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STEREOCHEMISTRY OF α-AMINOACETOPHENONE OXIMES

STUDY OF SOLVENT EFFECTS

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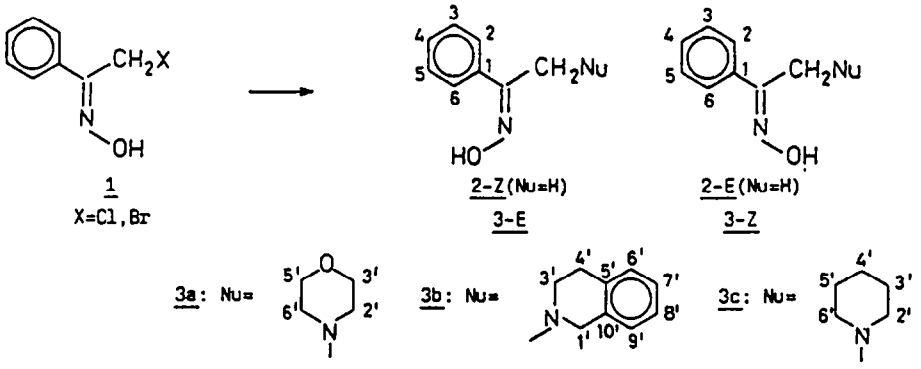
Abstract - The aminolysis of Z-α-halogenoacetophenone oximes results in different mixtures of E- and Z-α-aminoacetophenone oximes depending on the solvent used. Assignment of configuration can be achieved by ^{13}C NMR spectroscopy even if only one isomer is available using a strong solvent dependence of the methylene chemical shift in the case of the Z-isomers. This effect is due to the presence of different conformations in the solvents chloroform and dimethyl sulfoxide. Together with a study by vapor pressure osmometry the results provide an unambiguous proof of intramolecular hydrogen bonding of Z-α-aminoacetophenone oximes in chloroform.

Investigations of the reaction of Z-α-bromoacetophenone oxime (1,X=Br) with nucleophiles such as $NaBH_4$ and secondary amines indicate a complete change in configuration of the oxime moiety both in aqueous medium[1] and in ether[2] yielding the 2-Z and 3-E isomers only.



However, in our study[3] on the dehydrogenation of α-aminoacetophenone oximes we obtained E/Z mixtures by reacting 1,X=Cl with amines in methylene chloride. Recent continuation[4] of this work again demonstrated the formation of an isomeric mixture using 1,X=Br and 1,2,3,4-tetrahydroisoquinoline in ether as solvent.

To obtain information on the presumed solvent dependence of the stereoselectivity, the reaction of three amines with 1,X=Cl[5] was carried out both in methanol and in ether and the isomer ratio in the product mixture was quantitatively determined by HPLC.

As can be seen from Table 1, the protic solvent methanol strongly favors the formation of the E-isomer in all cases, while in ether the reaction is less stereoselective. Qualitatively the same trend is observed by ^1H NMR analysis of the product mixtures.

Table 1. Percentages of isomers obtained by aminolysis of 1,X=Cl (in brackets from 1,X=Br) in methanol and in ether.

	3a-E (%)	3a-Z (%)	3b-E (%)	3b-Z (%)	3c-E (%)	3c-Z (%)
CH_3OH	91	9	93	7	88	12
$(CH_3CH_2)_2O$	74	26	71(75)	29(25)	71	29

Configurational Assignment

The configurations of the oxime isomers 3a-E/3a-Z and 3c-E/3c-Z have been assigned previously using various methods[1,2,6,7], which however do not seem to be unambiguous. An even more problematic situation is found in the case of 3b, since only one isomer was isolated and both configurations have in turn been ascribed to this isomer by the same authors[6,8].

A general and unambiguous method for the configurational assignment of aliphatic oximes has been introduced[9,10]. It is based on ^{13}C NMR spectroscopy but still requires both isomers to be measured. Since this method has been successfully applied to the isomers of acetophenone oxime 2[11], we tried to confirm or establish the configuration of the isomeric α-amino acetophenone oximes 3a - 3c via ^{13}C NMR spectroscopy and included 2 for comparison.

Melting points and ^1H NMR data of the pure isomers are given in Table 2. In the case of the α-amino derivatives 3a - 3c there are some consistent trends of the ^1H chemical shifts, indicating correct configurational assignment of the isomers. Thus the tetrahydroisoquinoline derivative 3b described by Chow and Colon[6,8] (mp 135-136°C; δOH 10.5 and δCH_2N 3.89 in $CDCl_3$) is now shown to be the Z-isomer 3b-Z, since the new E-isomer 3b-E gives rise to upfield shifted resonances both for the OH and the CH_2N protons in the same solvent.

Table 2. Melting points and ^1H chemical shifts (in ppm relative to TMS) in $CDCl_3$ or DMSO-d_6 of the E- and Z-isomers of compounds 2 and 3a - 3c.

compound	mp (°C)	solvent	-OH	H2,H6/H3-H5	$-CH_2Nu$	amino group
2-Z	78-80	$CDCl_3$	9.6-9.0	7.7-7.25	2.21	---
2-E	58-59	$CDCl_3$	9.25	7.63/7.55-7.25	2.31	---
3a-E	121-122	$CDCl_3$	8.8-7.8	7.6/7.5-7.3	3.36	3.67 H3',5'; 2.51 H2',6'
		DMSO-d_6	11.22	7.6/7.5-7.25	3.32	3.50 H3',5'; 2.39 H2',6'
3a-Z	148-149	DMSO-d_6	11.72	7.83/7.55-7.25	3.66	3.54 H3',5'; 2.43 H2',6'
3b-E	133-134	$CDCl_3$	9.6-8.9	7.65/7.5-7.25	3.55	7.2-6.9 H6'-H9'; 3.71 H1'; 2.82 H3',4'
		DMSO-d_6	10.93	7.65/7.5-7.3	3.51	7.05 H6'-H9'; 3.58 H1'; 2.72 H3',4'
3b-Z	138-139	$CDCl_3$	12.2	7.72/7.5-7.3	3.95	7.25-6.95 H6'-H9'; 3.80 H1'; 2.92 H3',4'
		DMSO-d_6	11.47	7.8/7.5-7.2	3.84	7.08 H6'-H9'; 3.65 H1'; 2.74 H3',4'
3c-E	135-136	DMSO-d_6	11.12	7.8-7.3	3.33	2.39 H2',6'; 1.43 H3'-H5'
3c-Z	116-118	DMSO-d_6	11.68	7.85/7.6-7.3	3.64	2.43 H2',6'; 1.42 H3'-H5'

The ^{13}C NMR spectra (Table 3) have been recorded both in $CDCl_3$ and in DMSO-d_6. Assignment of the resonances was achieved by the analysis of the ^1H coupled and selectively ^1H decoupled spectra. The ^{13}C chemical shift data show large and consistent differences for the α-methyl and

Table 3. ^{13}C NMR spectra of the E- and Z-isomers of compounds 2 and 3a - 3c. (Chemical shifts in ppm relative to TMS).

compound	solvent	concentration (mg/ml)	C=N	CH_2Nu	C1	C2,6	C3,5	C4
2-Z	$CDCl_3$	300/1.4	154.0(s)	21.4(q)	133.7(s)	127.7(d)	127.9(d)	128.8(d)
	DMSO-d_6	225/1.5	150.9(s)	21.0(q)	134.4(s)	127.7(d)	127.6(d)	128.1(d)
2-E	$CDCl_3$	350/1.5	155.8(s)	12.4(q)	136.3(s)	125.9(d)	128.3(d)	129.1(d)
	DMSO-d_6	350/1.2	152.7(s)	11.5(q)	136.9(s)	125.4(d)	128.1(d)	128.4(d)
3a-E	$CDCl_3$	350/1.4	153.0(s)	62.1(t)	132.7(s)	128.1(d)	127.8(d)	128.7(d)
	DMSO-d_6	320/1.4	151.5(s)	61.8(t)	133.3(s)	128.1(d)	127.4(d)	128.0(d)
3a-Z	$CDCl_3$	50/1.5	153.5(s)	55.4(t)	135.5(s)	126.1(d)	128.3(d)	129.1(d)
	DMSO-d_6	350/1.4	152.5(s)	50.5(t)	136.0(s)	126.0(d)	127.8(d)	128.2(d)
3b-E	$CDCl_3$	280/1.4	153.9(s)	61.3(t)	132.5(s)	128.1(d)	127.7(d)	128.7(d)
	DMSO-d_6	280/1.4	152.1(s)	61.0(t)	133.3(s)	128.1(d)	127.4(d)	127.9(d)
3b-Z	$CDCl_3$	70/1.5	153.6(s)	55.0(t)	135.6(s)	126.1(d)	128.3(d)	129.0(d)
	DMSO-d_6	325/1.5	153.0(s)	49.9(t)	135.9(s)	126.1(d)	127.7(d)	128.1(d)
3c-E	$CDCl_3$	70/1.7	154.4(s)	62.7(t)	132.9(s)	128.1(d)	127.8(d)	128.7(d)
	DMSO-d_6	300/1.4	152.1(s)	62.2(t)	133.6(s)	128.1(d)	127.3(d)	127.8(d)
3c-Z	$CDCl_3$	250/1.4	153.1(s)	57.4(t)	135.8(s)	125.9(d)	128.2(d)	128.8(d)
	DMSO-d_6	280/1.4	153.1(s)	51.1(t)	136.2(s)	126.0(d)	127.7(d)	128.0(d)

compound	solvent	concentration (mg/ml)	C-atoms of the amino group
3a-E	$CDCl_3$	350/1.4	53.3(t) C2',6'; 66.6(t) C3',5'
	DMSO-d_6	320/1.4	53.0(t) C2',6'; 66.0(t) C3',5'
3a-Z	$CDCl_3$	50/1.5	53.1(t) C2',6'; 66.6(t) C3',5'
	DMSO-d_6	350/1.4	53.3(t) C2',6'; 66.1(t) C3',5'
3b-E	$CDCl_3$	280/1.4	55.6(t) C1'; 50.1(t) C3'; 28.8(t) C4'; 134.3,134.0(s) C5',10'; 128.3,126.3,125.8,125.3(d) C6' - C9'
	DMSO-d_6	280/1.4	55.2(t) C1'; 49.7(t) C3'; 28.4(t) C4'; 134.3,133.8(s) C5',10'; 128.1,126.1,125.7,125.2(d) C6' - C9'
3b-Z	$CDCl_3$	70/1.5	55.3(t) C1'; 50.3(t) C3'; 28.6(t) C4'; 133.2,133.1(s) C5',10'; 128.5,126.3(2),125.8(d) C6' - C9'
	DMSO-d_6	325/1.5	55.4(t) C1'; 50.2(t) C3'; 28.6(t) C4'; 134.5,133.6(s) C5',10'; 128.1,126.1,125.7,125.2(d) C6' - C9'
3c-E	$CDCl_3$	70/1.7	54.4(t) C2',6'; 25.8(t) C3',5'; 24.2(t) C4'
	DMSO-d_6	300/1.4	53.7(t) C2',6'; 25.5(t) C3',5'; 23.9(t) C4'
3c-Z	$CDCl_3$	250/1.4	53.9(t) C2',6'; 25.6(t) C3',5'; 23.6(t) C4'
	DMSO-d_6	280/1.4	54.0(t) C2',6'; 25.5(t) C3',5'; 23.7(t) C4'

α-methylene carbons between the two isomers (Table 4) amounting to 9.5 ppm for 2 and 11.1-11.3 ppm for 3a - 3c, all measured in DMSO-d_6. In $CDCl_3$, on the other hand, the chemical shift differences for the α-amino acetophenone oximes 3a - 3c are drastically reduced.

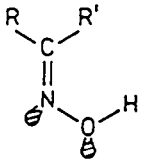
Table 4. Differences between the chemical shifts of the α-methyl and α-methylene carbon atoms in ppm of the two isomers of compounds 2 and 3a - 3c.

compound	2	3a	3b	3c
$\Delta\delta E/Z$ (DMSO-d_6)	9.5	11.3	11.1	11.1
$\Delta\delta E/Z$ ($CDCl_3$)	9.0	6.7	6.3	5.3

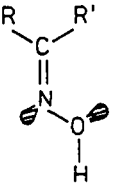
From Table 3 it is clearly apparent, that only the α-CH_2 resonances of the Z-isomers of compounds 3a - 3c are strongly influenced by the solvent. Thus for α-amino acetophenone oximes this effect can be used as a means of determining their configuration even when only one isomer is present: if the sample shows a strong solvent dependence of the ^{13}C chemical shift of the CH_2 resonance, it has to be the Z-isomer, if not, it must be the E-isomer. As will be demonstrated in the next section , the strong influence of the solvent is due to a conformational change in the Z-isomer.

Conformational Analysis

Studies of oximes in the gas phase[12], in solution[13] and in the solid state[14] revealed a strong preference of the s-trans conformation. This fact has been explained[15] by expulsion of the lone pairs in the s-cis conformation.



s-cis



s-trans

Self-association, detected by Beckmann as early as 1888[16], is expected to be another important factor, contributing to the stabilization of the s-trans conformation. Thus, X-ray structure analyses[14] as well as studies of oximes in solution by IR spectroscopy[17] demonstrated the simultaneous involvement of the oxime nitrogen and the hydroxy group in intermolecular hydrogen bonding to form cyclic oligomers exclusively. The remarkable stability of the cyclic trimer has been attributed by Luck[18] to the linear O-H···N arrangements in this form.

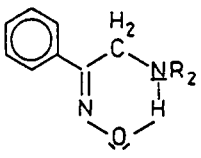
Recently, Roberts et al.[19] showed via ^{15}N NMR spectroscopy that self-association is minimized in the hydrogen-bond acceptor solvent dimethyl sulfoxide. In a further study by ^{13}C NMR, Allen and Roberts[20] detected substantial downfield shifts for the C=N carbon on hydrogen bonding to the nitrogen, while the resonances of the α-carbons did not show significant shifts. Therefore, the change of solvent from $CDCl_3$ to DMSO-d_6 should result in upfield shifts for the C=N carbons only, which indeed is observed (Table 5) for both isomers of 2 and for the E-isomers of compounds 3a - 3c. The same situation is found for acetoxime, studied by Gurudata[21]. This similar behavior is in accordance with the expectation, that in both solvents the s-trans conformation should generally be favored.

Table 5. Solvent dependent differences (in ppm relative to TMS) in the chemical shifts of the C=N and α-CH_3/α-CH_2 carbons of the two isomers of compounds 2 and 3a - 3c.

compound	2-Z	2-E	3a-E	3a-Z	3b-E	3b-Z	3c-E	3c-Z
$\Delta\delta_{C=N}$ $CDCl_3$/DMSO-d_6	3.1	3.1	1.5	1.0	1.8	0.6	2.3	0.0
$\Delta\delta_{\alpha-C}$ $CDCl_3$/DMSO-d_6	0.4	0.9	0.3	4.9	0.3	5.1	0.5	6.3

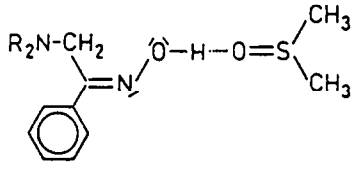
In sharp contrast, the same solvent change does not appreciably affect the C=N resonances of the Z-isomers of 3a - 3c, but instead dramatic upfield shifts are now observed for the α-CH_2 carbons (Table 5). Since previously, there have been indications for the presence of intramolecular hydrogen bonds in Z-α-amino acetophenone oximes[2,6], a straightforward explanation for the unusual chemical shift differences seems only to be found by postulating a complete conformational change going from one solvent to the other. Therefore, it is concluded, that self-association does not compete successfully with intramolecular hydrogen bonding, but, on the other hand, dimethyl sulfoxide is powerful enough to break the six-membered chelate ring.

δ 55.0 - 57.4



3-Z in $CDCl_3$
s-cis

δ 49.9 - 51.1



3-Z in DMSO-d_6
s-trans

Confirmation for the special situation of the Z-isomers of compound 3a - 3c we obtained by vapor pressure osmometry, showing clearly, that with increasing concentration in chloroform only the E-isomers form aggregates, while the Z-isomers remain as monomeric entities.

Concerning the solvent induced chemical shift differences in the case of the Z-isomers (Table 5), the absence of an effect on the C=N carbon shift is easily explained by the absence of a strong hydrogen bonding to the C=N nitrogen in both solvents, whereas the dramatic shift of α-CH_2 signals is apparently without a precedence. Since steric γ-effects can reach large magnitudes, one might speculate on an unusual accumulation or compensation in the two conformations of the factors[22] determining this effect. A possible major contribution to the large upfield shift of the CH_2 carbon resonance in the s-trans conformation relative to that in the s-cis conformation may be found in the steric interaction of the CH_2 hydrogen(s) and the lone electron pair(s) of the oxygen in the former conformation. Such a shielding effect has been suggested to account for the large CH_3 upfield shifts in ortho-cresol and analogous compounds[23].

Experimental

^{1}H NMR spectra were recorded on either a Hitachi R-24B, a Varian CFT-20 or a Varian XL-100 instrument. ^{13}C NMR spectra were recorded on the Varian XL-100 spectrometer. The HPLC studies were performed with a Hewlett-Packard HP 1084 B system. The vapor pressure osmometry was performed with a Knauer Universal instrument.

The α-halogenoacetophenone oximes (1,X=Cl,Br) were prepared according to the literature procedure[24]; for 1,X=Br however, we used $NH_2OH \cdot HBr$ instead of $NH_2OH \cdot HCl$. The acetophenone oximes 2-E and 2-Z were made following the instructions of Janny[25] and of Smith and Kaiser[1] respectively. E-α-aminoacetophenone oximes 3a-E and 3c-E have been prepared by aminolysis according to the usual procedures[1,2], Z-α-aminoacetophenone oximes 3a-Z - 3c-Z were formed on oximation of the

corresponding α-aminoacetophenones[8,26]. The pure E- and Z-isomers were obtained by recrystallization or silica gel chromatography (melting points: Table 2). The new isomer 3b-E was prepared as described below.

1-Phenyl-2-(1,2,3,4-tetrahydro-2-isoquinolinyl)ethanone-(E)-oxime (3b-E)

0.85g(5 mmol) Z-α-chloroacetophenone oxime (1,X=Cl) and 1.3g (10 mmol) 1,2,3,4-tetrahydroisoquinoline were stirred for 1 h in 50 ml methanol at room temperature. After evaporation to dryness, the residue was washed with water. Recrystallization from ethanol yielded 0.7g (52.6%) 3b-E, mp 133-134°C. ^{1}H and ^{13}C NMR data are given in Tables 2 and 3. IR (KBr): 3660 - 3160 cm^{-1} (OH). m/z: 266 (M^{+}). Anal.: Calcd. for $C_{17}H_{18}N_2O$: C, 76.66; H, 6.81; N, 10.52. Found: C, 76.75; H, 6.86; N, 10.43%

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References and Notes

1. J.H. Smith, J.H. Heidema, E.T. Kaiser, J.B. Wetherington, and J.W. Moncrief, J. Am. Chem. Soc. 94, 9274 (1972); J.H. Smith and E.T. Kaiser, J. Org. Chem. 39, 728 (1974).
2. C.A. Grob and H. Fischer, Helv. Chim. Acta 45, 2530 (1962).
3. H. Moehrle and R. Engelsing, Chem. Ber. 106, 1172 (1973).
4. B. Grimm, Dissertation FU Berlin (1978).
5. This starting compound was preferred, since in the usual preparation of α-bromoacetophenone oxime[24] a halogen exchange yields a mixture of 1,X=Cl and 1,X=Br.
6. Y.L. Chow and C.J. Colon, J. Org. Chem. 33, 2598 (1968).
7. H. Moehrle, B. Gusowski, and R. Feil, Tetrahedron 27, 221 (1971).
8. Y.L. Chow and C.J. Colon, Can. J. Chem. 45, 2559 (1967).
9. G.C. Levy and G.L. Nelson, J. Am. Chem. Soc. 94, 4897 (1972).
10. G.E. Hawkes, K. Herwig, and J.D. Roberts, J. Org. Chem. 39, 1017 (1974).
11. G.W. Buchanan and B.A. Dawson, Can. J. Chem. 55, 1437 (1977).
12. I.N. Levine, J. Mol. Spectr. 8, 276 (1962); I.N. Levine, J. Chem. Phys. 38, 2326 (1963).
13. K.E. Calderbank and R.J.W. Le Fèvre, J.Chem. Soc. 1949, 1462; G.J. Karabatsos and R.A. Taller, Tetrahedron 24, 3347 (1968); M. Loudet and H. Sauvaitre, Bull. Soc. Chim. Fr. 1972, 2640.
14. T.K. Bierlein and E.C. Lingafelter, Acta Cryst. 4, 450 (1951); J.B. Wetherington and J.W. Moncrief, Acta Cryst. B29, 1520 (1973).
15. N.L. Owen and N. Sheppard, Proc. Chem. Soc. 1963, 264.
16. E. Beckmann, Ber. Dtsch. Chem. Ges. 21, 766, 1163 (1888); E. Beckmann, Z. Phys. Chem. 2, 715 (1888).
17. G. Geiseler and J. Fruwert, Z. Phys. Chem. Neue Folge 26, 111 (1960); W. Luck, Ber. Bunsenges. Phys. Chem. 65, 355 (1961).
18. W. Luck, Naturwiss. 52, 25 (1965); W.A.P. Luck in "The Hydrogen Bond", eds. P. Schuster, G. Zundel, and C. Sandorfy, North-Holland Publ. Co., Amsterdam, 1976, Vol. 2, p.527.
19. R.E. Botto, P.W. Westerman, and J.D. Roberts, Org. Magn. Res. 11, 510 (1978).
20. M. Allen and J.D. Roberts, Can. J. Chem. 59, 451 (1981).
21. N. Gurudata, Can. J. Chem. 50, 1956 (1972).
22. J.B. Lambert and A.R. Vagenas, Org. Magn. Res. 17, 265, 270 (1981).
23. D.A. Netzel, Org. Magn. Res. 11, 58 (1978).
24. H. Korten and R. Scholl, Ber. Dtsch. Chem. Ges. 34, 1904 (1901).
25. A. Janny, Ber. Dtsch. Chem. Ges. 15, 2781 (1882).
26. N.H. Cromwell and H. Hoeksema, J. Am. Chem. Soc. 66, 870 (1944).