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THE CONFORMATIONAL BEHAVIOUR OF HYDROXAMIC ACIDS

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Abstract—N-Formyl-N-alkylhydroxylamines, N-formyl-α-N-hydroxyamino-acid esters and some N-acetyl analogues exist as Z/E equilibrium mixtures, as shown by H-NMR and IR. The dependence of the Z/E ratio on the nature of N-substituents, acyl groups and solvent was studied. The Z-isomer is preferred for bulky N-substituents and non-polar solvents, and for the O-protonated form. Free energies of activation for rotation about the carbonyl-nitrogen bond were calculated in a series of formylhydroxamic acids.

Bond lengths in the hydroxamic acid group and its planarity indicate partial carbon–nitrogen double bond character[1] as found in amides. Hydroxamic acid conformations are therefore expected to be stable, and rotation about the carbonyl–nitrogen bond to be restricted. Slightly restricted rotation about the carbonyl–nitrogen bond has been reported for highly substituted compounds, such as N,O-diacetyl-N-methylhydroxylamine[2] and clearly revealed at low temperatures by the NMR spectra of the simple formhydroxamates HCO–NR–OR', where R=CH_3, $C_6H_5CH_2$ and R'=H or CH_3.[3,4]

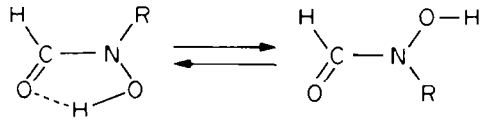
The purpose of this study was to determine in what way the hydroxamic acid conformation is influenced by substituents at nitrogen, by acyl groups and solvents. A series of N-formyl and N-acetyl derivatives of N-alkylhydroxylamine and N-hydroxyamino acid esters were studied.

The solid-state structures of hydroxamic acids show planar *cis*(Z)-conformation.[1,5,6] Exceptions are N-hydroxyurea[7] and N,N'-dihydroxy-N,N'-diisopropylhexane-diamide[1] which exist in planar trans (E)-conformation.

The intramolecular hydrogen bond N–O–H . . . O=C favouring the *cis*-conformation is absent in the crystal[1,5] but is observed in solution.[8] Therefore formylhydroxamic acids were mainly used as convenient models because of the restricted carbonyl–nitrogen bond rotation observed in N-formyl-N-alkyl-hydroxylamines.[3,4,9]

N-Formyl-N-alkylhydroxylamines were synthesized by formylation of N-alkyl-O-benzoylhydroxylamine hydroxychlorides[11,12] by the standard method[10] in the presence of sodium acetate or sodium formate, followed by hydrolysis of the O-benzoyl group. The physical properties of N-formyl-O-benzoyl-N-alkylhydroxylamines and N-formyl-N-alkylhydroxylamines are given in Tables 1 and 2, respectively.

The NMR spectra obtained for N-formyl-N-alkylhydroxylamines Table 3 at room temperature show double signals of formyl and α-protons of the substituent at nitrogen. Formyl proton signals are observed at δ7.50–7.80 ppm for the Z-isomer, and at δ8.00–8.30 ppm for the E-isomer. The chemical shifts of α-protons of the N-substituent are considerably more dependent on the nature of the substituent at nitrogen. Precise data are given in Table 3. The assignment of these signals to isomers with *cis*(Z) and *trans*(E) N-hydroxyamid bonds is based on the fact that the signals for E-conformation are much farther downfield, obviously because the alkyl group in E-conformation is nearer to the carbonyl group. The double signals are clear evidence for the *cis*(Z) ⇄ *trans*(E) equilibrium.



cis (Z) trans (E)

Scheme 1.

E-conformation in N-formyl-N-alkylhydroxylamines is an effect of the steric interaction between carbonyl and alkyl groups. The percentage of E-conformer in the Z/E equilibrium decreases with increase of the volume of the substituent at nitrogen, exactly as it does for N-alkylformamides.[13]

In the NMR spectra of N-formyl-N-methylhydroxylamine and N-formyl-N-benzylhydroxylamine in $CDCl_3$, Walter and Schaumann[3] observed 32 and 34% of E-isomer, respectively. We also confirmed the existence of 33% of E-conformer for N-formyl-N-benzylhydroxylamine by NMR and, as shown in Table 3, revealed the presence of E-isomer in proportions ranging from 25% for R = $C_6H_5CH(CH_3)$ and 20% for R = $(CH_3)_2CH$- and cyclohexyl, to 14% for R=$CH_3CH_2CH(CH_3)$. Thus, N-formyl-N-t-butyl-hydroxylamine seems to exist only in the Z-conformation, a conclusion which has been confirmed by IR spectra.

A concentrated solution of N-formyl-N-t-butylhydroxylamine in chloroform shows a broad absorption band at 3300 cm^{-1} attributable to a strongly hydrogen-bonded hydroxyl group, and a strong band at 1620 cm^{-1}, indicative of a chelated carbonyl group. Since the position of these bands remains unchanged even after dilution of the solution to 10^{-4} mole l^{-1}, the conclusion must be that the hydrogen-bonding is intramolecular.

On the other hand, N-t-butyl-N-hydroxy-N'-phenylurea[14] which only exists in E-conformation showed a ν_{O-H} band at 3560 cm^{-1} in dilute carbon tetrachloride solution. Hence, if the IR spectra of hydroxamic acids represent the Z ⇄ E equilibrium, these should be characterized in diluted solutions by two ν_{O-H}, bands, i.e. a

Table 1. N-Acyl-N-alkyl-O-benzoylhydroxylamines, R–C(=O)–N(OCOC$_6$H$_5$)–R'

R	R'	Yield (%)	M.p. (°C)	%N Calc.	%N Found
H	-CH/CH$_3$/CH$_2$CH$_3$	95	oil	6.33	6.40
H	-CH$_2$C$_6$H$_5$	65	oil	5.49	5.55
H	-CH/CH$_3$/$_2$	60	oil	6.76	6.40
H	-C/CH$_3$/$_2$	90	59–60	6.33	6.20
H	-CH/CH$_3$/C$_6$H$_5$	80	oil	5.20	5.20
H	cyclo-C$_6$H$_{11}$	90	87–8	5.67	5.60
H	-CH$_2$-CH$_2$COOCH$_3$*/	70	oil	5.91	5.70
CH$_3$	-C/CH$_3$/$_3$	97	oil	5.95	5.77
CH$_3$	cyclo-C$_6$H$_{11}$	73	oil	5.67	5.83

*O-benzyl derivative (IR in CHCl$_3$ $\nu_{C=O}$ amide group 1670 cm^{-1}, $\nu_{C=O}$ ester group 1725 cm^{-1}).

Table 2. N-Acyl-N-alkylhydroxylamines, R–C(=O)–N(OH)–R'

R	R'	Yield (%)	M.p. (°C)	%N calc.	%N Found	IR data in CHCl$_3$/diluted solutions/ ν C=O/cm^{-1}/ amide	ν C=O/cm^{-1}/ ester	ν O=H/cm^{-1}
H	-CH(CH$_3$)CH$_2$CH$_3$	84	59–61	11.97	11.98			
H	-CH$_2$C$_6$H$_5$	90	33–5	9.27	9.03			
H	-CH(CH$_3$)$_2$	97	oil	13.59	13.23			
H	-C(CH$_3$)$_3$	97	55–6	11.97	11.87	1620	—	3300
H	-CH(CH$_3$)C$_6$H$_5$	85	67–8	8.48	8.38	1630	—	3340
H	cyclo-C$_6$H$_{11}$	63	85–6	9.79	9.68			
H	-CH$_2$-CH$_2$-COOCH$_3$	70	54–5	9.52	9.43	1650	1725	3350
CH$_3$	-C(CH$_3$)$_3$	92	oil	10.62	10.72	1655		3550
CH$_3$	cyclo-C$_6$H$_{11}$	90	83–4	8.92	9.07	1650		3535, 3275
CH$_3$	CH(CH$_3$)CH$_2$CH$_3$	68	oil	10.62	10.28			
CH$_3$	-CH(CH$_3$)C$_6$H$_5$	60	72–5	7.82	8.05			

sharp band at about 3560 cm^{-1} responsible for the E-conformer, and a broad band at about 330 cm^{-1} related to the intramolecularly hydrogen-bonded Z-conformer.

In fact, the IR spectrum of N-formyl-N-phenylethylhydroxylamine in diluted chloroform solution showed a broad, strong, intramolecularly bonded ν_{O-H} band at 3340 cm^{-1}, and a sharp, weak band at 3530 cm^{-1}.

As mentioned earlier, E-conformation was found in N-hydroxyurea[7] whose geometry is influenced by hydrogen bonding of the amino group. Thus, if the electron-donor group were introduced into the α-carbon of the substituent at nitrogen, it might be possible to form a new intramolecular hydrogen bond which would stabilize the E-conformation, as for N-hydroxyurea. Hence, the NMR spectra of a series of N-formyl-N-hydroxyamino acid methyl esters synthesized by us (Table 4) showed, as expected, the existence of Z⇄E equilibrium in 1:1 ratio resulting from the fact that the formyl proton and the α-protons of the substituent at nitrogen were doubled in a ratio of 1:1. The values of their chemical shifts depended on the kind of amino acids. Exact data are given in Table 6.

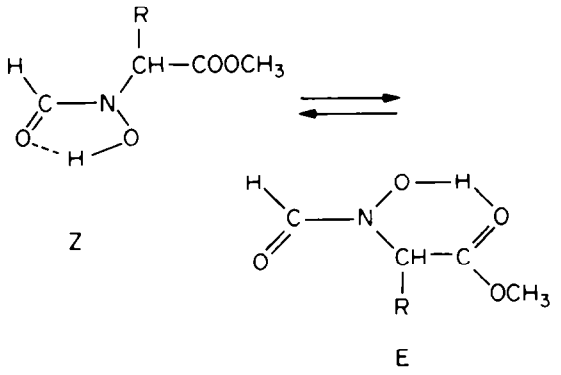
Most of the IR spectra of N-formyl-α-N-hydroxyamino-acid esters showed two broad carbonyl bands: N-hydroxyamide at 1660 cm^{-1}, and the ester at 1715–1720 cm^{-1}, and a broad hydroxyl absorption band due to intramolecular hydrogen-bonding at about 3450 cm^{-1}. For comparison, the infrared spectra of the O-protected derivatives of these esters, as N-formyl-α-N-benzyloxyamino acid esters (for physical properties and IR data see Table 5) showed an amide carbonyl band at 1680 cm^{-1} and an ester carbonyl band at 1730 cm^{-1}, wherefrom it must be concluded that the N-hydroxyamide and the ester carbonyl groups are both hydrogen-bonded. Hence, Z and E-isomers are probably stabilized by an intramolecular hydrogen bond, as shown in Scheme 2.

The NMR spectra of the N-formyl-β-N-hydroxyalanine methyl ester (see Table 3) which was prepared to examine the effect of the position of the carboalkoxyl group on the Z/E ratio, and to confirm the above conclusion, showed only 30% of E-isomer as compared with the 50% found in the corresponding α-N-hydroxyamino acid derivatives. Thus, the N-formyl-β-N-hydroxyalanine methyl ester contains no six-membered hydrogen-bonding ring to stabilize E-conformation, as confirmed by the IR spectrum of that compound. In chloroform, the $\nu_{C=O}$ absorption band of the ester group

Table 3. NMR spectral of N-formyl-N-alkylhydroxylamines, H–C–N–R (O, OH)

R	H–C=O						N–C–H						%Z			
	in $CDCl_3$		in DMSO		in TFA		in $CDCl_3$		in DMSO		in TFA		in $CDCl_3$	in DMSO	in TFA	
	Z	E	Z	E	Z	E	Z	E	Z	E	Z	E				
$C_6H_5CH_2$-	7.50	8.00					4.30	4.45*					67			
CH_3O_2C–CH_2–CH_2-	7.80	8.15					3.67, t						67			
$C_6H_5CH(CH_3)$-	7.70	8.03		8.45		8.06	4.66	5.42	5.22	5.57		4.83	75	60	100	
$(CH_3)_2CH$-	7.78	8.10					3.73	4.33					80			
cyclo–C_6H_{11}–	7.75	8.17	8.15	8.37	8.07	8.37	3.35	4.00	3.60	4.17	3.60	4.10	80	60	87	
CH_3CH_2–$CH(CH_3)$-	7.75	8.30	8.12	8.46	8.05	8.43	3.45	4.15	3.75	4.31	3.63	4.20	86	60	87	
$(CH_3)_3C$-	7.75												100			

*At −30°.



Scheme 2.

appeared at 1725 cm^{-1} and had the same frequency as the $\nu_{C=O}$ band of the ester group of the N-formyl-β-N-benzyloxyalanine methyl ester (Table 1). Comparison of the amide carbonyl absorption band for N-formyl-N-benzyloxy-β-alanine ester at 1670 cm^{-1} with that for N-formyl-N-hydroxy-β-alanine ester at 1650 cm^{-1}, revealed a chelated carbonyl group in the N-hydroxy-derivative. The value of 3350 cm^{-1} of ν_{O-H} absorption in diluted chloroform solution is indicative of the predominance of Z-conformation in the β-N-hydroxyalanine derivative, according to previous suggestions.

The Z/E ratio should therefore be similar for N-formyl-γ-N-hydroxyamino acid esters and N-formyl-N-alkylhydroxylamines. In fact, the ^{1}H-NMR spectrum of 3-(N-formyl-N-hydroxyamino)-propylphosphonic acid revealed 80% of Z-isomer.[9]

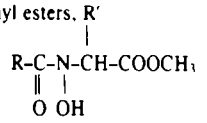
Both rotamers can always be detected, in formamides (HCO–NHR), whereas in higher amides (R'CO–NHR) only those forms are found where the residues R' and R are trans to each other.[16] However, the possibility that there exists an intramolecular hydrogen-bonding in the N-hydroxyamide system, should increase the amount of the Z-form in acetohydroxamic acid derivatives in relation to the corresponding N-alkylacetamides.

Thus, on the basis of one single ν_{O-H} absorption band appearing at 3550 cm^{-1} in diluted solutions, we found that N-acetyl-N-t-butyl-hydroxylamine exists as E-isomer, as previously observed for N-t-butyl-N-hydroxy-N'-phenylurea.[14]

The presence of two ν_{O-H} absorption bands for N-acetyl-N-cyclo-hexylhydroxylamine in diluted $CHCl_3$–CCl_4 solution (1:9) at 3535 and 3275 cm^{-1} pointed to the presence of both the Z and the E conformations. A broad hydroxyl absorption band at 3275 cm^{-1} represented the intramolecular hydrogen bonding stabilizing the Z-conformer. In the NMR spectrum of N-acetyl-N-cyclohexylhydroxylamine we identified 20% of Z-isomer. For comparison, N-acetyl-N-sec-butylhydroxylamine and N-acetyl-N-α-phenylethyl-hydroxylamine were characterized by 25 and 15% of Z-conformer, respectively. The predominance of E-conformation in N-acetyl-N-alkyl-hydroxylamine pointed to higher steric interactions between the acetyl group and the alkyl substituent.

Thus, in the case of N-acetyl-α-N-hydroxyamino acid esters (physical properties are given in Table 4) there should only be E conformation, because the E-form is stabilized by the intramolecular hydrogen bond like it is in N-formyl-N-hydroxyamino acid esters. The NMR spectra of acyl derivatives only show one single signal for the α-protons of the N-substituent, even at −110°. The

Table 4. N-Acyl-α-N-hydroxyamino-acid methyl esters, R'



R	R*	Yield (%)	M.p. (°C)	%N Calc	%N Found	IR data in $CHCl_3$: ν C=O(cm^{-1}) amide	ν C=O(cm^{-1}) ester	ν O-H/cm^{-1}
H	H	80	60–3[a]	10.52	10.18			
H	CH_3[b]	95	oil	9.52	9.85	1665	1720	3460
H	C_2H_5	94	oil	8.69	8.44			
H	$C_6H_5CH_2$	92	oil	5.91	6.09	1666	1720	3490
H	$CH(CH_3)_2$	93	oil	8.00	7.67	1660	1715	3445
H	$CH_2CH(CH_3)_2$	97	oil	7.40	7.34	1665	1720	3460
H	$CH(CH_3)C_2H_5$[c]	95	oil	7.40	7.46	1655	1713	3450
H	CH_2–$COOCH_3$[d]	96	oil	6.83	6.80			
CH_3	H	89	oil	9.52	9.70	1655	1733	3460
CH_3	CH_3[e]	77	126–7	9.93	9.66	1660	1733	3460
CH_3	$C_6H_5CH_2$	80	oil	5.58	5.69	1660	1730	3455
CH_3	$CH(CH_3)_2$	73	oil	7.40	7.34			
CH_3	CH_2–$COOCH_3$	65	oil	6.39	6.19			

[a] lit.[20] m.p. 71–2°
[b] $\alpha_D^{20} = -62.0/c = 3$ in MeOH/ for L-config.
[c] $\alpha_D^{20} = -73.3/c = 1.5$, in MeOH/ for D-config.
[d] $\alpha_D^{20} = -14.3/c = 2$ in MeOH/ for L-config.
$\alpha_D^{20} = +13.3/c = 2$ in MeOH/ for D-config.
[e] As p-nitrobenzyl ester.

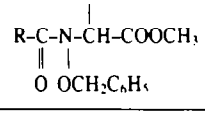
chemical shift values of these protons are comparable to those of the α-protons of the E-conformer in N-formyl derivatives, e.g. 4.16 and 5.03 ppm values for α-protons of N-formyl-N-hydroxy-phenylamine and 5.15 ppm for α-protons of N-acetyl-N-hydroxyphenylalanine methyl ester. Exact data are given in Table 7.

The conformational assignment of these compounds in solution is evident on the basis of IR data. There were bands at 3400 cm^{-1} (ν_{O-H}), at 1720 cm^{-1} ($\nu_{C=O}$ ester group), and at 1660 cm^{-1} ($\nu_{C=O}$ amide group), whereas analogous frequencies of the carbonyl group for N-acetyl-N-benzyloxyamino acid esters (see Table 5) appeared at 1740 cm^{-1} (ester group) and at 1660 cm^{-1} (amide group). Hence, it is evident that only the ester group participates in the intramolecular hydrogen bond.

Another indication in favour of the E-conformation for N-acyl-N-hydroxyamino-acid derivatives can be derived from conformational investigations of N-acyl-N-hydroxydipeptide esters.[15]

The increase in the amount of E-isomers can be due to

Table 5. N-acyl-α-N-benzyloxyamino acid methyl esters, R'



R	R*	Yield (%)	M.p. (°C)	%N Calcd.	%N Found	IR data in $CHCl_3$: ν C=O(cm^{-1}) amide	ν C=O(cm^{-1}) ester
H	H	90	oil	6.28	6.28		
H	CH_3[a]	86	oil	5.91	5.56	1670	1730
H	C_2H_5	80	oil	5.58	5.39		
H	$C_6H_5CH_2$	88	oil	4.28	4.34	1680	1735
H	$CH(CH_3)_2$	78	oil	5.28	5.56	1680	1730
H	$CH_2CH(CH_3)_2$	74	oil	5.02	5.36		
H	$CH(CH_3)C_2H_5$[b]	80	oil	5.02	4.70	1665	1730
H	CH_2—$COOCH_3$[c]	79	oil	4.75	4.72		
CH_3	H	58	oil	5.91	5.68	1665	1740

[a] $\alpha_D^{20} = -18.0$ (c = 6, in MeOH) for L-config.
[b] $\alpha_D^{20} = -33.3$ (c = 1.5 in MeOH) for D-config.
[c] $\alpha_D^{20} = -6.8$ (c = 2 in MeOH) for L-config.
$\alpha_D^{20} = +7.5$ (c = 2 in MeOH) for D-config.

Table 6. Spectral of N-formyl-N-hydroxyamino acid methyl esters. R
|
H-C-N-CH-COOCH$_3$
|| |
O OH

	H-C=O					N-C-H					%Z			
	in $CDCl_3$		in DMSO		in TFA		in $CDCl_3$		in DMSO		in TFA		in $CDCl_3$	in DMSO	in TFA
	Z	E	Z	E	Z	E	Z	E	Z	E	Z	E			
H-	7.88	8.32	8.17	8.55			4.50	4.92	4.90	5.13	4.65	5.12	50	50	
CH_3-	7.96	8.30	8.30	8.51	8.15	8.43	4.50	4.92	4.90	5.13	4.65	5.12	50	50	80
CH_3CH_2-	7.94	8.40	8.23	8.59	8.10	8.50	4.12	4.80	4.60	4.87	4.35	4.90	50	50	80
$(CH_3)_2CH$-	7.75	8.20					3.72	4.60					50	50	
$(CH_3)_2CH$-CH_2-	7.91	8.40	8.31	8.59			4.20	5.02	4.78	5.05			50	50	
$CH_3CH_2CH(CH_3)$-	7.80	8.23					3.84	4.70					50	50	
$C_6H_5CH_2$-	7.29	8.00					4.16	5.03					50	50	
CH_3O_2C-CH_2-	8.00	8.30	8.25	8.48			4.83	5.30	5.15	5.38					

the disappearence of the five membered intermolecular hydrogen-bonding ring which prefers Z-conformation. Thus, in O-protected hydroxamic acids, e.g. in HCO-NR-OR', where R=R'=CH_3, Walter and Schaumann[3] observed about 75% of the E-form at −27.5°. We found about 75% of E-isomers at −30°C in N-formyl-N-benzyloxyalanine and in N-formyl-N-benzyloxy-butyric acid esters (cf. 50% of E-form in analogous N-hydroxy-derivatives).

A similar favouring of the E-isomer is observed upon increase of solvent polarity, due to competition with the intermolecular hydrogen bond. Hence, the NMR spectra of N-formyl-N-α-phenylethylhydroxylamine, N-formyl-N-cyclohexylhydroxylamine and N-formyl-N-s-butyl-hydroxylamine run in DMSO at room temperature showed 40% of E-conformer, whereas 25, 20 and 14%, respectively, of the E-form were detected in $CHCl_3$. Pertinent data are presented in Table 3.

In contrast to the NMR spectra of N-formyl-N-alkyl-hydroxylamines, the NMR spectra of N-formyl-N-hydroxyamino acid esters in DMSO did not differ from the NMR spectra run in $CHCl_3$. Understandable differences were only observed in the chemical shifts of the N-substituent of the α-protons of the Z and E isomers, but not in the Z/E ratio.

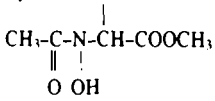
On the other hand, protonation of the N-hydroxyamide carbonyl group should lead to decreasing the amount of the E-conformer owing to higher steric interactions of the protonated carbonyl group with the N-alkyl group. NMR spectra run in trifluoroacetic acid only showed 12% of E-isomer in N-formyl-N-cyclohexyl- and N-formyl-N-s-butyl-hydroxylamines, and 20% of the E-form in N-formyl-α-N-hydroxyamino acid esters. Similar effects were observed in the NMR spectra of N-alkylformamides in TFA.[13]

The temperature dependence of nuclear resonance has very often been used to investigate rotation about the partial double bond in amides.[16] The energy barrier to carbonyl nitrogen bond rotation has been estimated as free enthalpy of activation ΔG_c^*, calculated from "slow exchange peak separation" ($\Delta\nu$) and coalescence temperature (T_c). The ΔG_c^* values of selected formhydroxamic acids are presented in Table 8.

Comparison of the ΔG_c^* values for formhydroxamic acids ($\Delta G_c^* \approx 16$ kcal mol^{-1}) and O-benzyl-formhydroxamic acids ($\Delta G_c \approx 14$ kcal mol^{-1}) with $\Delta G_c^* =$ 20.9 kcal mol^{-1} for N,N-diethylformamide[21], $\Delta G_c^* =$ 20.6 kcal mol^{-1} for N-N-diisopropylformamide[21] and $\Delta G_c^* = 21.6$ kcal mol^{-1} for N-methyl-N-benzyl-formamide shows the height of the rotation barrier to decrease clearly in formhydroxamic acids. Rotation about the amide bond (C–N) is hindered by the participation of the limiting structure $R^1R^2\text{-}\overset{+}{N}\text{=}C\begin{matrix}O^-\\ \diagdown\\ \diagup\\ R\end{matrix}$ in the ground state. Replacement of the alkyl group on the nitrogen by the hydroxyl group reduces the double-bond character of the N-hydroxyamide bond, hence also the rotation threshold. The hydroxyl group as electron-attracting substituent decreases ΔG_c^* by diminishing the contribution of the double-bond structure. The deviation of 1–2 kcal mol^{-1} from the values for hydroxy free formylhydroxamic acid and O-protected formylhydroxamic acid is probably an effect of hydrogen bond formation.

Finally, the present study indicates the following: (a) Z-conformation is preferred for N-unsubstituted hydroxamic acids, mainly in their solid state[1,5,6] (b) N-

Table 7. NMR spectral of N-acetyl-N-hydroxyamino acid methyl esters, R



R	-C-H in $CDCl_3$
H-	4.82
CH_3-*	5.15
$C_6H_5CH_2$-	5.35
$(CH_3)_2CH$-	4.80
$CH_3O_2CCH_2$-	5.40

*As p-nitrobenzyl ester.

Table 8. Energy barrier to amide bond rotation in formhydroxamic acids H-C-N-R'

		$\Delta\nu$(Hz)		T_c(°C)		$\Delta G_c^{\ddagger}$* (kcal/mol)	
		in $CDCl_3$	in DMSO	in $CDCl_3$	in DMSO	in $CDCl_3$	in DMSO
H	$-CH_2-COOCH_3$	35	30	52	44.5	16.2 ± 0.2	16.0 ± 0.5
H	$-CH(CH_3)-COOCH_3$	26	20	47.5	38.5	16.2 ± 0.2	15.9 ± 0.1
H	$-CH(CH_2CH_3)-COOCH_3$	38	28	55	46.5	16.4 ± 0.4	16.1 ± 0.3
H	$-CH(CH_2-CH(CH_3)_2)-COOCH_3$	38	22	54	45	16.2 ± 0.7	16.2 ± 0.4
H	$-CH(CH_3)-CH_2CH_3$	43	28	55	47	16.3 ± 0.4	16.1 ± 0.1
H	$-CH(C_6H_5)-CH_3$	28	28	35	35	15.5 ± 0.5	15.5 ± 0.6
$C_6H_5CH_2$-	$-CH(CH_2CH_3)-COOCH_3$	5		0.5		14.7 ± 0.4	
$C_6H_5CH_2$-	$-CH(CH_3)-COOCH_3$	12		−3.0		14.2 ± 0.2	

*The free enthalpy of activation in accordance with the Eyring equation. The errors are calculated by the method of least-squares.

formyl-N-alkyl- and N-acyl-N-alkyl-hydroxylamines show Z⇄E equilibrium in solution. The Z/E ratio depends on solvent polarity. A polar solvent increases the amount of E-conformer. (c) a more bulky substituent at nitrogen in formhydroxamic and acetohydroxamic acids increases the amount of the Z-conformer in Z⇄E equilibrium; (d) introducing the acetyl group instead of the formyl group leads to an increased the amount of E-conformer (e) electronodonor groups in α-position of the N-substituent increase the amount of the E-conformer; (f) as in amides, protonation of the hydroxamic acid grouping decreases the amount of E-conformer.

EXPERIMENTAL

N-Formyl-N-alkylhydroxylamines were synthesized by standard formylation[10] of N-alkyl-O-benzoyl-hydroxylamines[11,12] hydrochlorides in the presence of equimolar amounts of anhydrous sodium acetate or sodium formate, followed by removing the benzoyl group in the following manner. To 10 mmole of N-formyl-N-alkyl-O-benzoylhydroxylamine (Table 1) in MeOH was added 20 mmole of N NaOH. After 15 min methanol was evaporated under reduced pressure and the soln was acidified with acetic acid. The product was extracted with ethyl acetate, dried over anhydrous $MgSO_4$ and evaporated to dryness. Physical properties are given in Table 2.

N-Formyl-α-N-hydroxyamino acid esters were prepared by standard formylation[10] of N-benzyloxamino acids[17] followed by esterification with methyl iodide in DMF in the presence of $NaHCO_3$ as described by Bocchi *et al.*[18] The N-formyl-N-benzyloxyamino acid esters (Table 5) were reduced by the method described earlier.[19] Their properties are presented in Table 4.

N-Acetyl-N-alkylhydroxylamines were prepared by reaction of acetyl chloride with N-alkyl-O-benzoyl-hydroxylamines followed by hydrolysis of the O-benzoyl group as described above. Acetylation of N-benzyloxyamine acids followed by esterification of the acids so obtained according to Bocchi *et al.*[18] then by removal of the benzyl group gave N-acetyl-α-N-hydroxyamino acid esters. The physical properties of N-acetylhydroxamic acids are presented in Tables 2 and 4.

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