

CHIROPTICAL PROPERTIES OF PYRROLIDINE DERIVATIVES*

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CD spectra of (*S*)-(-)-2-phenyl-1-methylpyrrolidine (*I*) and (*S*)-(-)-1-methyl-2-(2-tolyl)pyrrolidine (*II*) were calculated. Rotational strengths were calculated by direct procedure based on the CNDO/S-CI wave function. The most stable conformations were determined by total gradient optimization of molecular geometry and their molar fractions were calculated. CD spectra, constructed from the molar fractions and rotational strengths, agreed well with the experimental ones. Absolute configuration of compound *II* was established by the chemical correlation with (*S*)-(-)-hygrinic acid.

In one of our previous communications we reported a quantum chemical method capable of describing Cotton effects for compounds in which the symmetry of aromatic chromophore was perturbed by introduction of a chiral substituent¹. This method consists in calculation of preferred conformations using empirical potential functions and optical rotational strengths by summing the contribution of one-electron mechanism and mechanism of coupled oscillators. When comparing theoretical results with an experimental CD spectrum, the latter was separated into Gaussian or Lorentzian bands and these separated bands were compared with the rotational strengths obtained by calculation. In our previous work² we replaced this procedure with a new one, which was more suitable for flexible compounds. We assume that each conformer of a flexible compound contributes to the spectrum by its Cotton effects and the resulting spectrum represents a superposition of all these effects. Contributions of the single conformers depend not only on the ring size and rotational strength of the transition in question, but also on the conformer population. We used this procedure in the present communication for calculation of CD spectra of (*S*)-(-)-2-phenyl-1-methylpyrrolidine (*I*) and (*S*)-(-)-1-methyl-2-(2-tolyl)pyrrolidine (*II*). The optimized geometries were taken as a basis for the CNDO/S wave function calculation³ in the usual del Bene and Jaffé parameterization⁴ including configurational interaction. Thirty six singly excited configurations were considered, taking the six highest occupied and six lowest unoccupied orbitals. The CNDO/S-CI wave function thus obtained was employed for the direct rotational strength calculations using the programme of Gould and Hoffmann^{1,5}. A detailed procedure is described in our previous paper².

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Calculation of Preferred Conformations and Mole Fractions

1-Methyl-2-phenylpyrrolidine (*I*) and 1-methyl-2-(2-tolyl)pyrrolidine (*II*) are relatively flexible compounds. Their energy is influenced by the following degrees of freedom: rotation of the phenyl or 2-tolyl group, configuration of the methyl group



- I*, R = C₆H₅
II, R = 2-CH₃-C₆H₄

on the nitrogen atom, and conformation of the five-membered ring. For a starting estimation of geometry of stable conformers whose coordinates served as the basis for the gradient procedure, we considered the following changes: 1) the phenyl (2-tolyl) group pseudoaxial or pseudoequatorial 2) the methyl group pseudoaxial or pseudoequatorial. For each of the eight geometries the dependence of molecular energy on rotation (*i.e.* on the angle of the phenyl or 2-tolyl group) was followed by the EHT method.

We obtained 15 and 13 stable conformers for the compound *I* and *II*, respectively. Eight conformers of lowest energy were taken as the starting geometry for the gradient optimization method working in the CNDO/2 basis set⁶ in the standard parameterization⁷. Optimization of the geometries was interrupted when the energy gradient became smaller than 1 kJ/mm because for this value both the geometry and energy are determined with sufficient accuracy and the error of mole fraction calculations is smaller than 0.1%.

In the case of compound *I* further CD spectral calculations were done with only four conformers of lowest energy. In all the four conformations the five-membered ring adopts a slightly twisted envelope form (the angle between the opposite C—C bonds in this envelope ranges between 4° and 10°). The calculated energies, rotational strengths, mole fractions and molar ellipticities are given in Table I. Obviously, the final CD spectrum is contributed practically solely by the conformer *Id* whereas the population of the remaining conformers is too small to be discernible. The formula shows the bond and dihedral angles of the optimized geometries together with the interatomic distances.

In the case of compound *II* we encounter an analogous situation. As follows from energy values of seven energetically most advantageous conformers, the resulting spectrum is determined exclusively by the conformer *IIf* because the energy of the other conformers is too high and their molecular fraction is thus negligible. Also in this case the five-membered ring exists in a slightly twisted envelope form. Figs 1

TABLE I

Calculated values for (*S*)-(-)-1-methyl-2-phenylpyrrolidine (*I*) and (*S*)-(-)-1-methyl-2-(2-tolyl)-pyrrolidine (*II*)

Con-former	Energy kJ, mol ⁻¹ α	Dipole moment Cm · 10 ⁻³⁰ mole fraction	Rotational strength C ² m ³ s ⁻¹ · 10 ⁻⁵⁶	λ nm	$[\theta]$ deg m ² mol ⁻¹
<i>Ia</i>	24.26	5.95	— 7.4	259.87	— 0.29
	92°	0.000055	57.0	210.00	2.01
			229.1	188.20	7.23
<i>Ib</i>	33.79	6.22	9.6	261.07	0.38
	156°	0.000001	— 221.8	211.56	— 7.86
			— 837.2	189.15	— 26.54
<i>Ic</i>	192.58	6.65	— 17.4	259.89	— 0.69
	64°	0.000000	269.5	210.41	9.50
			1 857.9	188.49	58.70
<i>Id</i>	0.00	5.71	3.4	261.38	0.13
	28°	0.9999435	— 77.7	213.45	— 2.78
			230.8	189.96	7.35
<i>IIa</i>	78.32	6.30	— 2.5	267.77	— 0.10
	92°	0.0000000	— 143.4	217.82	— 5.24
			1 317.0	192.39	42.48
<i>IIb</i>	228.33	5.32	1.3	267.87	— 0.05
	239°	0.0000000	157.1	217.38	5.72
			— 963.9	192.27	— 31.06
<i>IIc</i>	102.25	5.69	— 6.4	267.70	— 0.26
	33°	0.0000000	— 7.9	216.31	— 0.29
			— 760.5	190.68	— 24.30
<i>IId</i>	263.53	6.66	— 10.7	269.95	— 0.44
	87°	0.0000000	— 300.9	220.08	— 11.39
			1 601.0	194.55	52.20
<i>IIe</i>	178.68	5.84	— 2.7	268.82	— 0.11
	60°	0.0000000	366.9	218.50	13.44
			— 400.2	212.34	— 1.99
<i>IIf</i>	0.00	5.45	— 5.2	268.67	— 0.21
	52°	1.0000000	28.8	216.34	1.05
			— 259.8	212.34	— 9.25
<i>IIg</i>	201.90	5.68	— 10.7	267.85	— 0.43
	256°	0.0000000	66.0	217.53	2.41
			158.7	207.14	5.51

and 2 depict the calculated CD spectra of compounds *I* and *II* together with their experimental spectra taken in cyclohexane. As seen from the figures, the agreement is very good.

Absolute Configuration of the Studied Compounds

Ab sulte configuration of the compound *I* has already been determined by chemical correlation with hygrinic acid⁸. Compound *II* was correlated in an analogous way. Reaction of 2-tolylmagnesium bromide with 1-methyl-2-pyrrolidone afforded 1-methyl-2-(2-tolyl)-2-pyrroline which was converted into its perchlorate. The salt was reduced with lithium aluminium hydride or formic acid to give the racemic base *II* which was resolved into optical antipodes with (-)-dibenzoyltartaric acid. Absolute configuration of the levorotatory enantiomer *II* was determined by the following reaction sequence: nitration with nitric acid gave the nitro derivative which was reduced to the amine. Diazotation, followed by hydrolysis afforded the corresponding phenol whose oxidation with chromium trioxide in concentrated sulfuric acid gave (*S*)-(-)-hygrinic acid, isolated as its cupric salt.

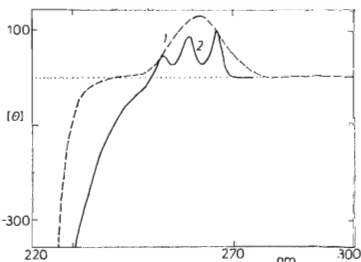


FIG. 1
Comparison of experimental (—, in cyclohexane) and calculated (-----) CD spectra of (*S*)-(-)-1-methyl-2-phenylpyrrolidine (*I*)

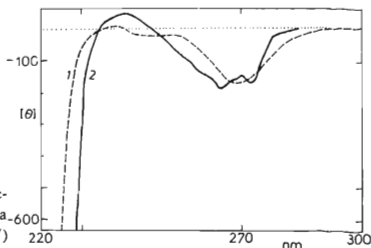


FIG. 2
Comparison of experimental (—, in cyclohexane) and calculated (-----) CD spectra of (*S*)-(-)-1-methyl-2-(2-tolyl)pyrrolidine (*II*)

EXPERIMENTAL

(S)-(–)-1-Methyl-2-phenylpyrrolidine (*I*)

A mixture of 1-methyl-2-phenyl-1-pyrrolinium chloride (250 g), concentrated formic acid (750 g) and fused potassium formate (750 g) was heated to 160°C for 5 h. After alkalization, the product was steam-distilled, the distillate neutralized with hydrochloric acid and concentrated to a small volume. The base, liberated with alkali, weighed 143 g (70%), b.p. 92°C/2.1 kPa.

The product *I* (16.1 g) was converted into its salt with *O,O'*-dibenzoyltartaric acid (35.5 g). Six crystallizations from ethanol afforded the salt, m.p. 136°C, $[\alpha]_D^{20} = -62.3^\circ$ (*c* 2, ethanol). The liberated optically active base *I* boiled at 83–86°C/1.7 kPa, $[\alpha]_D^{20} = -53.6^\circ$ (neat).

(S)-(–)-1-Methyl-2-(2-tolyl)pyrrolidine (*II*)

1-Methyl-2-pyrrolidone (30 g) was heated with Grignard reagent, prepared from magnesium (19.4 g) and 2-bromotoluene (128 g) in ether (500 ml). After addition of barium hydroxide, the formed unsaturated base was steam-distilled, the distillate neutralized with hydrochloric acid and concentrated to a small volume. The obtained 1-methyl-2-(2-tolyl)-1-pyrrolinium chloride was treated with sodium perchlorate (41 g) in ethanol, affording 1-methyl-2-(2-tolyl)-1-pyrrolinium perchlorate. Five crystallizations from ethanol gave 18 g (28%) of the product, m.p. 138–139°C. For $C_{12}H_{16}ClNO_4$ (273.7) calculated: 52.65% C, 5.89% H, 5.12% N, 12.95% Cl; found: 52.55% C, 6.11% H, 5.21% N, 13.47% Cl.

a) Reduction of 1-methyl-2-(2-tolyl)-1-pyrrolinium perchlorate (38.4 g) with lithium aluminium hydride (5.8 g) in ether (350 ml) produced 21.4 g of racemic product *II*, b.p. 109–111°C/2.1 kPa.

b) A mixture of 1-methyl-2-(2-tolyl)-1-pyrrolinium chloride, 98% formic acid (49 ml) and freshly fused potassium formate (49 g) was heated to 160°C till evolution of carbon dioxide ceased (about 4 h). After cooling, the mixture was made alkaline with concentrated potassium hydroxide solution and the base was steam-distilled. The aqueous distillate was neutralized with 5*M*-HCl to methyl orange. The solution (about 5 000 ml) was concentrated and the indicator removed by boiling with charcoal. After filtration, the base was liberated with concentrated potassium hydroxide solution and taken up in ether (3 × 30 ml). The combined ethereal layers were dried over solid potassium hydroxide and filtered. Ether was removed by distillation through a column and the base was distilled, b.p. 105–109°C/1.31 kPa; yield 6.6 g.

Compound *II* (21.4 g) was mixed with *O,O'*-dibenzoyltartaric acid (43.8 g) in ethanol (250 ml). Seven crystallizations from ethanol gave 9.7 g of dibenzoyltartrate, m.p. 148.5–151°C, $[\alpha]_D^{20} = -65.0^\circ$ (*c* 2, ethanol). The liberated base boiled at 107–108°C/2.5 kPa, $[\alpha]_D^{20} = -76.0^\circ$ (neat).

Correlation of *(S)*-(–)-1-Methyl-2-(2-tolyl)pyrrolidine (*II*) with *(S)*-(–)-Hygrinic Acid

A cooled and stirred solution of *(S)*-*II* (4.9 g; 28 mmol; $[\alpha]_D^{20} = -49.1^\circ$ (neat, 1.0 dm)) in chloroform (4 ml) was nitrated with a mixture of nitric acid (4.2 ml; $d_{20} = 1.34 \text{ g cm}^{-3}$) and concentrated sulfuric acid (5.6 ml). The reagent was added dropwise at such a rate as to keep the temperature between 5–10°C. The mixture was then stirred at room temperature for 15 min, heated to 70°C for 20 min, cooled, diluted with water and made alkaline by dropwise addition of sodium hydroxide solution under stirring and cooling. The product was extracted with chloroform (5 × 50 ml), the chloroform extracts were combined, dried over calcined sodium sulfate, filtered and taken down. The residue was dissolved in 25% hydrochloric acid (42 ml) and granulated tin (14 g) was added. After reflux for 4 h, the mixture was cooled and treated with concentrated solution of sodium hydroxide. The liberated base was steam-distilled and the distillate (about

3 500 ml) was neutralized with hydrochloric acid and concentrated (500 ml). The amine was liberated by addition of concentrated solution of sodium hydroxide and taken up in ether (6×40 ml). The ethereal layers were combined, dried over solid potassium hydroxide, filtered and the solvent was distilled off through a Vigreux column. Distillation gave 3.3 g of the amine, b.p. $153-158^\circ\text{C}/1.1$ kPa. Its ^1H NMR spectrum confirmed the presence of amino group bonded to the aromatic nucleus.

A solution of the amine (3.3 g) in $2\text{M-H}_2\text{SO}_4$ (100 ml) was cooled to 0°C and diazotized with sodium nitrite (2g) in water (20ml). After each addition of sodium nitrite the flask was stoppered and shaken till the nitrous gases were absorbed. After reflux for 1 h, chromium trioxide (21.4 g; equivalent to the phenol derivative) and concentrated sulfuric acid (18.5 ml) were added and the mixture was refluxed for 4 h. At the beginning of the heating considerable evolution of carbon dioxide occurred and the colour changed from reddish brown to green. After cooling, the mixture was diluted with water and while hot it was treated with hot aqueous barium hydroxide solution to precipitate the SO_4^{2-} and Cr^{3+} ions. The amount of barium hydroxide was calculated for sulfuric acid and sulfate ions present in the mixture. The mixture was then titrated with barium hydroxide solution until it gave a negative test for SO_4^{2-} ions. (The solution must not be over-titrated because barium salt of hygrinic acid is insoluble.) The precipitated barium sulfate was filtered from the hot mixture and washed with hot water. The filtrate was concentrated to about 300 ml and boiled with freshly prepared cupric hydroxide. The precipitated cupric oxide was filtered off and the filtrate, containing blue cupric salt of hygrinic acid, was taken down. The residue was taken up in chloroform and the cupric salt was precipitated with ether. The obtained salt (0.5 g) was dissolved in ethanol (100 ml) and decomposed by introduction of hydrogen sulfide for 1 h. After filtering the precipitated cupric sulfide, the filtrate was taken down and the residue crystallized from ethanol-ether, m.p. $167-170^\circ\text{C}$, $[\alpha]_{\text{D}}^{20} = 18.2^\circ$ (c 2.1, water).

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