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AROMATIC SOLVENT-INDUCED SHIFTS IN THE ^{1}H-NMR SPECTRA OF NITRONES

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Abstract: In the ^{1}H-NMR spectra of model compounds **1-3** in hexadeuteriobenzene the signals of protons at the E-side of the nitrone group are more extensively shifted to higher field by the effect of the aromatic solvent than the signals of protons at the Z-side. Utilizing this effect the existence of usual C,N-dialkylnitrones in the Z-form was confirmed. C-Acylnitrones as **8** and **9**, however, exist in both of the isomeric forms, the equilibrium being strongly influenced by the solvent.

INTRODUCTION

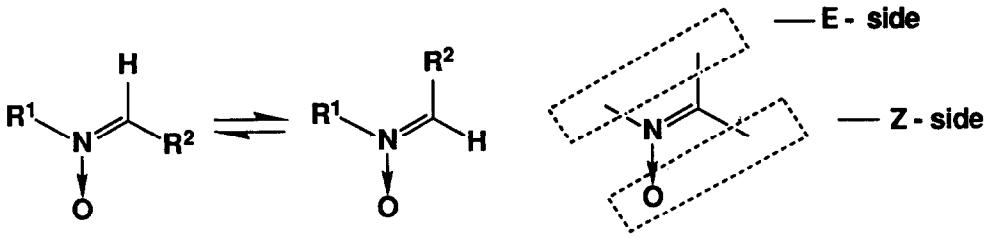
Acyclic nitrones can exist in two isomeric forms with different geometric arrangement of the substituents, that are the Z- and the E-isomer[1]. Whereas for ketonitrones frequently an equilibrium between both of the isomers could be established, usually only one isomeric form of the aldonitrones was detected, for which the Z-configuration is generally accepted. Equilibria between Z- and E-isomers are so far found only for aldonitrones with special functional groups at the α-carbon atom, such as alkoxycarbonyl[2] and highly substituted phenyl groups[3,4]. Concerning C,N-dialkylnitrones it is claimed that N-ethyl-ethylidenamine-N-oxide exists as a 9:1 mixture of Z- and E-isomers, however, the ^{1}H NMR signals of only one isomer are given[5]. In context with our work on the inter[6]- and intramolecular[7] 1.3-dipolar cycloadditions of C,N-dialkylnitrones we were strongly interested in the problem of their Z-E isomerization. Since we found one example for which the E-nitrone could be detected together with the Z-nitrone[7], we decided to study this problem by the aid of the ^{1}H NMR ASIS-effect[8], including cyclic nitrones as models with fixed configuration. For comparison acyl nitrones were also studied.

RESULTS AND DISCUSSION

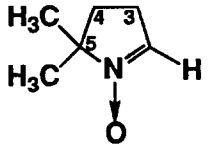
Due to the anisotropic effect of the nitrone group the proton at the α-carbon atom of the E-isomer should be deshielded. Hence it should exhibit an NMR signal at lower field compared to the corresponding signal of the Z-isomer.

However, the difference is usually small. Thus, if only one isomer exists, it is difficult to recognize from the position of this signal unambigiously whether it is the Z- or the E-isomer, although the existence of the E-isomer alone is rather improbable. Measurement of the ^{1}H NMR spectrum in two solvents, a non aromatic and an aromatic one, should then give stronger confidence.

As was pointed out[8] aromatic solvents are not symmetrically orientated around such molecules as nitrones in contrast to most of the other solvents. Due to repulsion between the free electron pairs of the oxygen atom and the π-electrons of the aromatic ring they prefer to arrange in a manner that the E-side of the nitrone is more shielded than the Z-side.



As a consequence on changing from a non-aromatic solvent such as deuteriochloroform to an aromatic solvent as hexadeuteriobenzene the shift of the proton signals at the Z-side to higher field is less then the shift of the proton signals at the E-side. Utilizing this effect we measured the ^{1}H NMR spectra of nitrones **1-7** in deuteriochloroform and hexadeuteriobenzene. The results are summarized in Table 1.



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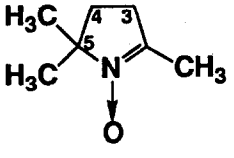

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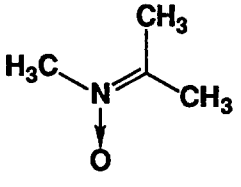

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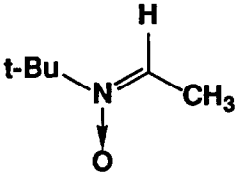

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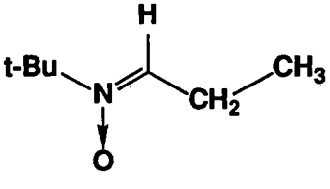

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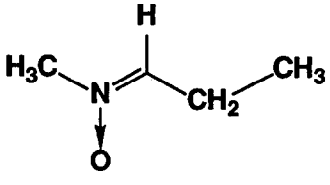

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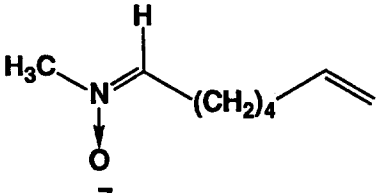

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Table 1. Comparison of chemical shifts of the ^{1}H NMR spectra of nitrones **1-7** in $CDCl_3$ and C_6D_6.

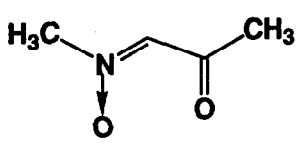
	Z-side				E-side				N-substituent			
		$CDCl_3$	C_6D_6	Δ		$CDCl_3$	C_6D_6	Δ		$CDCl_3$	C_6D_6	Δ
1	H	6.79	6.30	0.49	CH_2-(3)	2.57	1.75	0.82	$C(CH_3)_2$	1.39	1.17	0.22
2	CH_3	2.00	1.75	0.25	CH_2-(3)	2.60	1.87	0.73	$C(CH_3)_2$	1.35	1.21	0.14
3	CH_3	2.13	1.90	0.23	CH_3	2.16	1.20	0.96	CH_3	3.70	3.10	0.60
4	CH_3	1.99	1.80	0.19	H	6.95	6.22	0.73	$C(CH_3)_3$	1.48	1.20	0.28
5	CH_2	2.50	2.46	0.04	H	6.78	6.30	0.48	$C(CH_3)_3$	1.49	1.22	0.27
6	CH_2	2.43	2.30	0.13	H	6.68	5.90	0.78	CH_3	3.60	3.17	0.43
7a					H	6.70	5.91	0.79				
7b	H	6.85	6.31	0.54								

7a = Z-isomer; **7b** = E-isomer

The data of the model compounds **1-3** give an idea of the magnitude of the shift differences for the Z- and the E-side in these two solvents. Inspection of the values of aldonitrones **4-6** clearly indicates that they exist as Z-isomers as is also expected on steric reasons. The least shift of the signals for both sides of the molecule is observed for nitrone **5**. This seems to depend on the increased steric shielding of the nitrone moiety by the substituents as is reflected by a comparison of the values of **5** with those of **4** as well as with those of **6**. The data of nitrone **7** also confirm the suggestion that the major isomer is the Z-nitrone.

To study the problem of Z-E isomerization of C-acyl-N-alkylnitrones the ^{1}H NMR spectra of compounds **8-10** were measured in hexadeuteriobenzene and deuteriochloroform and additionally in hexadeuteriodimethyl sulfoxide. Whereas for **10** in all three solvents only one isomer could be detected, the spectra of nitrones **8** and **9** reveal the existence of two isomeric forms. The chemical shifts of the signals of the nitrone proton along with the values for the aromatic solvent-induced shift differences and the ratio of isomers are given in Table 2.

Classification of the isomeric forms of **8** and **9** was again performed with the aid of the aromatic solvent induced shift (ASIS) effect. The ASIS effect of **10** needs special comment. Compared with the shift differences of nitrone **4-7** the value of 0.62 seems quite normal for a Z-nitrone, in particular it is even greater than for nitrone **5** which is also substituted by a N-tert-butyl group. On the other hand, by comparison with the shift differences of **9Z** and **9E** an unambigious classification of **10** seems difficult. However, it must be considered that the ASIS effect is decreased by the N-tert-butyl group (see **5** vs. **6**). Finally, the presence of the phenyl group should enhance the shift difference in particular for the Z-isomer of **9**. Since the ASIS effect for **10** is distinctly greater than for **9-E**, **10** must exist as Z-isomer, as is expected for steric reasons.



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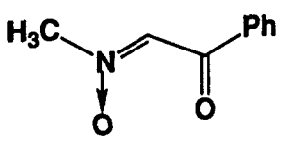

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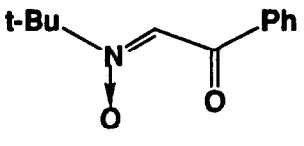

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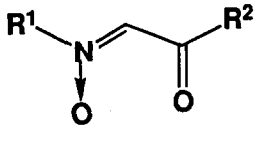
Table 2. Comparison of chemical shifts of the α-H in the ^{1}H NMR spectra of nitrones **8-10** in $(CD_3)_2SO$, $CDCl_3$ and C_6D_6

		$(CD_3)_2SO$ (I)	$CDCl_3$ (II)	C_6D_6 (III)	Δ I/III	Δ II/III
8	Z	7.70	6.97	6.62	1.08	0.35
	E	7.44	7.40	7.14	0.30	0.26
ratio	*Z/E*	*7:1*	*1:3*	*1:3*		
9	Z	8.47	7.84	6.60	1.87	1.24
	E	8.53	8.30	7.89	0.64	0.41
ratio	*Z/E*	*1.25:1*	*1:7*	*1:15*		
10	Z	8.14	7.89	7.27	0.89	0.62

The appearance of the E-isomers of nitrones **8** and **9** is caused by the repulsive interaction of the two strong dipoles, the NO and CO moiety, which destabilizes the Z-isomer. The situation for acylnitrones is even more complicated. In principle, there are now two preferred comformations for both of the isomers in which an optimal conjugation between nitrone and carbonyl group is possible. Furthermore the phenyl group of **9** and **10** tends to occupy a position which enables extensive conjugation with carbonyl group. Thus a number of factors determine the thermodynamic stability of the two isomeric forms.



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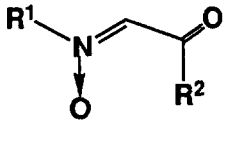

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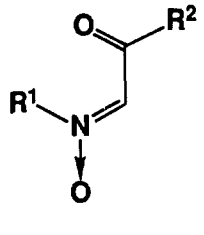

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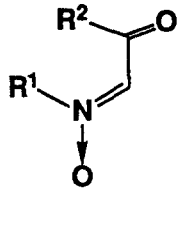

eE

For the N-tert-butyl substituted nitrone **10** the destabilization of the E-isomer by the steric interaction at the E-side is so strong that only the Z-isomer exists in detectable concentration in either of the solvents. For nitrones **8** and **9** the smaller steric effect disfavoring the E-form is counterbalanced by the dipolar interaction which destabilizes the zZ-form. In principle, in the eZ form the destabilizing dipolar interaction of the zZ form is at least extensively diminished. However, this conformation suffers from the increased steric interaction between R^2 and the nitrone oxygen.Thus detectable equilibria between both of the isomers arise for **8** and **9** in either of the three solvents. It can be assumed that the portion of Z-isomer being in equilibrium with E isomer is higher for nitrone **8** than for **9**, because the steric effect of R^2 is less strong for the former.

In general the situation resembles to that of alkoxycarbonyl nitrones studied by Inouye et al.[2] In less polar solvents as benzene or chloroform the intramolecular dipole-dipole interaction is extensively effective, favoring the E-isomers of **8** and **9**, respectively. In dimethyl sulfoxide, however, the solvent molecules arrange preferentially in a way that their dipoles are orientated antiparallel to the NO- and CO-dipoles[2], diminishing the intramolecular dipolar destabilization of the E-isomer. Thus, in dimethyl sulfoxide the Z-isomer predominates.

EXPERIMENTAL PART

^{1}H- and ^{13}C NMR spectra were recorded with Bruker WH 400 and AC 300. - Solvents were purchased by Janssen ($CDCl_3$) and Merck (C_6D_6 and $(CD_3)_2SO$). - Nitrones **1-7** were prepared by known procedures[6].

N-Methyl-(2-oxo-propylidene)amine N-oxide **(8)**: A saturated solution of sodium carbonate was added dropwise to 120 mL of an aqueous solution of methylglyoxal (4.0 g, 0.055 mol) and N-methylhydroxylamine hydrochloride (4.6 g, 0.055 mol) at 0°C until neutralization had occurred. Subsequently the solution was stirred for 1.5 hours and then extracted three times with 20 ml dichloromethane in each case. The organic solution was dried with $MgSO_4$ at -5°C. After filtration the solvent was removed at 0° under vacuum to give 3.3 g of a yellow oil (60% yield). Since the compound is not stable for a longer period of time, it was prepared only shortly before the measurements were performed.
^{1}H NMR (C_6D_6): Z-isomer: δ = 2.47 (s, CH_3-CO), 3.04 (s, CH_3-N), 6.62 (s, CH=N). - E-Isomer: 1.65 (s, CH_3-CO), 3.76 (s, CH_3-N), 7.14 (s, CH=N). - ($CDCl_3$): Z-isomer: δ = 2.37 (s, CH_3-CO); 3.68 (s, CH_3-N), 6.97 (s, CH=N). - E-Isomer: 2.08 (s, CH_3-CO), 3.92 (s, CH_3-N), 7.40(, CH=N). - [$(CD_3)_2SO$]: Z-isomer: δ = 2.23 (s, CH_3CO), 4.02 (s, CH_3-N), 7.70 (s, CH=N). - E-isomer: 2.44 (s, CH_3-CO), 3.83 (s, CH_3-N), 7.44 (s, CH=N). - ^{13}C NMR ($CDCl_3$): Z-isomer: δ = 30.1 (q, $\underline{C}H_3$-CO), 52.7 (q, CH_3-N), 132.4 (d, CH=N), 189.0 (s, C=O). - E-Isomer: 30.9 (q, $\underline{C}H_3$-CO), 56.5 (q, CH_3-N), 135.2 (d, CH=N), 193.2 (s, C=O).

N-Methyl-(2-oxo-2-phenylethylidene)amine N-oxide[9] **(9)**: ^{1}H NMR (C_6D_6): Z-isomer: δ = 2.77 (s, CH_3), 6.60 (s, CH=N), 6.90 (m, 3H, Ar-H), 7.77(d, 2H, Ar-H), - E-isomer: δ = 3.78 (s, CH_3), 6.95 (t, 2H, Ar-H), 7.05 (t, 1H, Ar-H), 7.49 (d, 2H, Ar-H), 7.89 (s, CH=N). - ($CDCl_3$): Z-isomer: δ = 3.96 (s, CH_3), 7.47-7.87 (m, 5H, Ar-H), 7.84 (s, CH=N). - E-Isomer: 4.29 (s, CH_3), 7.51 (t, 2H, Ar-H), 7.61 (t, 1H, Ar-H), 7.89 (d, 2H, Ar-H), 8.30 (s, CH=N). - [$(CD_3)_2SO$]: Z-isomer: δ = 3.90 (s, CH_3), 7.54 (t, 2H, Ar-H), 7.66 (t, 1H, Ar-H), 7.91 (d, 2H, Ar-H), 8.47 (s, CH=N). - E-Isomer: 4.17 (s, CH_3), 7.55 (t, 2H, Ar-H), 7.68 (t, 1H, Ar-H), 7.91 (d, 2H, Ar-H), 8.53 (s, CH=N). - ^{13}C-NMR ($CDCl_3$): Z-isomer: δ = 56.1 (q, CH_3), 133.3 (d, J = 194 Hz, CH=N), 183.0 (s, C=O), Ar-C: 128.2, 128.7, 130.5 (3d), 136.8 (s), - E-isomer: δ = 53.7 (q, CH_3), 133.6 (d, 191 Hz, CH=N), 182.4 (s, CO), Ar-C: 128.0, 129.0, 131.1 (3d), 137.7 (s).

N-tert-Butyl-(2-oxo-2-phenylethylidene)amine N-oxide **(10)**: From 5 g of phenylglyoxal hydrate (0.033 mol) in 150 ml of toluene the water was removed by azeotropic distillation (3 h). Then 2.98 g of tert-butylhydroxylamine (0.033 mol) were added to the

hot solution which was stirred until room temperature was reached. After filtration the solution was concentrated to one tenth of its volume. Orange crystals separated on cooling, 85% yield, m.p. 83-85°C.

$C_{12}H_{14}NO_2$ (205.3) Calcd C 70.21 H 7.38 N 6.83 Found C 70.34 H 7.37 N 6.78. - MS (FD): m/e = 205 (100%, M^+). - IR (KBr): 1660 m^{-1}. - ^{1}H-NMR ($CDCl_3$): δ = 1.61 (s, tBu), 7.43-7.58 (m, 3H, Ar-H), 7.81-7.84 (m, 2H, Ar-H), 7.89 (s, CH=N). - ^{13}C-NMR ($CDCl_3$): δ = 28.2 (q, C($\underline{C}H_3)_3$), 74.1 (s, $\underline{C}(CH_3)_3$), 125.6 (d, J = 180 Hz, CH=N), 185.7 (s, C=O). - Ar-C: 128.1, 128.6, 133.1 (3d), 137.2 (s).

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