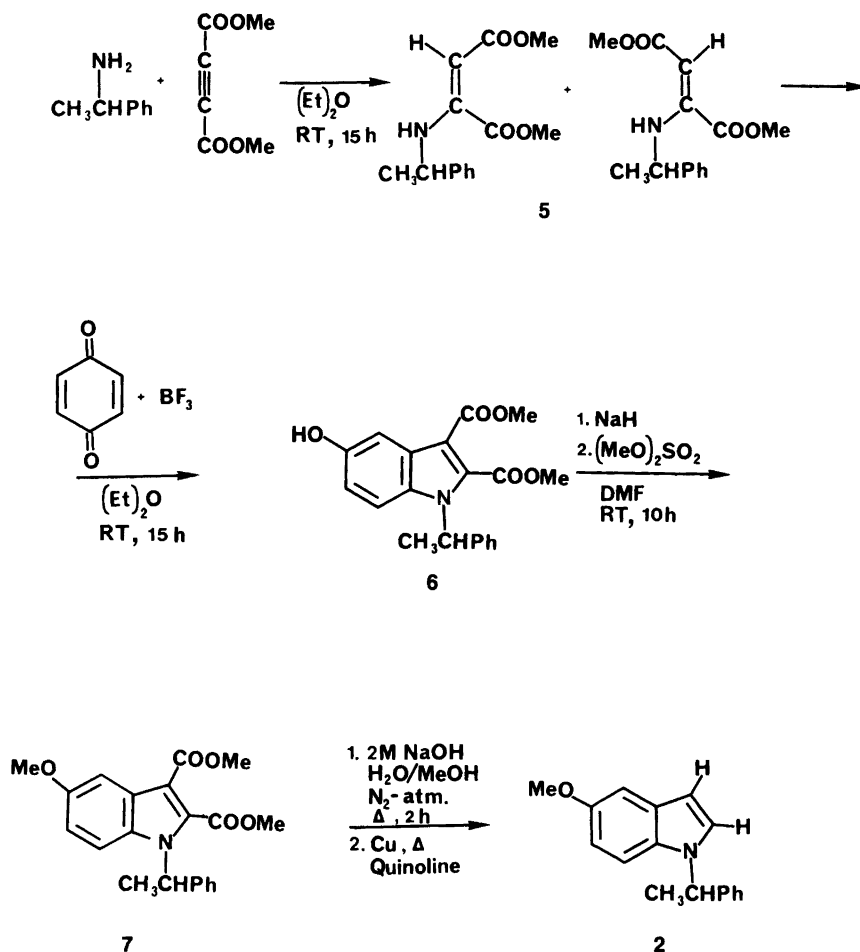
* For Part II, see Ref. 1.

[§] To whom correspondence should be addressed.

dependence of the CD spectrum in combination with calculations of the rotational strengths (**R**) of the transitions in the two conformers. The conclusion was that the CD spectra of **1** and **3** with the same configuration appear with opposite signs for the strongest bands because the *anti* form is dominant in **1** and the *syn* form in **3**. The inevitable simplifications in the semi-empirical approach we have used to calculate the **R** values^{2,3} have led to understandable reservations concerning them and, as pointed out by one of the referees in the previous work, it would be of great value to an assessment of the reliability of the method and the strength of arguments used if the absolute configurations of some of the com-

pounds, among them **1**, could be determined unequivocally.

Despite several efforts we could not previously prepare 1-(1-phenylethyl)indole (**1**) in optically active form with known absolute configuration. However, by using the enamine formed from dimethyl acetylenedicarboxylate and (*S*)-1-phenylethylamine in the Nenitzescu reaction as described by Domschke,⁴ we have now succeeded in preparing (*S*)-5-methoxy-1-(1-phenylethyl)indole (**2**). We are now pleased to report that the assignment of the absolute configurations of the resolved enantiomers of 1-(1-phenylethyl)indole based on theoretical rotational strength calculations was correct.



Scheme 2.

Experimental

Syntheses. (*S*)-5-Methoxy-1-(1-phenylethyl)indole was prepared essentially according to the method described by Domschke,⁴ starting from (*S*)-1-phenylethylamine and dimethyl butynedioate (Scheme 2). The enamine (**5**) was obtained as a mixture of 2-(1-phenylethylamino)-maleate (*E* isomer) and 2-(1-phenylethylamino)-fumarate (*Z* isomer), easily separated by flash chromatography. The *E* isomer is slowly converted to the more stable *Z* isomer at slightly elevated temperature (60°C). The 5-hydroxy precursor (**6**) was methylated with NaH/dimethyl sulfate in DMF before hydrolysis; the latter was conveniently performed in 2M aqueous NaOH solution at reflux temperature under N₂, whereas Domschke,⁴ working with the 5-OH compound, preferred to use highly concentrated alkaline solution. The bisdecarboxylation was performed in boiling quinoline, instead of by heating without a solvent as proposed in Ref. 4. Except for flash chromatography of the enamine (**5**) on silica gel (Merck 60 mesh 230–400) with toluene/ethyl acetate (90:10) as eluent, the product in each step was, after work-up, used directly in the next step without further purification. The identity of all the intermediates in this reaction sequence was confirmed by ¹H NMR spectroscopy, and in all cases only minor impurities were observed. Flash chromatography after the final step on silica gel [toluene/40–60 light petroleum (50:50)] followed by recrystallization from methanol/water (95:5) afforded **2** as colourless crystals (m.p. 99–100°C) in an overall yield of 64% based on the enamine. Anal. C₁₇H₁₇NO: C, H, N. MS, IP 70 eV [*m/e* (% rel. int.)]: 251 (41, M), 147 (62), 132 (40), 105 (100). ¹H NMR (300 MHz, CDCl₃, 23°C): 1.90 (3H, d, *J* 7.1 Hz, CH₃CH), 3.82 (3H, s, CH₃–O), 5.60 (1H, q, *J* 7.1 Hz, CHCH₃), 6.48 (1H, d, *J* 3.2 Hz, H-3), 6.77 (1H, dd, *J* 2.2, 9.0 Hz, H-6), 7.1–7.35 (8H, m).

Attempts were made to prepare **2** by the Nenitzescu reaction starting from the enamine of (*S*)-1-phenylethylamine and methyl propiolate. The reaction failed, however, to give the desired product, both in diethyl ether/BF₃ medium, as above, and in acetic acid, as previously described.¹

CD spectra. The CD spectra were recorded on a Jasco Model J-500A spectrometer. The cell for

variable temperature measurements has been described elsewhere.⁵ The temperature was regulated by boiling off liquid nitrogen from an attached Dewar vessel and was monitored by a copper-constantan thermocouple dipping into the sample. The samples were 0.8–3.2 mM in methanol and the baseline correction was made using the racemate of the same concentration instead of pure solvent alone. Correction for thermal contraction of methanol was made for each spectrum relative to 293 K.⁶

Results and discussion

The assignments of the transitions in the CD spectra, in the notation of Platt,⁷ and the molecular mechanics (MM) calculations are as in the previous article.¹

The CD spectra of the first eluted enantiomer (*E*₁) from the chromatographic resolution of **1** and that of (*S*)-**2** (Fig. 1) are almost mirror images of each other with respect to the wavelength axis, except for the ¹L_b band, which is bathochromically shifted in **2** due to the 5-methoxy group.⁸ Furthermore, the temperature dependence of the CD spectrum of **2** is similar to that of **1**, which is expected since the 5-methoxy group ought to have a negligible effect on the *syn-anti* equilibrium, as was experimentally (DNMR) observed for **3** and **4**. Thus, we may safely assign the *E*₁ enantiomer of **1** the *R* configuration. The close resemblance of the CD spectra of **1** and **2** (Fig. 1), and of **3** and **4** (Fig. 2), except for the red shift of the ¹L_b bands of **2** and **4**, also indicates that the 5-methoxy substituent exerts a minor influence, both with respect to the dipole strength and polarization direction of the electronic transitions.

In the previous work, the *E*₁ enantiomer of **3** was assigned the *S* configuration on the basis of the close similarity of its CD spectrum to that of (*S*)-**4** (Fig. 2). On the other hand, the spectra of (*R*)-**1** and (*S*)-**3** exhibit a close resemblance, with the exception of the sign of the indole ¹L_a band, which is negative for (*R*)-**1** and positive for (*S*)-**3**. This clearly illustrates the danger in assigning the absolute configuration of a compound by comparison of the CD spectrum with that of a similar compound of known absolute configuration without taking the conformational differences between the molecules into account. In this case, the difference in adopted conformation between

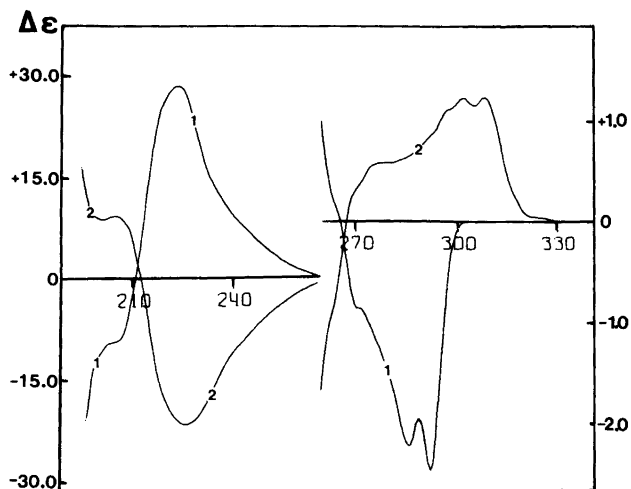


Fig. 1. (1) CD spectrum of the E_1 enantiomer of **1** in methanol. (2) CD spectrum of S -**2** in methanol.

1 and **3** almost cancels the effect of changing the absolute configuration for every band in the CD spectrum.

The rotational strengths calculated by the semi-empirical Schellman matrix formalism for the R configuration of **1** are shown in Table 1. In the *anti* **1** form, predicted to be dominant (MM calculations),¹ the signs of the rotational strengths (R) of the indole 1L_b , 1B_b and 1B_a transitions are in agreement with the experimental observations, whereas the wrong sign is obtained for the 1L_a band. However, the calculated $R(^1L_a)$

value is low, in agreement with the observed band, and nodal lines in the $R(^1L_a)$ map pass close to the shallow *anti* minimum. Furthermore, the sign of R for the benzene 1L_a band is also correctly predicted, whereas the 1L_b band is so weak that it is barely observed, and the 1B_b and 1B_a bands lie at too short wavelengths to be observed. These results for **1** give, a first glance, the impression that the calculations are credible for most of the observed transitions. However, considering the results for a number of compounds investigated, not only those with the 1-phenyl-

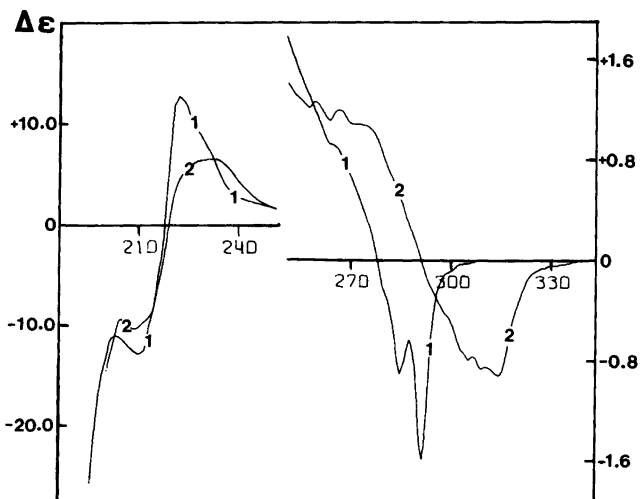


Fig. 2. (1) CD spectrum of the E_1 enantiomer of **3** in methanol. (2) CD spectrum of S -**4** in methanol.

Table 1. Rotational strength calculations for compound 1.^a

Compound	Conformation	R (D × BM)							
		Indole				Benzene			
		¹ L _b	¹ L _a	¹ B _b	¹ B _a	¹ L _b	¹ L _a	¹ B _b	¹ B _a
1a	<i>Syn</i>	+0.033	-0.060	-0.4	+0.50	+0.037	+0.75	-1.8	+1.0
	<i>Anti 1</i>	-0.035	+0.020 ^b	+0.8	-0.48	-0.032	-0.85	+1.7	-1.1
	<i>Anti 2</i>	-0.014	+0.060 ^b	+3.5	+0.48	+0.006 ^b	-0.37	-0.8	-1.9

^aR configuration. ^bClose to nodal line.

ethyl group but also with the 1-(*N,N*-dimethyl-carbamoyl)ethyl group as the chiral rotor, we may conclude that the agreement is fortuitous except for the indole ¹L_b and ¹L_a transitions. The calculated indole **R**(¹L_b) and **R**(¹L_a) values are, in general, in good agreement with respect to the sign with experimental **R** values of reasonable magnitude. In addition, there is a good correlation between the experimental and calculated dissymmetry factors ($\Delta\epsilon/\epsilon$) for the ¹L_b and ¹L_a bands, which gives some confidence in the calculations. Based on this, the *E*₁ enantiomer of **1** was assigned the *R* configuration, which has now been shown to be correct by the unambiguous synthesis of (*S*)-**2**.

The important conclusion derived from the example above is that rotational strength calculations of this type have to be used with great care. The calculations for a single molecule may predict the correct sign for a number of bands; however, with the same set of optical input parameters for another molecule possessing the same chromophores but with different spatial distribution, the agreement may be much less satisfactory, i.e. the agreement in the first case is merely fortuitous. Thus, it should be emphasized that the appropriate methodology is to check the reliability of the set of optical input parameters used in the calculations on at least some systems of known absolute configuration and with reasonably well-known conformations, before turning to systems of unknown configuration and/or conformation.

In the chromatographic resolution on TAC, the *E*₁ enantiomers of **1** and **3** have the *R* and *S* configuration, respectively. This clearly demonstrates, as pointed out by other workers,^{9,10} that assignment of absolute configuration on the basis

of chromatographic elution order should be used with caution, since conformational changes clearly may give rise to the reverse order of elution of the enantiomers with respect to the absolute configuration.

Finally, the less satisfactory agreement of the rotational strength calculations for the indole ¹B_b transition has prompted us to try to obtain better optical input parameters for this transition. In collaboration with other workers,¹¹ we have undertaken a linear dichroism (LD) study of indole in stretched polymer films, since the strong absorption of this transition has hitherto prevented LD studies in the crystalline state. Secondly, an *ab initio* calculation on indole by the complete active space SCF (CASSCF)¹² method using a split valence basis set is in progress.¹³

Acknowledgement. Financial support from the Swedish Natural Science Research Council is gratefully acknowledged.

References

1. Nilsson, I., Berg, U. and Sandström, J. *Acta Chem. Scand., Ser. B* **40** (1986) 625.
2. Bayley, P. M., Nielsen, E. B. and Schellman, J. A. *J. Phys. Chem.* **73** (1969) 228.
3. Rizzo, V. and Schellman, J. A. *Biopolymers* **23** (1984) 435.
4. Domschke, G. *J. Prakt. Chem.* **311** (1969) 807.
5. Roschester, J., Berg, U., Pierrot, M. and Sandström, J. *J. Am. Chem. Soc.* **109** (1987) 492.
6. Yergovich, T. W., Swift, G. W. and Kurata, F. *J. Chem. Eng. Data* **16** (1971) 222.
7. Platt, J. R. *J. Chem. Phys.* **19** (1951) 107.
8. Strickland, E. H. and Billups, C. *Biopolymers* **12** (1973) 1989.

9. Isaksson, R. and Roschester, J. *J. Org. Chem.* 50 (1985) 2519.
10. Pirkle, W. H., Welch, C. J. and Mahler, G. S. J. *J. Org. Chem.* 49 (1984) 2504.
11. Nordén, B. and Kubista, M. Department of Physical Chemistry, CTH, Gothenburg, Sweden. *Work in progress.*
12. Roos, B. O., Taylor, P. R. and Siegbahn, P. E. M. *Chem. Phys.* 48 (1980) 157.
13. Widmark, P. O. Department of Theoretical Chemistry, University of Lund, Sweden. *Work in progress.*

Received October 22, 1986.