

NOVEL E-Z EQUILIBRIUM OF N-ALKYL- $\alpha$ -ALKOXYCARBONYLNITRONE IN SOLUTION

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Four N-alkyl- $\alpha$ -alkoxycarbonylnitrones were prepared and their NMR spectra in  $C_6D_6$ ,  $CDCl_3$ , or  $CD_3SOCD_3$  were measured. From the analyses of the spectra, it was found that the nitrones exhibited a facile equilibrium in all solvents used and E/Z ratio in equilibrium depended largely on the polarity of the solvent.

Recently, N-benzyl- $\alpha$ -ethoxycarbonylnitrone (1) has been shown to be an effective synthon in the syntheses of  $\gamma$ -hydroxy amino acids.<sup>1)</sup> Thus, when the nitrone 1 was treated in *benzene* with methyl acrylate, two 1,3-dipolar adducts, 2 and 3, were obtained in 83% yield in the ratio of 4:1. The major adduct 2 could be successfully converted into *threo*- $\gamma$ -hydroxyglutamic acid. Although 1 was obtained in a crystalline form, the NMR spectrum of 1 in  $CDCl_3$  showed the presence of both E- and Z-isomers in the ratio of 2:1.

During the further investigation of synthesizing another  $\gamma$ -hydroxy amino acids, we were faced with a curious phenomenon: the E/Z ratio observed in  $CDCl_3$  was not necessarily reflected on the ratio of two isomeric products which were obtained by the dipolar addition reaction in *benzene*.<sup>2)</sup>

The present paper deals with the facts that N-alkyl- $\alpha$ -alkoxycarbonylnitrones exhibit novel solvent dependent E-Z equilibrium in solution.

The N-alkyl- $\alpha$ -alkoxycarbonylnitrones 4~6 were prepared by a similar procedure as previously described.<sup>1)</sup> A given quantity of each nitrones was dissolved in  $C_6D_6$ ,  $CDCl_3$ , or  $CD_3SOCD_3$  and the solutions were allowed to stand at room temperature. After 12 hours, NMR spectra of the solutions were measured. The results, with their properties, and the assignment to E- and Z-structures are summarized on Table 1.

In the cases of 1, 4, and 6 in  $CDCl_3$ , the benzylic protons are clearly recognized at 4.96, 4.98, and 4.83 ppm in Z type, while at 5.69, 5.70, and 6.86 ppm in E type, respectively. The assignment of the signal in higher field to the Z-isomer is based

Table 1. Physical properties of nitrones  $C_6H_5-CH-N=CH-COOR_2$   
 $\begin{array}{c} R_1 \\ | \\ C_6H_5-CH-N=CH-COOR_2 \\ | \\ O \end{array}$

Nitrones <sup>a)</sup> $\begin{array}{c} R_1 \\   \\ R_2 \\   \\ Et \\   \\ H \end{array}$	M.p. (°C)	IR (KBr)	NMR <sup>b)</sup>								
			in $C_6D_6$		in $CDCl_3$		in $CD_3SOCD_3$				
			=CH	benzylic	ester	=CH	benzylic	ester	=CH	benzylic	ester
<u>1</u>	84.0-86.5	1720 1565 1210sh 1200	Z E	6.76 (7.06) <sup>c)</sup>	4.33 0.96 4.03 0.83 3.84	7.09 7.17	4.96 5.69	1.27 4.22 1.30 4.25	7.84 (7.4-7.6) <sup>d)</sup>	5.12 5.71	1.21 4.17 1.27 4.25
<u>4</u>	90.0-92.0	1727 1570 1220 1205sh	Z E	6.76 (7.06) <sup>c)</sup>	4.32 3.40 3.22	7.08 7.17	4.98 5.70	3.77 3.78	7.88 (7.4-7.6) <sup>d)</sup>	5.12 5.69	3.68 3.79
<u>5</u>	131.5-132.5	1725 1700 1550br 1215 1205sh	Z E	(7.0-7.6) <sup>d)</sup>	5.90 3.42 8.59 (7.0-7.6) <sup>d)</sup>	(7.2-7.5) <sup>d)</sup>	6.28	3.71	7.94	6.77	3.65
<u>6</u>	72.5-74.5	1730 1550br 1220sh 1210	Z E	7.00 (7.20) <sup>c)</sup>	4.31 3.40 3.23	(7.31) <sup>c)</sup>	4.83	3.80	7.83 (7.3-7.7) <sup>d)</sup>	5.22	3.64 (3.74) <sup>c)</sup>
<u>7</u>	$\begin{array}{c} CH_3-N=CHC_6H_5 \\   \\ O \end{array}$ 82.5-84.5 (81-82) <sup>6)</sup>	1170	Z E	5.75 --e)	2.28 -- 6.38 7.54 --	(7.4-7.6) <sup>d)</sup>	3.91 --	7.45 8.30 --	7.72 --e)	3.64 --	7.31 8.12 --

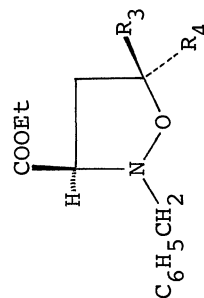
a) All new compounds gave satisfactory elemental analysis.

b) Measured on a JEOL MH-100 spectrometer. The ambient temperature of a probe was adjusted at 23°C. Spectra were obtained in 0.27 mol/l solution and after 12 h standing at room temperature (21°C).

c) Estimated from the results in time variation.

d) The corresponding proton could not be assigned to a specific value because its signal overlapped with those of aromatic protons.

e) None of the E-isomer was recognized.



2  $R_3=H$ ,  $R_4=COOMe$

3  $R_3=COOMe$ ,  $R_4=H$

Table 2. E/Z Ratio<sup>a)</sup> in solution at 21°C.

Nitrones	C <sub>6</sub> D <sub>6</sub>	CDCl <sub>3</sub>	CD <sub>3</sub> SOCD <sub>3</sub>
<u>1</u>	3.4	1.6	0.23
<u>4</u>	3.3	1.6	0.22
<u>5</u>	1.7	1.1	0.20
<u>6</u>	1.6 <sup>b)</sup> (1.9)	0.67 <sup>b)</sup> (0.95)	0.05 <sup>b)</sup> (0.13)
<u>7</u>	0.0	0.0	0.0

a) The ratio unchanged with differences in concentration.

b) Equilibrium was not attained. Values at equilibrium (2 days) are shown in parentheses.

Table 3. Variation of E/Z ratio vs. time at 23°C.

										Rate (s <sup>-1</sup> )	
<u>4</u>	t(min)	4	6	8.5	12	14.5	20	30	(12h)	$k_Z = 1.1 \times 10^{-3}$ $k_E = 6.9 \times 10^{-4}$	
	E/Z	0.13	0.25	0.42	0.64	0.85	1.1	1.6	1.6		
<u>5</u>	t(min)	3	(12h)								
	E/Z	1.1	1.1								
<u>6</u>	t(min)	6	11	20	30	60	(12h)	(45h)	(73h)	$k_Z = 2.1 \times 10^{-4}$ $k_E = 2.2 \times 10^{-4}$	
	E/Z	0.0	0.10	0.19	0.34	0.57	0.67	0.95	0.95		

on the neighbouring deshielding effect of the ester group. This is also coincident with the tendency that the signal due to an *anti*-proton (=CH of Z-isomer) is always higher than that of a *syn*-proton (E-isomer) as exemplified in the cases of S-oxides or oxime.<sup>3)</sup> The E/Z ratio was calculated from the peak areas of these signals. On the other hand, only the signal due to the benzylic proton of the Z-isomer is observed at 6.28 ppm in the NMR spectrum of 5 in CDCl<sub>3</sub>. The corresponding signal due to the E-isomer is overlapped with those of the aromatic protons. In these cases the E/Z ratio was calculated from the equation,  $E/Z = (A_{CH_3} - 3 \times A_{CH}) / 3 \times A_{CH}$ , where  $A_{CH_3}$  and  $A_{CH}$  are peak areas of the ester methyl and of the benzylic proton of Z-isomer, respectively.

As clearly shown on Table 2, the E/Z ratio varies drastically with the solvent: in nonpolar solvent, E-isomer predominates, while in polar one Z-isomer does.

These results open the question whether N-alkyl- $\alpha$ -alkoxycarbonylnitrones exist as a mixture of E- and Z-isomers also in *crystalline* state. To clarify this point, time-variation of the NMR spectrum of 4, 5, or 6 in CDCl<sub>3</sub> was measured. As shown on Table 3, the E/Z ratio of 4 varied with time: the Z-isomer was predominant just after the crystals dissolved but the E-isomer gradually increased with elapse of time and, after 30 min, it reached to the equilibrium point. The similar phenomenon was also observed in 6, but the rate of isomerization was much slower than that of 4.

A convenient explanation of these phenomena will be as follows. From the equilibrium mixture of E- and Z-isomers in a given solution, Z-isomer separates exclusively as a crystal and, thus crystalline nitrones 4 and 6 are not a mixture of both isomers but are composed of the Z-isomer only. When the crystal dissolved

in solvent, Z-isomer isomerizes to E-isomer until the equilibrium attains. The equilibrium point differs largely with the solvent used.

On the other hand, the nitrone 5 exhibited a facile isomerization and, only after few min, the equilibration attained in all three solvents. IR spectrum of 5 in KBr disk shows two absorption in the carbonyl region in contrast to those of other nitrones 1, 4, and 6 (Table 1), and this may speculate that the crystals of 5 are composed of a mixture of E- and Z-isomers. However, *different* crystals obtained from benzene, ether, or benzene/hexane solution showed *identical* IR spectra contrary to an expectation that crystals of different E/Z ratio should give different IR spectra. Thus, we could not defined the nature of 5 in a crystalline state.

Generally, aldonitrones are assigned as existing in the stable Z-isomer<sup>4)</sup> and only one report referred the geometrical isomerization. When 2-t-butyl-3-phenyl-oxazirane was treated with boron trifluoride in benzene, (E)-N-t-butyl- $\alpha$ -phenyl-nitrone initially formed isomerized completely to the Z-isomer within 24 h.<sup>5)</sup> In the case of nitronic ester, both E- and Z-isomers were recognized as existing both in crystalline state and in solution, but neither isomerization nor equilibration in solution were observed.<sup>6)</sup> In order to compare with the present results, N-methyl- $\alpha$ -phenylnitrone(7) was prepared according to the known procedure<sup>7)</sup> and its NMR spectra were measured in three solvents (Table 1). That none of E-isomer was recognized in every case is coincident with the generally accepted explanation.<sup>4)</sup>

The present results are *the first evidences*<sup>8)</sup> *on existence of facile E-Z equilibration of nitrones in solution.* The presence of the conjugated ester group seems to be essential in such isomerization and the difference in rate [phenyl(5) > hydrogen(4) > ethyl(6)] will arise from the electronic nature of the substituent at the benzylic position.

#### References and notes

- 1) Y. Inouye, Y. Watanabe, S. Takahashi, and H. Kakisawa, *Bull. Chem. Soc. Jpn.*, **52**, 3763 (1979).
- 2) The nitrone 4 was treated with acrolein in benzene followed by catalytic hydrolysis and subsequent hydrolysis to give allohydroxyproline and hydroxyproline in the ratio of 1.61:1, while 5 gave 3.66:1.
- 3) E. Block, L. K. Revelle, and A. A. Bazzi, *Tetrahedron Lett.*, **21**, 1277 (1980) and the references cited therein.
- 4) J. Thesing and W. Sirrenberg, *Chem. Ber.*, **91**, 1978 (1958).
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- 7) O. Exner, *Collect. Czech. Chem. Commun.*, **16**, 258 (1951).
- 8) The phenomena were also observed under protection against light. For the photo-sensitized E-Z equilibration of  $\alpha$ -cyano- $\alpha$ ,N-diphenylnitrone, see: K. Koyano and I. Tanaka, *J. Phys. Chem.*, **69**, 2545 (1965).

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