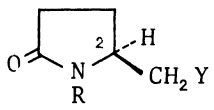
CHEMISTRY LETTERS, pp. 461-464, 1977. Published by the Chemical Society of Japan

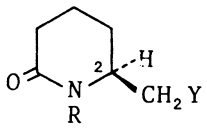
THE INFLUENCES OF SUBSTITUENT AND CONFIGURATIONAL GEOMETRY ON THE CIRCULAR DICHROISM OF LACTAMS

Toshio WAKABAYASHI,* Yoshinori KATO, Kenzo WATANABE, and Masahiko SAITO
Teijin Institute for Biomedical Research
4-3-2 Asahigaoka, Hino, Tokyo 191

Chiroptical properties of five- and six-membered monocyclic lactams 1-10 of known absolute configuration have been studied. It was found that the N-methyl group dominantly contributed to the n→π* Cotton effects of δ-lactams; N-methylated lactams 7-10 exhibit positive Cotton effects while the unsubstituted lactam 6 shows a negative Cotton effect.

Intense attention has been paid in recent years on optical rotation studies on the amide chromophore, as it is the smallest subunit of proteins.[1] In connection with our asymmetric synthesis of substituted pyrrolidones[2] and piperidones[3] we have investigated a relationship between the Cotton effect





1 R=H, Y=CO_2H
2 R=CH_3, Y=CO_2H
3 R=CH_3, Y=CO_2CH_3
4 R=CH_3, Y=CH_2OH
5 R=CH_3, Y=CH_2Br

6 Y=H, Y=CO_2H
7 R=CH_3, Y=CO_2H
8 R=CH_3, Y=CO_2CH_3
9 R=CH_3, Y=CH_2OH
10 R=CH_3, Y=CH_2Br

and the absolute configuration. The five- or six-membered lactams are good model compounds for a study of optical activity of the amide chromophore since they are considered to be conformationally rigid.

The absolute configurational determination of (S)-5-oxo-2-pyrrolidineacetic acid (1) and (S)-6-oxo-2-piperidineacetic acid (6) and the derivatization of the compounds 2, 3, 7, 8 and 9 have recently been reported.[2,3] Reduction of the ester 3 with $NaBH_4$ gave the compound 4. The bromides 5 and 10 were obtained by treatment of 4 and 9 with phosphorous tribromide, respectively.

Table CD Data of Lactams of MeOH[a]

Compound	[θ]	λ(nm)
(S)-5-oxo-2-pyrrolidineacetic acid (1)	-6,400	215
(S)-1-methyl-5-oxo-2-pyrrolidineacetic acid (2)	-2,400	223
methyl (S)-1-methyl-5-oxo-2-pyrrolidineacetate (3)	-2,200	223
(S)-5-(2-hydroxyethyl)-1-methyl-2-pyrrolidone (4)	-4,800	217
(S)-5-(2-bromoethyl)-1-methyl-2-pyrrolidone (5)	-3,200	219
(S)-6-oxo-2-piperidineacetic acid (6)	-3,900	220
(S)-1-methyl-6-oxo-2-piperidineacetic acid (7)	+1,700[b]	228
methyl (S)-1-methyl-6-oxo-2-piperidineacetate (8)	+1,300[b]	227
(S)-6-(2-hydroxyethyl)-1-methyl-2-piperidone (9)	+600[b]	229
(S)-6-(2-bromoethyl)-1-methyl-2-piperidone (10)	+900[b]	228

a) All the CD spectra were recorded on JASCO spectropolarimater, J-20.

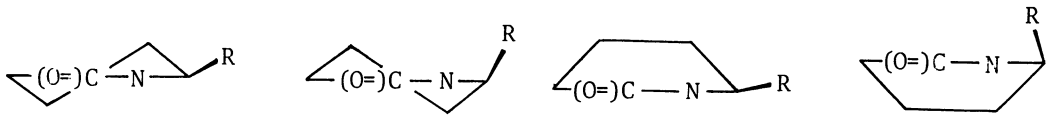
b) Corrected for 59% optical purity of the sample used.

The CD data of the lactams are summarized in Table. All the pyrrolidones 1-5 with side chains of (S)-configuration at C-2 showed the negative $n\rightarrow\pi^*$ Cotton effect. Urry[4] recently reported the crystal structure of (S)-5-iodomethyl-2-pyrrolidone in which the amide hydrogen was placed in the plane of the amide group. Either (S)-5-oxo-2-pyrrolidineacetic acid (1) or its N-methylated compound (2) shows the negative sign of $n\rightarrow\pi^*$ Cotton effect.

Since these lactams obey Schellman's quardrant rule on the sign of the n→π* Cotton effect of amides,[5] the N-substituted methyl group in 2 is considered to be also in the plane of the amide group. The negative Cotton effects of other pyrrolidones 3, 4 and 5 suggest that N-methyl group is in the plane of the amide group in these compounds, also. Furthermore it should be pointed out that CD of (S)-pyroglutamic acid has a positive Cotton effect,[6] but (S)-5-oxo-2-pyrrolidineacetic acid 1 with the same absolute configuration shows the opposite sign. These results are consistent with Urry's observation in the substituent effects on the sign of Cotton effect.[4]

On the other hand the corresponding six-membered piperidones with C-2 substituents of (S)-configuration behave differently. The remarkable effect caused by a N-methyl group is the inversion in the sign of n→π* Cotton effects; the N-methylated lactam 7 exhibits a positive sign, while 6 shows a negative sign.

Ogura et al. recently reported the reversal of the n→π* Cotton effects between (-)-menthone lactam and N-methyl-(-)-menthone lactam.[7] They explained the results by the conformational equilibrium of a sevenmembered lactam.



A B C D

R: C-2 substituent

The remarkable effect of the N-methyl substituent on the n→π* Cotton effect of a sixmembered lactam will be also interpreted by the conformational equilibrium. Of four different ring conformations A, B, C and D for the δ-lactams 6-10, the conformer D can be excluded because of the flagpole arrangement of the acetic acid group. The negative Cotton effect of the lactam 6 coincided with the one anticipated on the basis of the chirality[8] of a preferred half-chair conformer A. N-Methylated compounds 7-10 will be more stable in the half-chair conformer B than in the conformers A and C by the repulsion between the N-methyl group and the acetic acid group.

Above results involve the novel demonstration of a high sensitivity of Cotton effect to the substituent on N-atom in δ-lactams and are also useful for determination of the absolute configuration of the series of C-2 substituted pyrrolidones or C-2 substituted piperidones.

Acknowledgement.

We thank Drs. T. Noguchi and S. Ishimoto for their support.

References

1. a. B. J. Litman and J. A. Schellman, J. Phys. Chem., 69, 978 (1965).
   b. D. W. Urry, Proc. Nat. Acad. Sci. U.S., 60, 394 (1968).
   c. D. W. Urry, ibid., 60, 1114 (1968).
   d. N. J. Greenfield and G. D. Fasman, J. Amer. Chem. Soc., 92, 177 (1970).
   e. H. Ogura, H. Takayanagi and K. Furuhata, Chemistry Lett., 387 (1973).
2. T. Wakabayashi, Y. Kato and K. Watanabe, Chemistry Lett., 1283 (1976).
3. T. Wakabayashi, K. Watanabe, Y. Kato and M. Saito, Chemistry Lett., 223 (1977).
4. J. A. Molin-Case, E. Fleischer and D. W. Urry, J. Am. Chem. Soc., 92, 4728 (1970).
5. J. A. Schellman, Accounts Chem. Res., 1, 144 (1968).
6. D. W. Urry, Ann. Rev. Phys. Chem., 19, 477 (1968).
7. H. Ogura, H. Takayanagi, K. Kubo and K. Furuhata, J. Am. Chem. Soc., 95 8056 (1973).
8. O. Červinka, L. Hub, F. Snatzke and G. Snatzke, Collection Czechslov. Chem. Comm., 38, 897 (1973).

(Received January 20, 1977)