Enantiomer Resolution, Barrier to Ring Inversion, Circular Dichroism Spectrum and Absolute Configuration of Cycloocta[2,1-*b*:3,4-*b'*]dipyridine

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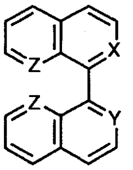
The chiral cycloocta[2,1-*b*:3,4-*b'*]dipyridine **3b** has been cleanly resolved into enantiomers by chromatography on swollen, microcrystalline triacetylcellulose, using ethanol as the mobile phase. A trace of ammonia had to be added to prevent acid-catalysed racemization. The free energy barrier to ring inversion was found to be close to 25 kcal mol^{-1}, and rather insensitive to the temperature. The experimental CD spectrum could be reasonably well simulated by CNDO/S calculations, indicating that the first eluted enantiomer has the *R* configuration. According to the calculations, the long-wavelength CD band has no clear n→π* character.

The problem of the relative steric requirements of hydrogen atoms and nitrogen lone pairs in saturated systems has been the subject of much discussion and some controversy.[1,2] The interpretation of experimental results may be complicated by intervention of stereoelectronic effects,[3,4] working in opposition to the 'purely' steric effects. Thus, the *anti* form of ethylamine is *ca.* 0.6 kcal mol^{-1} more stable than the *gauche* form[5,6] although steric energy should favour the latter. The *anti* form is stabilized by a favourable lone pair-σ^*_{C-C} interaction.

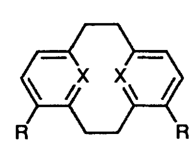
The situation seems to be more clear cut in sp^2-hybridized systems, where the apparent steric requirement of the nitrogen lone pair is always smaller than that of a hydrogen atom.

Examples are provided by 1,1'-binaphthyl (**1a**) and its aza analogues **1b–d**. The free energy barrier to inversion of **1a** is 24.0 kcal mol^{-1},[7] and that of the 2-aza analogue **1b** is 22.7 kcal mol^{-1} in 1 mol dm^{-3} HCl in methanol (protonated) and 18.6 kcal mol^{-1} in pure methanol (free base).[8] Inversion barriers for the 2,2'- and 8,8'-diaza analogues **1c** and **1d** have not been reported, but attempts to resolve them were reported to be unsuccessful.[9,10] While the transition state for rotation of **1a** has two close H-2---H-8' interactions,[11] the free base of **1b** has one H-2---H-8' and one N---H-8, and those of **1c** and **1d** have two N---H interactions. Comparison of the barriers for **1a** and **1b** shows that the contribution of one N---HC interaction to the free activation energy is *ca.* 5 kcal mol^{-1} lower than that of a CH---HC interaction. It should be stressed that the difference in length between C–C and C–N bonds also plays a role for the steric effects in these systems.



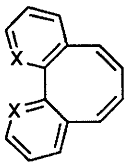
1a; X = Y = Z = CH
1b; X = N, Y = Z = CH
1c; X = Y = N, Z = CH
1d; X = Y = CH, Z = N

The ^{1}H NMR spectrum of [2.2]metacyclophane (**2a**) shows no temperature dependence below 200 °C, and the dimethyl derivative **2b** has been prepared in an optically active form with no tendency to racemize at ambient temperature,[12] indicating an inversion barrier higher than 27 kcal mol^{-1}. The diaza analogue of **2a** (**2c**) shows temperature dependence of the ^{1}H NMR spectrum already at ambient temperature, and bandshape analysis at 80 °C gave $\Delta G^{\ddagger}_{inv}$ = 14.8 kcal mol^{-1},[13] indicating a difference larger than 12 kcal mol^{-1} between a CH---HC and a N---N interaction in this particular geometry.



2a; X = CH, R = H
2b; X = CH, R = CH$_3$
2c; X = N, R = H

Two of us have found the energy barrier to ring inversion of dibenzo[*a*,*c*]cyclooctatetraene† (**3a**) to be 30.0 kcal mol^{-1} by thermal racemization of pure enantiomers[14] obtained by chromatography on microcrystalline triacetylcellulose (TAC).[15] Since the diaza analogue **3b** is now available,[16] we have found it of interest to evaluate the effect of aza substitution on the inversion barrier. It was also attractive to try to resolve **3b** into enantiomers and try to determine the absolute configurations of the enantiomers by comparison of experimental and theoretical circular dichroism (CD) spectra.



3a; X = CH
3b; X = N

Results and Discussion

Molecular mechanics calculations on **3b** gave a structure with a tub-formed cyclooctatetraene ring, quite similar to that of **3a**,[17] and with a C_2 axis (Fig. 1). The dihedral angle between the pyridine rings was calculated to be 62.4°, that between the

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† IUPAC recommended name: dibenzo[*a*,*c*]cyclooctene.

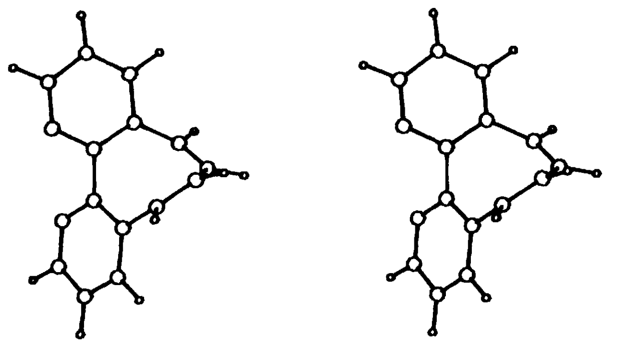


Fig. 1 Stereoview of **3b** from molecular mechanics calculations

Table 1 Rate constants and thermodynamic parameters for ring inversion of **3b** in ethanol containing ammonia[a]

T/K	$k_{inv}/10^{-4}$ s^{-1}	$\Delta G^{\ddagger}_{inv}$/kcal mol^{-1}
307.7	0.136	24.88
322.1	0.83	24.92
331.7	2.49	24.95
341.2	7.3	24.96

[a] $\Delta H^{\ddagger}_{inv}$: 24.53 ± 0.02 kcal mol^{-1}; $\Delta S^{\ddagger}_{inv}$: −1.2 ± 0.1 cal mol^{-1}.

Table 2 UV and CD spectra of **3b** in ethanol

	λ/nm (ε or Δε/dm^3 mol^{-1} cm^{-1})
UV	274 (5960), 200 (24 700, end absorption)
CD	290 (−3.79), 251 (+42.7), 225 (+36.2), 210 sh (−11.9), 197 (−74.8)

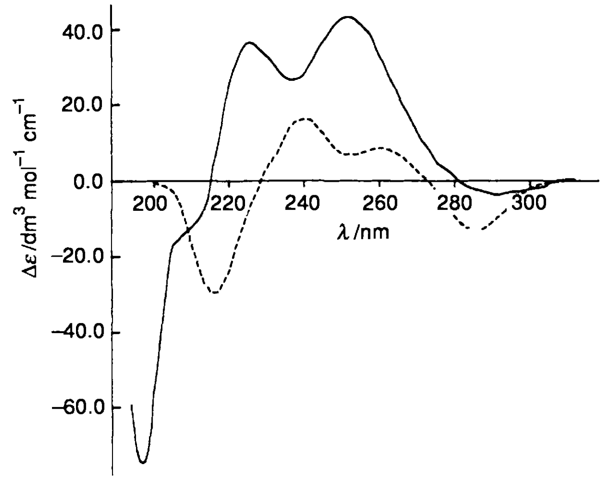


Fig. 2 Experimental CD spectrum of the first eluted enantiomer of **3b** in ethanol (——) and theoretical CD spectrum for the R configuration (----)

bridge double bonds to be 62.8° and that between a double bond and a ring to be 65.2°. Thus, a significant conjugation must exist over the entire conjugated system.

The molecule is chiral, but initial attempts to resolve it by chromatography on TAC with ethanol as the mobile phase had only moderate success. Two strongly overlapping bands with opposite signs of rotation were observed in the chromatogram, but the first eluted fraction with positive rotation gave a very weak CD spectrum with rapidly disappearing intensity. However, NMR studies of rates of inversion of dibenzo and dipyrido analogues of **3b** with saturated four-carbon bridges have indicated a strong acid catalysis,[18] and it could be suspected that minute traces of acid in the ethanol catalysed the racemization of **3b** and impeded the resolution at ambient temperature. This was confirmed by addition of 1% (v/v) of concentrated aqueous ammonia to the sample solution before injection in the chromatographic system. Much better resolution was obtained with baseline separation after two chromatographic cycles. The enantiomers racemized only slowly at ambient temperature in the presence of ammonia and gave CD spectra at −5 °C, which were mirror images. A similar case of catalysis of a conformational process (rotation about a C=C bond) by traces of acid in the solvent has been reported.[19]

The enantiomers could be racemized thermally in ethanol containing ammonia. By monitoring the intensity of a strong CD band at 251 nm at controlled temperatures, the rates and free energy barriers to ring inversion were determined in the temperature range 34–68 °C. The free energy barriers showed only very low temperature sensitivity in this range, corresponding to a small negative activation entropy (Table 1). This is as expected in view of the similar rigidity of the ground state and the transition state structures. The barrier for **3b** is *ca.* 5.0 kcal lower than for **3a**, practically the same difference as between **1a** and **1b**, although in the first case a N---N interaction and in the second a CH---N interaction provides a crucial contribution to the transition state energy. The reason for the unexpectedly small difference between the barriers of **3a** and **3b** may be a more crowded transition state than for **1a** and **1b**. The acid catalysis of the ring inversion of **3b** is probably caused by a N–H–N hydrogen bond in the transition state.[18]

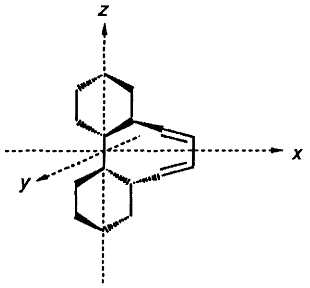
The UV spectrum of **3b** shows a maximum of moderate intensity at 274 nm, followed by monotonously increasing absorption to 200 nm (Table 2). The CD spectrum of the first eluted enantiomer showed a moderately strong negative band at 290 nm, stronger positive bands at 251 and 225 nm, and negative bands at 210 and 197 nm (Table 2 and Fig. 2). CNDO/S calculations on a molecule with the R configuration, with the geometry based on a molecular mechanics calculation, predict a first weak transition with fairly high negative rotational strength at 286 nm (Table 3). The calculated transition charges are mainly located in the diene bridge with smaller contributions from the ring atoms. The following transition, at 260 nm, is considerably stronger. It has positive rotational strength and the calculated orientation is along the long axis of the bipyridyl system. It can be compared with the 'A' transition in biphenyls[20–22] and it can probably be related to the experimental UV band at 274 nm and the CD band at 251 nm. If this assignment is correct, the transition follows the rule proposed by Mislow[21] for simple bridged biphenyls.

The following two transitions, weaker and with positive rotational strength, are oriented perpendicular to the z axis. Two strong, close-lying transitions with negative rotational strengths fall at 217 nm. Their transition moments are not symmetry adapted, but their resultant is x-polarized. The transitions at higher energy are quite weak with low rotational strength.

The theoretical CD spectrum was obtained by representing the calculated transitions as Gaussians (see the experimental section), and it shows a considerable similarity with the experimental spectrum, both with respect to the sequence of the band signs and with respect to the intensities (Fig. 2). Therefore, it seems reasonable to assume that the first eluted enantiomer has the R configurations.

The lowest energy singlet–singlet transition in the pyridine chromophore falls at *ca.* 280 nm and has n→π* character.[23,24] One could expect that interaction between the nitrogen lone pair orbitals in **3b** should lead to a splitting into a symmetric

Table 3 Calculated transition wavelengths, oscillator strengths (f), polarization directions, rotational strengths (R), and half bandwidths (Δ) for the R configuration of **3b**



Transition number	λ/nm	f	Polarization	R/DBM[a]	Δ/nm
1	286.1	0.007	z	−0.202	10.0
2	259.8	0.285	z	+0.140	10.0
3	239.5	0.139	x	+0.261	9.0
4	221.0	0.022	y	+0.07	8.0
5	216.8	0.149	x, y, z	−0.245	8.0
6	216.8	0.154	x, y, z	−0.236	8.0
7	206.3	0.005	x	+0.001	6.0
8	196.5	0.054	z	+0.010	6.0
9	196.0	0.015	x	+0.015	6.0
10	191.4	0.113	x	+0.032	6.0

[a] Debye × Bohr magnetons: DBM = 3.0934×10^{-53} A^2 m^3 s = 9.274×10^{-39} c.g.s. units.

and an antisymmetric combination, from which two low-energy $n \rightarrow \pi^*$ type transitions could originate. However, the CNDO/S calculations give no support to this idea. None of the ten first transitions reported in Table 3 has its origin in a molecular orbital, which has dominant contributions from nitrogen atomic orbitals. In theory, a $n \rightarrow \pi^*$ band should disappear in acid solution, but in practice this test cannot be performed with **3b** because of its rapid racemization in acid solution.

Experimental

Methods and Reagents.—The preparation of **3b** has already been described.[16] The chromatographic enantiomer separation was performed with the equipment described by Isaksson and Roschester,[25] using ethanol (flow rate 0.7 cm^3 min^{-1}) as the mobile phase. A sample of **3b** (5 mg) in ethanol (1 cm^3, containing 10 mm^3 of concentrated aqueous ammonia) was injected into the chromatographic system, and the eluate was passed through an UV (224 nm) and a polarimeter (365 nm) detector. The chromatogram displayed two partly overlapping bands ($k_1' = 0.20$, $k_2' = 0.49$,[26] with 1,3,5-tri-*tert*-butylbenzene as non-retained marker). Recycling of the first part of the first band (positive) and the last part of the second band (negative) gave baseline separation. The eluate was collected in flasks cooled with dry ice and containing concentrated aqueous ammonia (20 mm^3) and used directly for recording the CD spectrum and for the kinetic experiments. The concentration of the eluate was monitored with the aid of its UV spectrum.

Spectra.—The recording of the CD spectra and the kinetic experiments were performed with the aid of a JASCO Model J-500 A spectropolarimeter. The sample solution was contained in a 0.10 cm water-jacketed cell attached to a Haake Model N3 thermostat. The full spectrum was recorded at −5 °C and the kinetic runs at the temperatures given in Table 1.

The free energy barriers were calculated by the Eyring equation[27] with the rate constants k_{inv} obtained by eqn. (1).

$$k_{\text{inv}} = k_{\text{rac}}/2 \qquad (1)$$

The UV spectra were recorded with a Cary Model 2290 spectrophotometer.

Calculations.—The molecular mechanics calculations were performed with the MMP2-85 force field[28,29] using the MOLBUILD program[30] for construction of the input structure. The CNDO/S calculations of transition wavelengths and rotational strengths (Table 3) were performed using the program described in ref. 22. The theoretical CD spectrum was obtained by use of eqn. (2),[31] with R in Debye × Bohr

$$\Delta\varepsilon = 2.278\, \Sigma R_i\lambda_i/\Delta_i \exp - [(\lambda - \lambda_i)/\Delta_i]^2 \qquad (2)$$

magnetons (see Table 3), assuming a Gaussian shape of the bands and choosing half bandwidths at $1/e$ of the maximum intensity (Δ_i), which reproduce the bandwidths of the experimental spectrum.

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