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ABSOLUTE CONFIGURATION AND CIRCULAR DICHROISM OF 3-METHYL-2-PYRROLIDONE

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Lactams, especially substituted 2-pyrrolidones, have been extensively used as model compounds for the elucidation of the optically active transitions of the amide chromophore.[1] Two bands are generally observed in their circular dichroism spectra, one near 190 nm and another around 220 nm. The sign of the 220 nm Cotton effect, which is associated with the $n \longrightarrow \pi^*$ transition of the lactam chromophore, has been proposed to be governed by a quadrant rule.[2] If the pyrrolidone ring is assumed to be effectively planar the only source of dissymmetry in substituted pyrrolidones is the substituent itself. However, nonplanarity of the pyrrolidone ring may be an additional source of dissymmetry and may significantly influence the optical activity. Substituents may enhance the nonplanarity and the resulting skeletal contributions to the rotatory strength of the $n \longrightarrow \pi^*$ transition of the lactam group may reinforce or oppose the substituent contribution to the optical activity.

In this connection the chiroptical properties of 3-methyl-2-pyrrolidone are of special interest. (+)-3-Methyl-2-pyrrolidone, which was originally assigned the *R* configuration by Fleš and Ghyczy,[3] was found to display an $n \longrightarrow \pi^*$ Cotton effect of opposite sign to that predicted by the quadrant rule for the amide chromophore.[1] However, according to Schellman, this molecule should be specially prone to obey the quadrant rule as substituent and skeletal effects reinforce one another.[4] Agreement with theory seemed to be restored as Fleš admitted that the *R* configuration originally assigned to (+)-3-methyl-2-pyrrolidone was in error.[5]

In the present communication we present the results from a reinvestigation of the chiroptical properties of chiral 3-methyl-2-pyrrolidone. Having carefully scrutinized the publications establishing the absolute configuration of (+)-3-methyl-2-pyrrolidone,[3,6] we come to the conclusion that the original configurational assignment is correct. In addition, we have also made a new and independent investigation which proves that (+)-3-methyl-2-pyrrolidone in fact has the *R* configuration, as was originally proposed. (+)-3-Methyl-2-pyrrolidone has been correlated to (*R*)-(+)-methylsuccinic acid, the configuration of which has been rigorously established by the use of the quasiracemate method,[7] by a purely chemical method[8] and also by ORD[9] and CD measurements.[10] (*R*)-(+)-Methylsuccinic acid was converted to its dimethyl ester which on reduction with $LiAlH_4$ gave (*R*)-(+)-2-methyl-1,4-butanediol. By reaction with PBr_3 in pyridine the diol was converted to the corresponding dibromide. The latter, by cyclization with benzylamine, yielded (*R*)-(-)-*N*-benzyl-3-methylpyrrolidine ($[\alpha]_D^{22}$ -10.1° (*c* 3.2, ethanol)) having the opposite optical rotation to that of the product ($[\alpha]_D^{22}$ +9.0° (*c* 2.9, ethanol)) obtained by reduction of the benzoyl derivative of (-)-3-methylpyrrolidine. The latter compound was prepared by $LiAlH_4$ reduction of (-)-3-methyl-2-pyrrolidone obtained from (+)-2-methyl-4-phthalimidobutyric acid.[11] Since the reaction sequences described imply no change in the configuration of the chiral centers it follows that (-)-3-methyl-2-pyrrolidone must have the *S* configuration.

The quadrant rule for the amide $n \longrightarrow \pi^*$ transition[2] predicts a positive long wavelength Cotton effect for (*S*)-3-methyl-2-pyrrolidone. Molecular orbital calculations of the rotatory strength for the planar conformation of (*S*)-3-methyl-2-pyrrolidone also give positive values, though the magnitude varies considerably.[5,12,13] However, the observed Cotton effect is negative ($[\Theta]_{217}$ -5.900°, *c* = 0.02 g/100 ml methanol and $[\Theta]_{223}$ -2.200°, *c* = 0.02 g/100 ml hexane-dioxane (9:1)). The discrepancy between the calculated and experimental results suggests that nonplanarity of the pyrrolidone ring makes a substantial contribution to the circular dichroism of (*S*)-3-methyl-2-pyrrolidone

X-ray analysis[14] and theoretical calculations[4] have shown that the 2-pyrrolidone ring of γ-lactams is not necessarily planar. The structure of 3-methyl-2-pyrrolidone has not been studied experimentally but theoretical studies have indicated that the methyl group is held preferentially in a quasi-equatorial position with C4 displaced out of the plane of the lactam group.[4] The location of C4 relative to the lactam plane is related to the configuration at C3. On the basis of these calculations the preferred conformation of (*S*)-(-)-3-methyl-2-pyrrolidone may be assumed to be the "envelope form" depicted in Fig. 1.

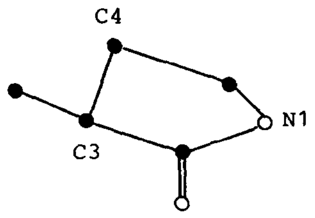
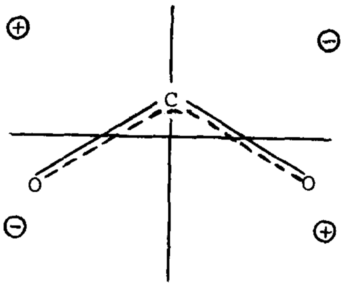


Fig. 1

It has been proposed by Konno *et al.* that in γ-lactams which have no lone pair electrons on the C3 substituent the sign of the $n \longrightarrow \pi^*$ Cotton effect is determined by the ring chirality.[15]

Recently, Weigang and coworkers introduced a new sector rule for lactams.[16,17] The lactam group is considered as a perturbed modification of the carboxylate anion which itself has C_{2v} symmetry and to which applies an octant rule with regular ketone octant rule signs (Fig. 2a). The effect of the symmetry lowering caused by the lactam nitrogen is a distortion of the YZ nodal plane to form a spherical surface. Although there is still some uncertainty about the degree of this distortion, it is likely that the methyl group of (*S*)-3-methyl-2-pyrrolidone is nearly nodal. It is also quite possible that C4 resides in the enlarged negative upper sector according to the new sector rule (Fig. 2b). This would explain the observed negative Cotton effect for the compound.



Signs for upper sectors

Fig. 2a

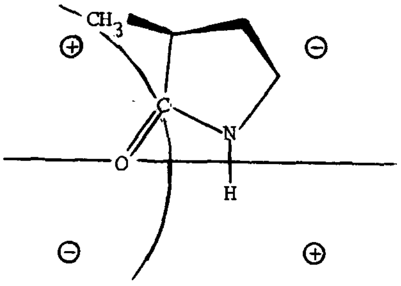
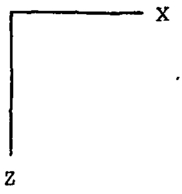


Fig. 2b



Y out of plane of paper

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