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Circular Dichroism of 3-Hydroxy-2-pyrrolidone

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(+)-3-Hydroxy-2-pyrrolidone has been prepared, its absolute configuration confirmed, and its circular dichroism spectrum recorded. For the same absolute configuration, this compound gives an $n\rightarrow\pi^*$ Cotton effect of the same sign as 3-amino-2-pyrrolidone, but of opposite sign to that of 3-amino-2-pyrrolidone hydrochloride and 3-methyl-2-pyrrolidone.

The $n\rightarrow\pi^*$ Cotton effect (CE) of lactams, especially substituted 2-pyrrolidones, has been extensively studied, both experimentally [1-3] and theoretically.[1,4,5] Several sector rules have been proposed for the prediction of the sign of this CE from molecular structure.[6-8] In this connection 3-substituted 2-pyrrolidones are of special interest as it has been found that the sign and the magnitude of the $n\rightarrow\pi^*$ CE are very sensitive to the nature of the C3 substituent.

It was shown [9] that the sign of the long-wavelength CE of (*S*)-3-methyl-2-pyrrolidone is opposite to that predicted by the quadrant rule for the amide $n\rightarrow\pi^*$ transition.[6] Furthermore, the sign of the $n\rightarrow\pi^*$ CE of (*S*)-3-amino-2-pyrrolidone, which is in agreement with that predicted by the same rule, is reversed on protonation of the amino group.[3,10] The circular dichroism (CD) spectrum of (*R*)-3-hydroxy-4,4-dimethyl-2-pyrrolidone shows a pronounced solvent effect; the $n\rightarrow\pi^*$ CE having opposite sign in water and methanol solution.[3] The negative CE observed [3] for (*R,R*)-3,4-dihydroxy-2-pyrrolidone obviously is the sum of the contributions from the 3- and 4-substituents as (*S*)-4-hydroxy-2-pyrrolidone has been shown [5] to exhibit a positive $n\rightarrow\pi^*$ CE. (The *R* configuration assigned [20] to (−)-4-hydroxy-2-pyrrolidone used in Ref. 5 probably is incorrect.[21]) Thus no definite conclusion regarding the contribution from a 3-hydroxy group to the optical activity of γ-lactams can [1] be made from published data. It was, therefore, deemed desirable to investigate the CD of chiral 3-hydroxy-2-pyrrolidone.

In addition to the $n\rightarrow\pi^*$ band at 210 – 225 nm, (*R*)-3-methyl-2-pyrrolidone [2] and (*S*)-3-amino-2-pyrrolidone [10] were found to display a CD band in the 190 nm region. Although the band was bathochromically shifted with decreasing solvent polarity it was assigned to a $\pi\rightarrow\pi^*$ transition. In acetonitrile solution (*S*)-3-amino-2-pyrrolidone showed a third CD band at 200 nm.[10] Among the factors which could be responsible for the appearance of this band, *e.g.* intermolecular association and a separate electronic transition, only the former could be eliminated.

(+)-3-Hydroxy-2-pyrrolidone was prepared from 2-hydroxy-4-phthalimidobutyric acid, resolved using (−)-1-phenylethylamine as resolving agent. Hydrazinolysis of (−)-2-hydroxy-4-phthalimidobutyric acid thus obtained afforded (+)-4-amino-2-hydroxybutyric acid which was cyclized to (+)-3-hydroxy-2-pyrrolidone.

The absolute configuration of (−)-4-amino-2-hydroxybutyric acid was found [11] to be *S* by partial deamination of (*S*)-(+)-2,4-diaminobutyric acid with sodium nitrite. On the basis of the stereochemical course of the nitrous acid deamination of aliphatic α-amino acids,[12] it was assumed that the deamination of (*S*)-2,4-diaminobutyric acid proceeded with retention of configuration. In order to confirm this configurational assignment, and hence the absolute configuration of (+)-3-hydroxy-2-pyrrolidone, the CD spectrum of (+)-4-amino-2-hydroxybutyric acid was compared with those of a number of closely related α-hydroxy-acids of known configuration. The CD curve recorded for (+)-4-amino-2-

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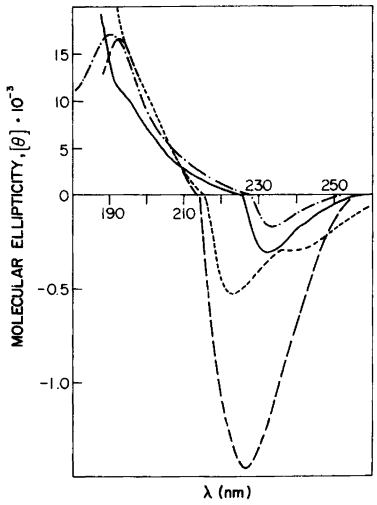
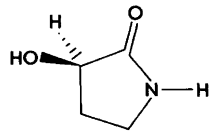


Fig. 1. Circular dichroism of (*R*)-3-hydroxy-2-pyrrolidone in water (———), ethanol (– – –), 2,2,2-trifluoroethanol (—·—) and acetonitrile (. . .). [Note the different scales on the ordinate.]

hydroxybutyric acid hydrochloride was essentially enantiomeric to those of (*S*)-α-hydroxyacids.[13] (+)-4-Amino-2-hydroxybutyric acid and (+)-3-hydroxy-2-pyrrolidone could thus be assigned the *R* configuration, in agreement with previous reports.[11]

The CD spectra of (*R*)-3-hydroxy-2-pyrrolidone (*1*) in water, ethanol, 2,2,2-trifluoroethanol and acetonitrile are shown in Fig. 1. Except for acetonitrile solution there is a single negative CD band above 215 nm. The non-Gaussian shape and low intensity of this band suggest an appreciable overlap with the much more intense positive CD band at shorter wavelength. The apparent location of the negative CD maxima at 226 – 234 nm therefore does not correspond to the actual spectral region of this transition which should be at shorter wavelengths. It has been shown that such frequency shifts, which commonly occur with adjacent Gaussians of opposite sign,[14] depend on their relative magnitudes and extent of overlap and that the *actual* frequency difference is generally much less



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than the *observed* value.[14] Thus, in ethanol solution, where the intensity of the CE is greatly enhanced (Fig. 1), the band should be closest to its real position. The $n\rightarrow\pi^*$ CE of (*S*)-3-amino-2-pyrrolidone in ethanol was reported [10] to appear at 222 nm, which is fairly close to the position (226 nm) of the negative CD band of (*R*)-3-hydroxy-2-pyrrolidone in the same solvent. On this basis we assign the negative CE's observed in water, ethanol and 2,2,2-trifluoroethanol to the $n\rightarrow\pi^*$ transition of the lactam chromophore. For the same absolute configuration, 3-hydroxy-2-pyrrolidone thus gives an $n\rightarrow\pi^*$ CE of the same sign as 3-amino-2-pyrrolidone but of opposite sign to that of 3-amino-2-pyrrolidone hydrochloride and 3-methyl-2-pyrrolidone. Konno *et al.*[3] proposed that in γ-lactams which have no lone pair electrons on the C3 substituent the sign of the $n\rightarrow\pi^*$ CE is determined by the ring chirality. On the other hand, if the C3 substituent has lone pair electrons the configuration at C3 determines the sign of the CE.[3] Our results are in agreement with their proposal.

The CD spectrum of (*R*)-3-hydroxy-2-pyrrolidone in acetonitrile is distinctly different from those in hydroxylic solvents (Fig. 1). Two bands are observed above 215 nm. On 250-fold dilution (to 4×10^{-4} M) the intensity of both bands diminished, more so for the band with an apparent maximum at 223 nm. Unfortunately, it was not possible to determine if the 223 nm band disappears on further dilution due to the low intensity of the CD signal. Lactams are known to associate in nonpolar solvents [2,15,16] and the appearance of two bands in acetonitrile could be due to such intermolecular association.

In ethanol and 2,2,2-trifluoroethanol positive maxima were observed at 192.5 and 190 nm, respectively, which is close to the wavelength maxima reported for the $\pi\rightarrow\pi^*$ band of (*S*)-3-amino-2-pyrrolidone [10] and (*R*)-3-methyl-2-pyrrolidone.[2] In water and acetonitrile the band appears as a shoulder at 191 and 196 nm, respectively. As in the case of the analogous 3-methyl [2] and 3-amino compounds,[10] the observed solvent effect on the band position appears to be the opposite of that expected for a $\pi\rightarrow\pi^*$ transition.

EXPERIMENTAL

Melting points, determined with a Thomas-Hoover Uni-melt capillary melting point apparatus, are uncorrected. Optical rotations at the sodium D line were measured in a 1 dm tube with a Perkin-Elmer 141 polarimeter. Microanalyses were done by

the Microanalytical Laboratory, University of California, Berkeley. CD measurements were made with a Jasco J-500 A spectropolarimeter at 20 °C with cell lengths of 0.1 – 10 mm. CD data are given below for the zero line intersections, lowest wavelengths measured, and the maxima and shoulders observed.

CD. (R)-3-hydroxy-2-pyrrolidone. Water (*c* 0.1): $[\theta]_{257}$ 0, $[\theta]_{232}$ −310, $[\theta]_{226}$ 0, $[\theta]_{191}$ +12.000, $[\theta]_{186}$ +24.400. Ethanol (*c* 0.1): $[\theta]_{255}$ 0, $[\theta]_{226}$ −1460, $[\theta]_{214.5}$ 0, $[\theta]_{192.5}$ +16.600, $[\theta]_{189}$ +14.100. 2,2,2-Trifluoroethanol (*c* 0.1): $[\theta]_{253}$ 0, $[\theta]_{234}$ −165, $[\theta]_{228}$ 0, $[\theta]_{190}$ +17.200, $[\theta]_{182}$ +11.400. Acetonitrile (*c* 1.0): $[\theta]_{270}$ 0, $[\theta]_{239}$ −300, $[\theta]_{223}$ −530, $[\theta]_{196}$ +13.400, $[\theta]_{188}$ +29.500.

(±)-2-Hydroxy-4-phthalimidobutyric acid was prepared according to a method first described by Talbot *et al.*[17] To a solution of 2-hydroxybutyrolactone[18] (62 g, 0.61 mol) in 250 ml of dimethylformamide was added potassium phthalimide (102 g, 0.55 mol). The reaction mixture was refluxed for 8 h and the solvent evaporated *in vacuo*. The residue was dissolved in water and the acid was precipitated by the addition of 5 N HCl. After two recrystallizations from water, 107 g (79 %) of product was obtained: m.p. 147 – 148 °C. Lit.[19] m.p. 147 – 148 °C.

(R)-2-Hydroxy-4-phthalimidobutyric acid. (−)-1-Phenylethylamine (46 g, 0.38 mmol) and (±)-2-hydroxy-4-phthalimidobutyric acid (95 g, 0.38 mmol) were mixed with cooling and 200 ml of ethanol was added. The mixture was warmed to effect solution and then left overnight at room temperature. The salt obtained (76 g) was recrystallized six times from about 30 % solutions in ethanol before constant melting point (152 – 153 °C) and optical rotation $[\alpha]_D^{22}$ +4.0° (*c* 2.0, 95 % ethanol) were obtained. The yield was 19.3 g (27 %). Anal. $C_{20}H_{22}N_2O_5$: C, H, N.

The resolved salt (17.0 g, 0.046 mol) was treated with 1 N HCl and the liberated acid was recrystallized twice from water: m.p. 152 – 153 °C, $[\alpha]_D^{22}$ −5.9° (*c* 1.5, 95 % ethanol), yield 8.6 g (75 % based on resolved salt). Anal. $C_{12}H_{11}NO_5.H_2O$: C, H, N.

(R)-4-Amino-2-hydroxybutyric acid. To 7.5 g (0.03 mol) of (*R*)-2-hydroxy-4-phthalimidobutyric acid in hot ethanol (300 ml) was added hydrazine hydrate (2.0 g, 0.04 mol) and the solution was refluxed for 2 h. The ethanol was evaporated *in vacuo*, the residue treated with water (125 ml) and the resulting mixture adjusted to pH 5 by the addition of acetic acid. The precipitated phthaloyl hydrazide was filtered off and washed with water. The filtrate was then concentrated *in vacuo* and the residue recrystallized twice from 90 % ethanol: m.p. 200 – 201 °C, $[\alpha]_D^{22}$ +28.0° (*c* 1.1, water), yield 2.6 g (73 %). Lit.[18] m.p. 199 – 201 °C, $[\alpha]_D$ +27.5° (*c* 1.0, water).

(R)-3-Hydroxy-2-pyrrolidone. (*R*)-4-Amino-2-hydroxybutyric acid (2.0 g, 0.017 mol) was left for 2 days at room temperature with 100 ml of absolute ethanol saturated with HCl. The residue after evaporation of the ethanol was dissolved in 50 ml chloroform – ethanol (4:1) and treated with a stream of dry ammonia. The precipitated ammonium chloride was removed and the solvent evaporated. The residue was left at +5 °C for 3 days in 150 ml of methanol saturated with ammonia. Evaporation of the solvent afforded a residue from which the title compound was extracted with chloroform: m.p. 102 – 103 °C (from ethanol – ether), $[\alpha]_D^{22}$ +121.9° (*c* 0.7, chloroform), yield 0.6 g (35 %). Anal. $C_4H_7NO_2$: C, H, N. Lit.[11] m.p. 103 – 104.5 °C, $[\alpha]_D^{25}$ −113° (*c* 0.77, chloroform) for the enantiomer.

REFERENCES

1. Urry, D. W. *Annu. Rev. Phys. Chem. 19* (1968) 477.
2. Greenfield, N. J. and Fasman, G. D. *J. Am. Chem. Soc. 92* (1970) 177.
3. Konno, T., Meguro, H. and Tuzimura, K. *Tetrahedron Lett.* (1975) 1305.
4. Richardson, F. S., Strickland, R. and Shillady, D. D. *J. Phys. Chem. 77* (1973) 248.
5. Geiger, R. E. and Wagniere, G. H. *Helv. Chim. Acta 58* (1975) 738.
6. Litman, B. J. and Schellman, J. A. *J. Phys. Chem. 69* (1965) 978.
7. Ogura, H., Takayanagi, H., Kubo, K. and Furuhata, K. *J. Am. Chem. Soc. 95* (1973) 8056.
8. Ong, E. C., Cusachs, L. C. and Weigang, O. E., Jr. *J. Chem. Phys. 67* (1977) 3289.
9. Ringdahl, B. and Dahlbom, R. *Tetrahedron Lett.* (1978) 3475.
10. Greenfield, N. J. and Fasman, G. D. *Biopolymers 7* (1969) 595.
11. Woo, P. W. K., Dion, H. W. and Bartz, Q. *Tetrahedron Lett.* (1971) 2617.
12. Brewster, P., Hiron, F., Hughes, E. D., Ingold, C. K. and Rao, P. A. D. S. *Nature 166* (1950) 179.
13. Craig, J. C. and Ringdahl, B. *To be published.*
14. Wellman, K. M., Laur, P. H. A., Briggs, W. S., Moscowitz, A. and Djerassi, C. *J. Am. Chem. Soc. 87* (1965) 66.
15. Urry, D. W. *J. Phys. Chem. 72* (1968) 3035.
16. Walmsley, J. A. *J. Phys. Chem. 82* (1978) 2031.
17. Talbot, G., Gaudry, R. and Berlinguet, L. *Can. J. Chem. 36* (1958) 593.
18. Opfermann, A. C. J. *Brit. Patent* (1953) 688 253; *Chem. Abstr. 48* (1954) 3996.
19. Saito, Y., Hashimoto, M., Seki, H. and Kamiya, T. *Tetrahedron Lett.* (1970) 4863.
20. Matsumoto, T., Trueb, W., Gwinner, R. and Eugster, C. H. *Helv. Chim. Acta 52* (1969) 716.
21. Pellegata, R., Pinza, M. and Pifferi, G. *Synthesis* (1978) 614.

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