Quantitative Description of Optical Activity using the Principle of Pairwise Interactions: 2,2′-Spirobi-indanes

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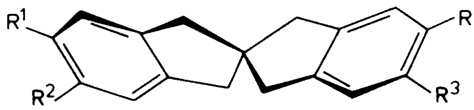
The molar rotations $[M]_{589}$ of chiral, optically active tri- and tetra-substituted 2,2′-spirobi-indanes are described by means of Kauzmann's Principle of Pairwise Interactions (PPI). Additionally, the relation derived from the PPI gives encouraging results for the description of the circular dichroism. The results obtained are compared with those gained by means of the Theory of Chirality Functions (TCF). Furthermore, Kauzmann's theory gives evidence as to which classes of molecules might benefit from application of a semiempirical method for the quantitative description of chiroptical properties. Thus, the great success of the TCF for classes of compounds with D_{2d} symmetry of the skeleton is due to the cancellation of all (pairwise) ligand–core interaction terms by symmetry.

In 1961 Kauzmann *et al.*[1] offered a semiempirical approach for the quantitative description of molar rotations of chiral, optically active molecules. This concept, being based on physical theories of optical activity, comprises a special type of cluster expansion and has been called Principle of Pairwise Interactions (PPI).† It describes the observable features of natural optical activity in terms of a superposition of contributions from chiral interactions of groups or parts constituting the molecule in question. When this theory was presented, no data for a convincing test were available and in consequence no further attention has been paid to it.

Later the Theory of Chirality Functions (TCF) formulated by Ruch and Schönhofer[2] increasingly attracted the attention of many research groups.[3-14] This approach, algebraic in nature, reduces the chiroptical phenomena to symmetry and transformation properties within the scope of a group theoretical treatment. Remarkably, a really successful description of chiroptical properties by means of the TCF has been restricted to molecules with a D_{2d} skeleton symmetry, namely allenes[3] and 2,2′-spirobi-indanes.[6,11,12] Even for these cases, however, only the optical rotations in the transparency region fit the pertinent chirality functions; the approach fails if chirality parameters from circular dichroism ($\Delta\varepsilon$,$[R]$) are used.[8]

Unfortunately, the set of compounds prepared for a test of polynomials based on the TCF did not simultaneously allow a test of the PPI. Thus, the optical rotations of disubstituted 2,2′-spirobi-indanes,[6] allenes,[3] and the mono- and di-substituted [2.2]metacyclophanes[7,8] reported so far are not suited for an evaluation of interaction terms necessary for an application of the PPI. Recently however, Schlögl and his co-workers described the syntheses and optical rotations of tri- and tetra-substituted 2,2′-spirobi-indanes.[11,12] This offers the opportunity for an evaluation of interaction parameters and a first comprehensive test of the PPI.

In this paper we report our results on the description of molar rotations of chiral 2,2′-spirobi-indanes by means of the PPI and on the applicability of the relation derived to other chirality phenomena, *e.g.* c.d. A further aspect of this paper is related to the striking general success of semiempirical approaches to the calculation of optical activity observables of molecules possessing a D_{2d} skeleton symmetry.



Scheme 1.

Results and Discussion

For the deduction of a set-up based on the PPI, an optically active β-substituted 2,2′-spirobi-indane is arbitrarily divided into five interacting groups: the 2,2′-spirobi-indane skeleton (G) and the substituents R^1, R^2, R^3, and R^4 (Scheme 1).

Following the approach of Kauzmann[1] a given chiroptical property χ is regarded as the sum of contributions from all possible chiral interactions within the molecule. This leads to equation (1), where m represents a two-way (pairwise) interaction term, and m', m'', and m''' are three-, four-, and five-way interaction terms. Owing to the achiral arrangement of the pertinent groups, some interactions do not contribute to the optical activity[1] of 2,2′-spirobi-indanes. Hence, $m_{1,2}$, $m_{3,4}$, and all two-way ligand–core interactions furnish no contribution and are consequently not contained in equation (1). The relative signs of the interaction terms m, m', m'', and m''' follow from symmetry considerations, *i.e.* enantiomeric interactions furnish contributions of opposite sign. Their absolute signs are to be determined experimentally. The higher interaction contributions m', m'', and m''' can be regarded as correction terms operating on the pairwise terms m and tentatively can be omitted.[1] Hence, equation (1) can be approximated by expression (2).

$$\chi = m_{1,3} + m_{1,4} + m_{2,3} + m_{2,4} + m'_{1,3,G} + m'_{1,4,G} + m'_{2,3,G} + m'_{2,4,G} + m'_{1,2,3} + m'_{1,2,4} + m'_{1,3,4} + m'_{2,3,4} + m''_{1,2,3,G} + m''_{1,2,4,G} + m''_{1,3,4,G} + m''_{2,3,4,G} + m''_{1,2,3,4} + m'''_{1,2,3,4,G} \quad (1)$$

$$\chi = m_{1,3} + m_{1,4} + m_{2,3} + m_{2,4} \quad (2)$$

Since the interaction terms m are not uniquely determined, for the practical application of equation (2) it is possible to

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† The general concept of Kauzmann contains all possible contributions to a chiroptical property originating from pairwise, three-way, and higher interactions. In this paper the term PPI denotes both this general concept and the abridged equations containing only pairwise interactions.

Table 1. Calculated [a] and experimental [b] molar optical rotations [*M*] (λ 589 nm) for trisubstituted 2,2′-spirobi-indanes

Compound	R^1	R^3	R^4	[*M*]	
				Calc.	Exp.
(1)	CH_3	C_2H_5	CH_3	+4.3	+5.5
(2)	CH_2OH	C_2H_5	CH_2OH	+0.1	+1.9
(3)	CHO	C_2H_5	CHO	−53.3	−54.8
(4)	CO_2H	C_2H_5	CO_2H	−33.9	−30.3
(5)	CO_2CH_3	CH_3	CO_2CH_3	−54.0	−53.6
(6)	CO_2CH_3	C_2H_5	CO_2CH_3	−43.4	−40.5
(7)	CN	C_2H_5	CN	−43.2	−46.3
(8)	CH_2OH	C_2H_5	CH_3	+4.0	+7.9
(9)	CHO	C_2H_5	CH_3	+12.2	+20.0
(10)	CO_2CH_3	C_2H_5	CH_3	+10.6	+16.0
(11)	CN	C_2H_5	CH_3	+12.1	+17.0
(12)	CH_3	C_2H_5	CH_2OH	+1.4	+0.9
(13)	CO_2CH_3	C_2H_5	CH_2OH	−0.6	+6.7
(14)	CO_2CH_3	C_2H_5	$CH{=}CH_2$	−62.8	−98.4
(15)	CH_3	C_2H_5	CHO	−17.1	−17.4
(16)	CH_3CO	CH_3	CHO	−55.8	−48.4
(17)	CO_2CH_3	CH_3	CHO	−62.4	−49.3
(18)	CO_2CH_3	C_2H_5	CHO	−51.8	−47.2
(19)	CH_3	C_2H_5	$CH{=}NN(CH_3)_2$	−53.7	−69.8
(20)	CO_2CH_3	CH_3	$CH{=}NN(CH_3)_2$	−161.3	−178.4
(21)	CO_2CH_3	C_2H_5	$CH{=}NN(CH_3)_2$	−150.7	−205.6
(22)	CHO	C_2H_5	CO_2CH_3	−48.1	−45.1
(23)	CH_3	C_2H_5	CH_3CO	−16.4	−11.6
(24)	CH_2OH	C_2H_5	CH_3CO	−21.5	−12.8
(25)	CHO	C_2H_5	CH_3CO	−42.9	−32.2
(26)	CO_2H	C_2H_5	CH_3CO	−43.5	−28.1
(27)	CO_2CH_3	CH_3	CH_3CO	−57.6	−46.5
(28)	CO_2CH_3	C_2H_5	CH_3CO	−47.0	−27.9
(29)	CH_2OH	C_2H_5	$C(CH_3)(OCH_2)_2$	−6.6	−4.7
(30)	CHO	C_2H_5	$C(CH_3)(OCH_2)_2$	−14.5	−10.9
(31)	CO_2CH_3	C_2H_5	$C(CH_3)(OCH_2)_2$	−13.4	−10.6
(32)	CH_3	C_2H_5	CO_2CH_3	−15.0	−15.4
(33)	C_2H_5	CH_3	CO_2CH_3	−25.6	−19.5
(34)	CH_2OH	C_2H_5	CO_2CH_3	−23.6	−18.8
(35)	CH_3CO	CH_3	CO_2CH_3	−56.2	−42.8
(36)	CN	C_2H_5	CO_2CH_3	−40.6	−40.8
(37)	CH_3	C_2H_5	CN	−16.2	−15.5
(38)	CO_2CH_3	CH_3	CN	−53.9	−40.9
(39)	CO_2CH_3	C_2H_5	CN	−43.3	−41.8
(40)	CO_2H	CH_3	NH_2	−40.6	−39.3
(41)	CO_2H	C_2H_5	NH_2	−30.0	−46.6
(42)	CO_2H	CH_3	$NHCOCH_3$	−72.3	−71.2
(43)	CO_2H	C_2H_5	$NHCOCH_3$	−61.7	−55.2

[a] Equation (2) using rotations of disubstituted compounds in ref. 6; no effort has been made to optimise the parameters used. [b] Refs. 11 and 12.

choose a reference substituent, so that every pairwise interaction term *m* in which the reference group is involved vanishes. This is not contained in the original paper of Kauzmann [1] and comprises an extension of this approach. The justification for this proceeding is briefly outlined in the Appendix.

For convenience, hydrogen is selected as the reference substituent. According to equation (2) the measured value of a chiroptical property ([*M*], Δε, [*R*]) of a given disubstituted 2,2′-spirobi-indane is formally equal to the corresponding pairwise interaction term between the substituents. Therefore, to perform a test of the PPI by means of a calculation of values for trisubstituted compounds the pertinent values for homo- and hetero-disubstituted 2,2′-spirobi-indanes must be available. Applying equation (2) to the molar rotations at λ = 589 nm, the values [*M*] compiled in Tables 1 and 2 are obtained. Agreement of the experimental data with the calculated values is in many cases highly satisfactory, although for tetrasubstituted compounds the deviations become more obvious.

These results may be compared with those obtained from the ' shortened Ansatz ' (3) based on the TCF (first approximation procedure). As has been demonstrated earlier expression (3) also yields excellent results with experimental optical rotations.[6] In contrast to equation (2) however, data from

$$\chi = (l_1 - l_2)(l_3 - l_4) = l_1l_3 - l_1l_4 - l_2l_3 + l_2l_4 \quad (3)$$

Table 2. Calculated [a] and experimental [b] molar optical rotations $[M]$ (λ 589 nm) for tetrasubstituted 2,2′-spirobi-indanes

Compound	R^1	R^2	R^3	R^4	$[M]$ Calc.	$[M]$ Exp.
(44)	C_2H_5	CH_3CO	C_2H_5	CH_3CO	+24.1	+9.4
(45)	C_2H_5	CO_2CH_3	C_2H_5	CO_2CH_3	+21.4	+19.2
(46)	CH_3	CH_3CO	CH_3	CH_3CO	+37.8	+23.6
(47)	CH_3	CO_2CH_3	CH_3	CO_2CH_3	+34.7	+42.6
(48)	CH_3	CHO	CH_3	CHO	+44.1	+53.5
(49)	CH_3	CN	CH_3	CN	+34.8	+42.0
(50)	CH_3	C_2H_5	CH_3	C_2H_5	−0.7	+1.5

[a,b] See footnotes to Table 1.

Table 3. Calculated [a] and experimental rotational strengths $[R]$ for trisubstituted spirans

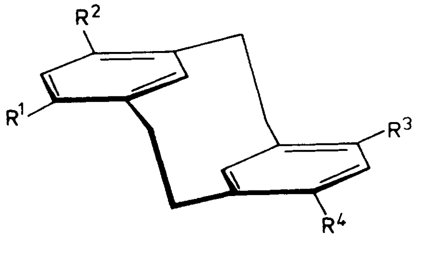
Compd.	^1L_b band $10^{40}[R]$ Calc.	^1L_b band $10^{40}[R]$ Exp. (λ)	^1L_a band [b] $10^{40}[R]$ Calc.	^1L_a band [b] $10^{40}[R]$ Exp. (λ)
(6)	−1.1	−1.9 (290)	−10.8 +15.2	−10.0 (253) +6.9 (238)
(28)	−1.9	−1.8 (289)	−7.8 +14.0	−8.4 (258) +12.2 (241)

[a] Equation (2); parameters used from the c.d. spectra of ref. 15.
[b] Bisignate band.

homo- and hetero-disubstituted spirans are sufficient for both the evaluation of parameters l_i and the following test. The validity of both equations (2) and (3) for the description of molar rotations of spirobi-indanes implies that the terms of equation (3) may be interpreted by means of the PPI. Since $m_{i,j}$ in equation (2) corresponds to $l_i l_j$ in equation (3), equation (3) comprises a dissection of the interaction terms $m_{i,j}$ into functions of individual ligand parameters $l_i.l_j$. Obviously, for the optical rotation at $\lambda = 589$ nm the (multiplicative) contribution of one substituent to the interaction term $m_{i,j}$ is always the same irrespective of the nature of the second ligand, and relation (4) is valid.

$$m_{i,j} = \sqrt{m_{i,i}}\,.\,\sqrt{m_{j,j}} \qquad (4)$$

This behaviour is of course restricted to chirality phenomena of spirobi-indanes and allenes which are in accord with both equations (2) and (3). As equation (3) can be regarded as a specialized form of equation (2), the applicability of equation (2) does not imply the applicability of equation (3) without an independent proof. This principal difference becomes obvious if the c.d. (*e.g.* the rotational strength $[R]$) of absorption bands is chosen as the chirality parameter observed. As has been shown recently,[8] equation (3), though useful for the description of $[M]$ of spirobi-indanes, is not in accord with the c.d. of the same derivatives, since it demands that a given chirality observation should have the same sign for all configurationally correlated homodisubstituted 2,2′-spirobi-indanes. This holds true for the molar rotation at $\lambda = 589$ nm but is not consistent with the experimental c.d. measurements of the pertinent compounds. In contrast, equation (2) deduced from the PPI is void of this disadvantage and the c.d. of trisubstituted compounds may be described by means of the data obtained for disubstituted spirobi-indanes. This is demonstrated by means of the compounds (6) and (28) (Table 1). Their rotational strengths $[R]$ in the ^1L_b and ^1L_a regions obtained by using equation (2) and interaction terms from the c.d. spectra of disubstituted compounds [15] are in good agreement with those found experimentally (Table 3).



Scheme 2.

It is striking that a description of chiroptical properties by simple formulae such as expressions (2) and (3) has so far been restricted mostly to molecules with D_{2d} skeletal symmetry. For example, with the chemically related [2.2]metacyclophanes (skeletal symmetry C_{2h}, Scheme 2), equation (5), due

$$\chi = l_1 - l_2 - l_3 + l_4 \qquad (5)$$

to the TCF, has been tested and shown to be insufficient.[7] An explanation for the failure of this simple quadrant rule (5) for the description of chiroptical properties of [2.2]metacyclophanes can be given on the basis of the PPI. Considering two-way (pairwise) interactions only, the relation (6) follows ($m_{1,2}$

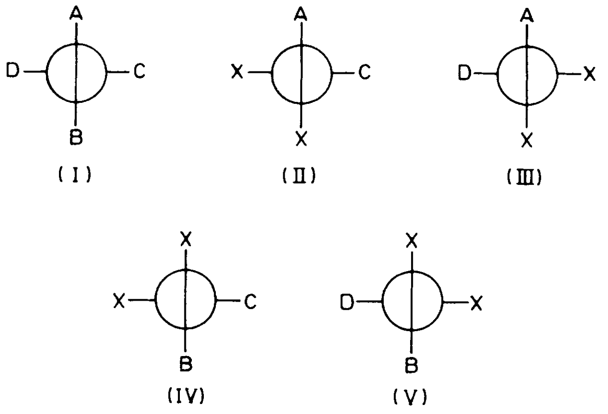
$$\chi = m_{1,3} + m_{2,4} + m_{2,3} + m_{1,4} + m_{1,G} + m_{2,G} + m_{3,G} + m_{4,G} \qquad (6)$$

and $m_{3,4}$ do not contribute to the chirality phenomena). In contrast to the spirans and allenes with D_{2d} skeletal symmetry, however, the two-way ligand–core interactions $m_{i,G}$ do not vanish as a result of symmetry, so that formula (6) contains eight pairwise interaction terms. Hence, it is not surprising that the chirality function (5) consisting of only four terms is inadequate for the description of the molar rotations of [2.2]metacyclophanes. Recently, Haase has proposed an extended chirality function [13] to overcome the discrepancies between calculated and experimental optical rotations of [2.2]metacyclophanes observed when using equation (5). However, in addition to the complexity of expression (6) and that offered in ref. 13, a practical application would be further complicated by the fact that no reference group can be chosen in such a way that every interaction term $m_{i,j}$ involving this reference group vanishes (see Appendix).

Appendix

The following proof demonstrates that pairwise interaction terms including a reference group vanish in molecules of D_{2d} skeletal symmetry.

Consider the five spirans (I)—(V) (projections in Scheme 3): each of the compounds (II)—(V) is obtained from compound (I) by selecting one of the four contributing ligand pairs and



Scheme 3.

replacing the other ligands by the reference X. One can easily verify that from equation (2), equation (7) follows. As

$$\chi(\mathrm{I}) = \chi(\mathrm{II}) + \chi(\mathrm{III}) + \chi(\mathrm{IV}) + \chi(\mathrm{V}) \qquad (7)$$

the compounds (II)—(V) are in a bi-unique correspondence to the four contributing pairs of compound (I), and $\chi(\mathrm{I})$ is given by the sum (7), their chirality observations $\chi(\mathrm{II}) \cdots \chi(\mathrm{V})$ fulfil all formal requirements of pairwise interaction terms in compound (I) and may therefore be identified with these. The mentioned indeterminateness of m is explained by the fact that the reference sort can be chosen arbitrarily. If a third ligand is replaced by X in compounds (II)—(V) then the molecule becomes achiral which means that the corresponding term vanishes. In the case of [2.2]metacyclophanes, however, a molecule with three substituents of the same sort is not achiral, so that a pairwise interaction term $m_{i,j}$ involving a reference substituent (of any reference sort chosen) will not be zero in general.

Experimental

The c.d. spectra of compounds (6) and (28) were taken with a Yobin-Yvon Mark III instrument carrying thermostatted (20 ± 1 °C) cylindrical quartz cuvettes (0.1—10 mm). U.v. spectra were recorded with a Cary-15 instrument at 20 °C (10 mm quartz cuvettes). As solvent spectroscopic grade ethanol (Uvasol, Merck) was used.

(−)-(2S)-*Diethyl 5′-Ethyl-2,2′-spirobi-indane-6,6′-dicarboxylate* (6).—C.d. $\lambda_{\max.}$ 290 ($\Delta\varepsilon$ −1.24), 282s (−0.96), 253 (−8.60), 238 (+6.93), 217 (−44.67), and 212 (+41.10); u.v. $\lambda_{\max.}$ 287 (ε 3 615), 280 (3 545), 244 (23 295), and 208 (64 724).

(−)-(2R)-*Ethyl 6′-Acetyl-5′-methyl-2,2′-spirobi-indane-5-carboxylate* (28).—C.d. $\lambda_{\max.}$ 315s ($\Delta\varepsilon$ −0.07), 289 (−0.99), 280 (−0.86), 258 (−5.57), 241 (+8.31), and 221 (−3.88); u.v. $\lambda_{\max.}$ 305s (ε 1 860), 288 (3 630), 278 (3 630), 247 (22 390), 212 (45 710), and 206 (48 980).

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