Correlation between optical rotation sign and conformation of γ-butyrolactones

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***trans*-4,5-Disubstituted-γ-butyrolactones are found to adopt different conformations by NMR spectroscopy; their optical rotation signs are found to depend on the conformations they assume.**

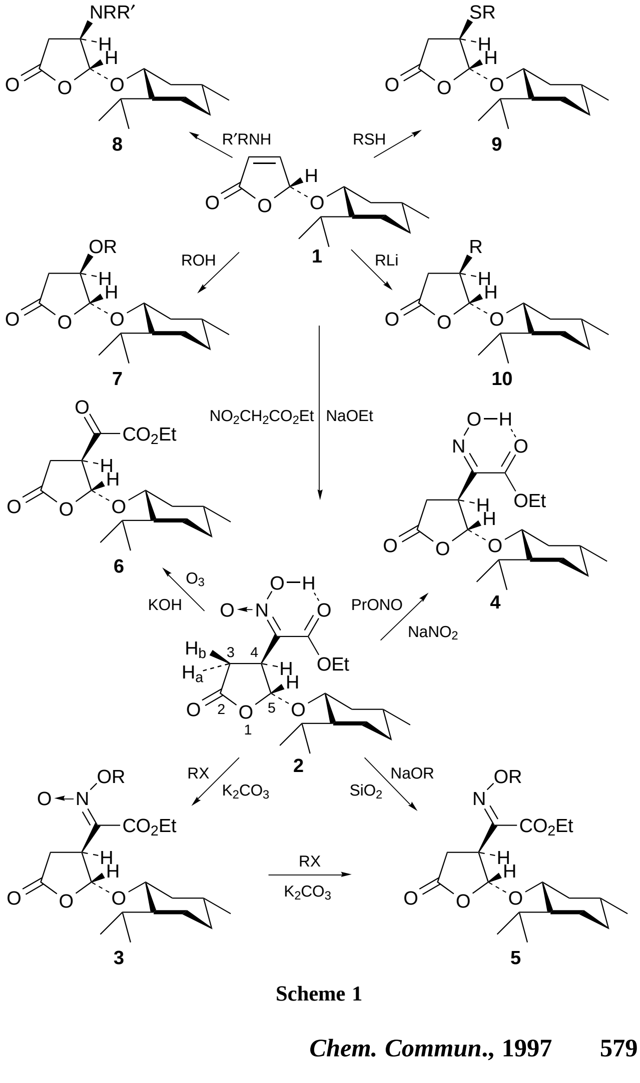
Since the beginning of the study of optically active substances, many attempts have been made to devise a method for calculating optical activity or at least to learn how to predict the sign of rotation. Although some empirical rules[1] concerning the optical activities have been found, the nature of optical activity of chiral molecules is still a problem that has not been solved. Empirical methods[2] for the prediction of the sign and amount of rotation based on bond refractions and polarizabilities of groups in a molecule have been suggested, which has given fairly good results in quite a few cases. Here we report our discovery of the correlation between optical rotation sign and conformation of *trans*-4,5-disubstituted-γ-butyrolactones.

Recently, in the study of the physical and spectral properties of a series of *trans*-4,5-disubstituted-γ-butyrolactones **2**–**10** derived from (*R*)-(−)-5-[(1*R*)-menthyloxy]furan-2(5*H*)-one[3] **1** (Scheme 1), we found that the optical rotation signs of the γ-butyrolactones correlate strictly with the relative order of the chemical shifts of the C_3 methylene protons H_{3a} and H_{3b} in the range of δ 2.0–3.0, as the substituent on the C_4 atom changes from one series to another. That is, the optical rotation signs of compounds **2**,[4] **3**,[4] **4**,[5] **5**[4] are all positive, where H_{3a} resonates at higher magnetic field than H_{3b}, or $\delta\ H_{3a} < \delta\ H_{3b}$; while the optical rotation signs of compounds **6**,[5] **7**,[5] **8**,[6] **9**,[7] **10**[8] are all negative, where H_{3a} resonates at lower magnetic field than H_{3b}, or $\delta\ H_{3a} > \delta\ H_{3b}$ (Table 1). This phenomenon appears somewhat confusing and unlikely considering that there is only one difference, the C_4 substituent, among these compounds. The possibility of the anisotropic effects of the C_4 substituents can be removed, because, although compounds **2**–**5** and compound **6** all have double bonds (C=N or C=O bonds), they still lead to a different relative order of the chemical shifts of H_{3a} and H_{3b}.

There seems to be only one interpretation for the interesting transposition of the chemical shifts of the C_3 methylene protons H_{3a} and H_{3b}, which is that the two series of compounds **2**–**5** and compounds **6**–**10** assume different conformations, respectively. γ-Butyrolactone is a five-membered ring and it is not surprising that it should adopt an envelope conformation. The preference for coplanarity of the lactone group[9] implies that the stable conformations of the γ-butyrolactone are restricted to an enantiomeric pair, in which the C_4 atom is either below (conformation I) or above (conformation II) the lactone plane (Fig. 1). The hydrogens or substituents at C_3, C_4 and C_5 atoms are expected to adopt quasi-axial or quasi-equatorial positions.[10]

In conformation I, H_{3b}, H_4 and H_5 are quasi-axial protons, while H_{3a}, menthyloxy and R^1 adopt the quasi-equatorial positions. On the contrary, in conformation II, H_{3a}, menthyloxy and R^2 assume the quasi-axial positions, while H_{3b}, H_4 and H_5 are quasi-equatorial protons. According to the proposed model[11] of the anisotropic effect of the carbonyl group, the quasi-equatorial protons of the C_3 methylenes in both conformations I and II should be in the shielding region of the C_2 carbonyl group while the corresponding quasi-axial protons should be in the deshielding region. As a result, in the two conformations I and II, the quasi-axial proton on the C_3 methylene is expected to resonate at lower magnetic field than the corresponding quasi-equatorial proton. Since for compounds **2**–**5** the relative order of the chemical shifts of H_{3a} and H_{3b} is $\delta\ H_{3a} < \delta\ H_{3b}$, it is self-evident that compounds **2**–**5** all assume conformation I. And because, for compounds **6**–**10**, the relative order of the chemical shifts of H_{3a} and H_{3b} is $\delta\ H_{3a} > H_{3b}$, it can also be seen that compounds **6**–**10** all adopt conformation II. Apparently, this result agrees with the previous observations that in steroidal α-acetoxy ketones,[12] α-halo ketones[13] and α-bromo cyclohexanones,[14] the α-protons of the carbonyl groups resonate at lower magnetic fields when axial than when equatorial.

In both conformations I and II, the geminal coupling constants of the C_3 methylene protons H_{3a} and H_{3b} alter in a narrow range, or ${}^2J_{3a,3b}$ = 15–18 Hz. H_{3a}, H_{3b} and H_4 protons

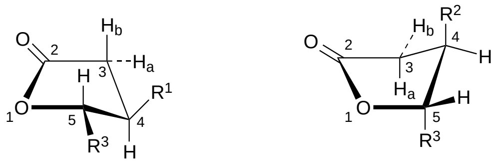


Scheme 1

Table 1

							J/Hz				
Compound	R	Mp/°C	[α] (c, solvent)[a]	δH_{3a}	δH_{3b}	$\Delta\delta$[c]	3a,3b	3a,4	3b,4	4,5	Ref.
2		146–147	+52 (1.0, $CHCl_3$)	2.64	2.94	−0.30	17.4	11.5	3.3	0	4
3a	Me	93–94	+64 (1.0, $CHCl_3$)	2.58	2.86	−0.28	16.6	11.5	3.4	0	4
3b	Et	71.5–72.5	+68 (1.0, $CHCl_3$)	2.55	2.83	−0.28	16.6	11.2	3.4	0	4
4		121–122	+118 (1.0, $CHCl_3$)	2.36	2.88	−0.52	17.2	11.5	3.2	0	5
5a	C_5H_9	oil	+104 (2.18, hexane)	2.36	2.76	−0.40	16.0	10.8	3.7	1.8	4
5b	C_6H_{11}	oil	+94 (0.72, hexane)	2.36	2.76	−0.40	16.0	10.8	3.7	1.8	4
6		58–61	−134 (0.83, CH_2Cl_2)[b]	2.97	2.78	+0.19	18.0	9.4	4.8	2.2	5
7a	Et	93–94	−146 (1.1, $CHCl_3$)	2.79	2.45	+0.34	17.8	6.0	1.4	0	5
7b	Pr	92–93	−132 (0.86, $CHCl_3$)	2.77	2.45	+0.32	18.0	6.0	1.6	0	5
8a	H, Bn	100.6–102.7	−101 (1.0, $CHCl_3$)[b]	2.8	2.3	+0.5	15	7	3	0	6
8b	Me, Bn	oil	−109 (1.0, $CHCl_3$)[b]	2.7	2.1	+0.6	15	8	2	0	6
9	Ph	77.8–78	−62 (1.0, $CHCl_3$)[b]	3.04	2.38	+0.66	15	8	3	0	7
10	Me	78.2–79.8	−147 (0.9, $CHCl_3$)[b]	2.82	2.09	+0.73	17.6	8.2	4.0	2.2	8

[a] Unless otherwise indicated, the specific rotations were measured at 578 nm at 25 °C. [b] Determined at 589 nm at 20 or 25 °C. [c] $\Delta\delta = \delta H_{3a} - \delta H_{3b}$.



I [α] > 0

2–5

II [α] < 0

6–10

R^1 = $C(NO_2H)CO_2Et$, $C(NO_2R)CO_2Et$, $C(NOH)CO_2Et$, $C(NOR)CO_2Et$

R^2 = $COCO_2Et$, OR, NRR′, SR, R

R^3 = menthyloxy

Fig. 1

constitute a typical ABX coupling system with the vicinal coupling constants $^3J_{3a,4}$ = 10.8–11.5 and $^3J_{3b,4}$ = 3.2–3.7 Hz in conformation I, and $^3J_{3a,4}$ = 5.8–9.4 and $^3J_{3b,4}$ = 1.2–1.8 Hz in conformation II. In both cases, the quasi-axial proton is deshielded 0.2–0.7 ppm by the C_2 carbonyl group with respect to the quasi-equatorial proton, which is in contrast to the situation of a six-membered ring where an equatorial proton is generally deshielded 0.1–0.7 ppm by the C–C bonds with respect to the corresponding axial proton.[15]

The conformational analysis of the *trans*-4,5-disubstituted-γ-butyrolactones described above is partially confirmed by the X-ray analysis of (4*R*,5*R*)-(−)pyrrolidin-4-yl-5-[(1*R*)-menthyloxy]-γ-butyrolactone, mp 134.6–134.8 °C, $[\alpha]^{20}_D$ −150 (c 1.0, $CHCl_3$).[6] Its ORTEP plot shows that it adopts an envelope conformation with the C_4 atom deviating above the lactone plane and H_{3a}, menthyloxy and pyrrolidinyl assuming the quasi-axial positions, which is exactly consistent with the predicted conformation II.

If the substituents R^1, R^2 and R^3 were displaced with hydrogens, it would be obvious that conformer I and conformer II should be enantiomers, or that one is the mirror image of the other. Since the absolute configuration of the C_4 and C_5 atoms are the same in both conformations I and II, therefore it appears to be significant that the optical rotation signs of the γ-butyrolactones depend on the conformations they assume rather than on the substituents on the lactone ring, in other words, conformer I creates a right-handed rotation, while conformer II results in a left-handed rotation. Because of the widespread occurrence of γ-butyrolactone rings in nature, *e.g.* in carbohydrates, steroids, alkaloids, nucleic acids and many other natural products, we think the conformational analysis of γ-butyrolactones by NMR spectroscopy and the correlation between optical rotation sign and conformation of γ-butyrolactones will be useful for prediction of optical activity and conformation of such compounds.

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