APPLIED ORGANOMETALLIC CHEMISTRY
Appl. Organometal. Chem. **14**, 604–610 (2000)

Derivatives of hydroxamic acids†

Jan Schraml*
Institute of Chemical Process Fundamentals, Academy of Sciences of the Czech Republic, Rozvojová 135, 165 02 Prague 6, Czech Republic

Despite the biological importance and rich chemistry of hydroxamic acids (HAs), their organometallic derivatives have received little attention so far. Fully silylated (trimethylsilyl and t-butyldimethylsilyl) derivatives which are promising for medicinal applications have a structure derived from that of the tautomeric hydroximic acid with an *E/Z* ratio depending on the nature of the acid. Aliphatic acids yield disilyl derivatives in an approximate *E/Z* ratio of 2:3; aromatic HAs produce solely *Z* isomer irrespective of the phenyl ring substituent. Silylation of aliphatic dihydroxamic acids proceeds independently on both ends if the two hydroxamic groups are separated by one methylene group at least. It was not possible to determine the *E/Z* ratio for oxalic and malonic acid derivatives. It is shown that ^{29}Si and ^{15}N NMR chemical shifts are useful for differentiation between hydroxamic and hydroximic structures, but for determination of *E* and *Z* configurations spin–spin coupling must be used until more data relating ^{29}Si, ^{13}C and ^{15}N chemical shifts to the configuration are available for this class of compounds. The dependence of chemical shifts on Hammett substituent constants in ring-substituted benzhydroxamic acids is discussed. Some errors found in the literature on hydroxamic acids are also explained.

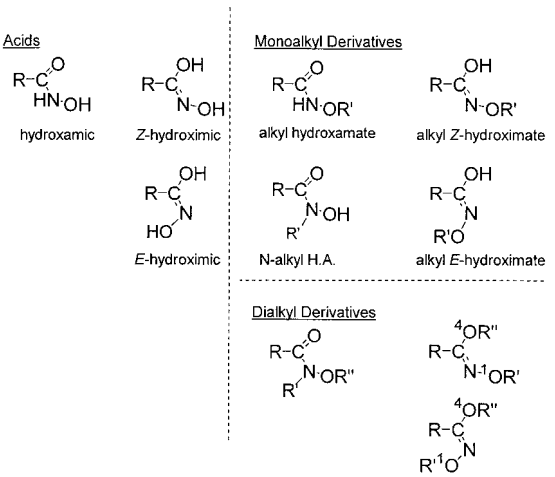
Keywords: TMS derivatives; TBDMS derivatives; hydroxamic acids; hydroximic acids; silylation; NMR spectra

INTRODUCTION

Rich chemistry, ability to form stable chelates and biological activity of many hydroxamic acids (HAs) makes this class of compounds important for biochemistry, analytical chemistry and medicinal applications.[1,2] Despite their importance, some current organic chemistry textbooks do not mention HAs at all[3,4] and their organometallic derivatives have so far received little attention (except for studies of complexation with heavy metals in connection with membrane transport, or industrial or analytical utilization).

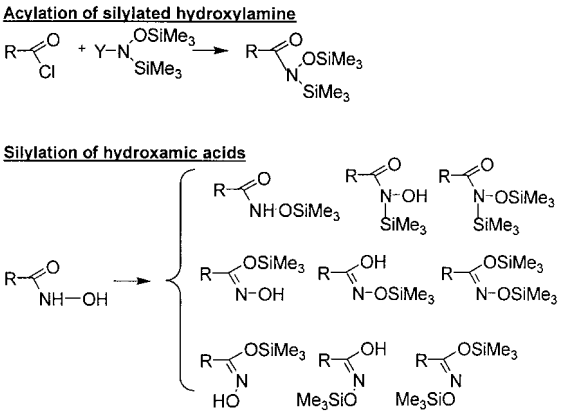
The HAs, discovered in 1869 by H. Lossen[5] when he worked in the laboratory of W. Lossen (after whom the well-known rearrangement is named), can possess the structures shown in Scheme 1, dissociate and assume various conformations (for leading references to the determined structures see Ref. 6). The two tautomeric structures will be referred to as hydroxamic and hydroximic acids, using the atom numbering indicated.

Organometallic derivatives of HAs can have the structures indicated in Scheme 1 with the substituent R containing an organometallic group.



Scheme 1

* Correspondence to: Jan Schraml, Institute of Chemical Process Fundamentals, Academy of Sciences of the Czech Republic, Rozvojová 135, 165 02 Prague 6, Czech Republic.
E-mail: schraml@icpf.cas.cz
† Presented at the XIIIth FECHEM Conference on Organometallic Chemistry, held 29 August–3 September 1999, Lisbon, Portugal.
Contract/grant sponsor: Granting Agency of the Academy of Sciences of the Czech republic; Contract/grant number: A4072605.
Contract/grant sponsor: Granting Agency of the Czech Republic; Contract/grant number: 203/999/0132.

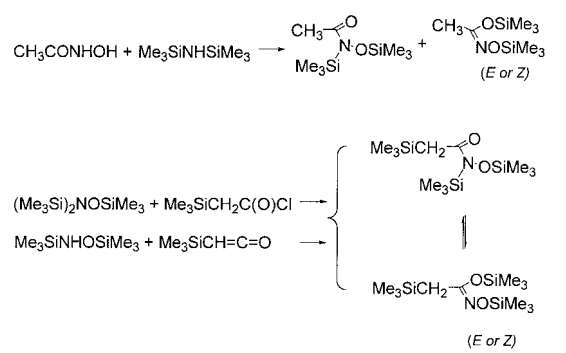


Scheme 2

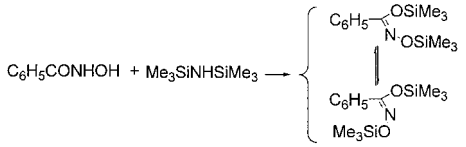
We have been interested in organosilicon derivatives especially after Chiu[7] suggested that R_3Si derivatives of HAs are suitable candidates for anticancer drugs (by controlling Si–N and Si–O bond hydrolysis one could control drug unmasking, hydrolysis by-products are non-toxic and R_3Si groups increase the lipophilicity needed to penetrate the brain barrier).

Though the organosilicon derivatives can be prepared by different routes, the most straightforward are acylation of silylated hydroxylamine[8] and silylation of HAs (Scheme 2). Though the latter can lead to a number of products depending on the reaction conditions and the nature of HA, it is more general. Since it is also closely related to our interest in ^{29}Si NMR tagging,[9] we have chosen this route.

Aliphatic HAs were silylated previously, e.g. by Bliefert's group.[10] Analogous products were also prepared by Mironov's group,[11] by different



Scheme 3



Scheme 4

methods (Scheme 3). Both research groups obtained a mixture of two products (A and B). Both groups believed that one product is a derivative of hydroxamic and the other of hydroximic acid (*E* or *Z* configurations were not considered).

Silylation of aromatic HAs (e.g. benzhydroxamic acid; Scheme 4) yielded what appeared (in the NMR spectrum) as a single product but the authors[12,13] assumed the presence of hydroxamic and hydroximic derivatives in a fast exchange.

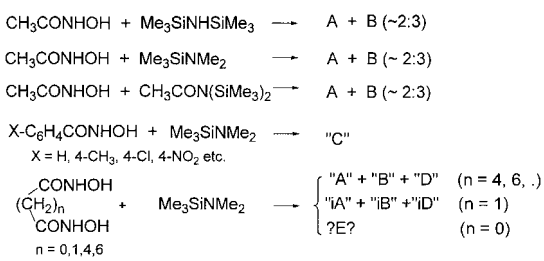
RESULTS AND DISCUSSION

Silylation

Our silylation experiments (Scheme 5), employing a variety of experimental conditions and of trimethysilylation reagents (hexamethyldisilazane, HMDSN; trimethylsilyldimethylamine, TMSDMA; bis(trimethylsilyl)acetamide, BSA, etc.) in an excess, reproduced the results of both the Bliefert and the Rigaudy groups in the cases of aliphatic HAs (a 2:3 mixture of isomers A and B) and aromatic HAs (one product in the NMR spectra), respectively. In the case of aliphatic dihydroxamic acids the product mixture appeared to depend on the distance between the two hydroxamic groups.

Product identification

Since the silylated HAs are moisture-sensitive



Scheme 5

honey-like liquids, the possibilities for their structure determination are essentially limited to NMR. In these derivatives the hydroxamic/hydroximic group offers only NMR spectra of insensitive nuclei and no usual coupling pathway. Though Lipczynska-Kochany and Iwamura[14] advocated the use of ^{17}O NMR for the studies of hydroxamic acids, it requires selective enrichment in ^{17}O in order to differentiate among various oxygen nuclei in the molecule and hence is of little value in this case. ^{13}C and ^{15}N NMR databases do not contain enough data which would enable the chemical shifts to be related to the proposed structures but the $J(^{13}C–^{13}C)$ coupling constants are related to the electron lone pair orientation[15] similarly to $J(^{15}N–^{1}H)$ couplings.[16] For similar reasons ^{29}Si NMR chemical shifts cannot be used for geometry (*E/Z*) determination but are good for differentiation between hydroxamic and hydroximic structures of disilyl derivatives: hydroxamic structures would contain Si–N ($\delta = -2$ to 10) and Si–O ($\delta = 18$ to 25) silicon while hydroximic structures contain only Si–O silicon.

Let us start with the A + B silylation product mixture, acetohydroxamic acid. The presence of two isomers (which can be differentiated in the spectra according to line intensity) and α hydrogens (CH_3 group) facilitates the structure determination. According to the ^{29}Si chemical shifts (A: $\delta = 20.69$ and 23.26; B: $\delta = 19.33$ and 23.84), both products have a hydroximic structure and so the reaction (Scheme 3, top) should be corrected to yield a mixture of isomers of hydroximic acid derivatives. Their ^{15}N chemical shifts (A: $\delta = -73.2$; B: $\delta = -87.9$) are substantially different from that in the parent HA ($\delta = -214.7$). This significant difference between ^{15}N chemical shifts in hydroxamic and hydroximic structures is of diagnostic value. The ^{15}N spectra measured with selective methyl proton decoupling indicate (Fig. 1) that there is no coupling between ^{15}N and CH_3 protons in the product A but $J = 3.3$ Hz in the product B (as seen when protons in A are selectively decoupled). Such three-bond couplings are larger in those isomers in which the nitrogen electron lone pair is closer to the coupled protons, in this case in the *Z* isomer. This conclusion is further supported by $^{1}J(^{13}C–^{13}C)$ couplings, determined by the usual 1D INADEQUATE experiment,[17] which are also found to be larger for the carbon closer to the nitrogen lone pair.[16] These results[18] are summarized in Scheme 6; silylation of acetohydroxamic acid produces *E* and *Z* hydroximic derivatives in a 2:3 ratio.

According to ^{29}Si and ^{15}N chemical shifts

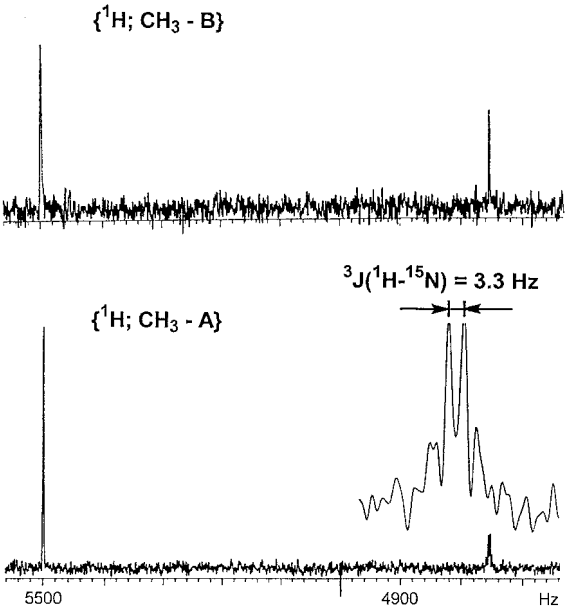
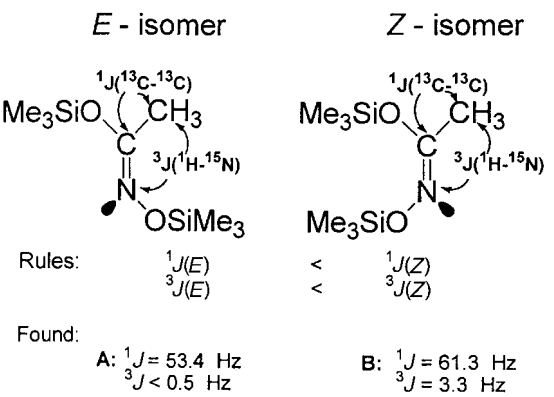


Figure 1 ^{15}N NMR spectra (50.7 MHz) of trimethylsilylated acetohydroxamic acid (products A and B) measured with a selective proton decoupling. Top: methyl protons of product B decoupled. Bottom: methyl protons of product A decoupled.

[$\delta(^{29}Si) = 19$ to 28; $\delta(^{15}N) = -65$ to 92], silylation of aromatic HAs leads also to a derivative of hydroximic acid (independently of the ring substitution). Use of different solvents (chloroform, dimethylsulfoxide, acetone) and low-temperature (−70 °C) spectra provided no indication of any exchange process (all the lines remained narrow) and so there is no reason to assume a fast exchange between any hydroximic isomers as suggested by Rigaudy *et al.*[12] In the absence of any α hydrogen



Scheme 6

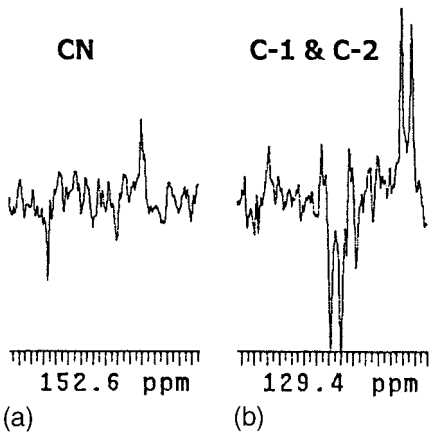


Figure 2 Relevant regions of ^{13}C 1D INADEQUATE spectrum of 4-F-$C_6H_4CONO[SiMe_2(tBu)]_2$. (a) CN carbon well separated; (b) C-1 carbon overlapped with C-2 carbon lines.

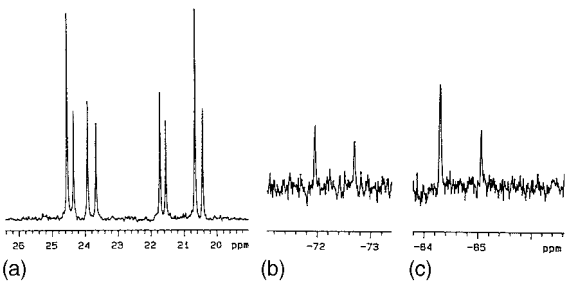
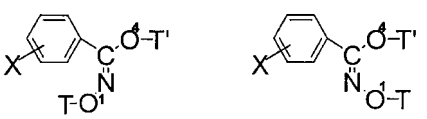


Figure 3 NMR spectra of trimethylsilylated dihydroxammalonic acid. (a) ^{29}Si NMR spectrum; (b,c) ^{15}N NMR spectrum in two parts.

only ^{13}C coupling constants can be used for geometry determination in this case. Fortunately, the coupling in question, $^1J(^{13}CN–^{13}C)$, can be determined from CN carbon satellites while the C-1 part of the ^{13}C 1D INADEQUATE spectrum is complicated by the presence of the lines of other carbons (Fig. 2). In the series being studied the coupling varied between 74.9 and 77.8 Hz. Since only one isomer is present, numerical values of *J* must be used for the geometry determination instead of relative magnitudes of *J* as in the case of acetohydroximic derivatives. Hence, to interpret the above *J* values, data on close model compounds had to be sought. (The precursors of the chosen models have an interesting history: they were studied already by Alfred Werner[19] in 1893 but the structure assigned to them on the basis of the Beckman rearrangement was reversed after the steric requirements of the Beckman rearrangement were better understood and dipole moments supported the reversed assignment,[20] which was proved by X-ray diffraction later.[21]) The data from models, Scheme 7, show clearly that only *Z*-hydroximic acid derivatives are produced by silylation of aromatic HAs independently of the ring substitution or silylation group involved ($SiMe_3$ or $SiMe_2CMe_3$).

The spectra of reaction products of silylation of aliphatic dihydroxamic acids depend strongly on the separation between the two hydroxamic groups. When the separation is large enough, e.g. four or more methylene groups as in dihydroxamadipic acid ($[CH_2CH_2C(O)NHOH]_2$), the two end groups are silylated independently and their NMR chemical shifts are also independent. The ^{29}Si NMR spectra are almost identical to those described above for the silylation product of acetohydroxamic acid, i.e. both end groups produce silyl *E* and *Z*

Models (X = H; T' = C_2H_5; T = H, $SiMe_2CMe_3$):



$^1J(^{13}CN–^{13}C)$ = 67.5 Hz $^1J(^{13}CN–^{13}C)$ = 72 – 74 Hz

Series studied: (T' = T= $SiMe_3$, $SiMe_2CMe_3$; X = NMe_2,... NO_2)

$^1J(^{13}CN–^{13}C)$ = 74.9 – 77.8 Hz

Scheme 7

derivatives of the hydroximic group in approximately the same ratio as observed in acetohydroxamic acid. When the two end groups get closer, as in dihydroxam-malonic acid, the spectra of the silylation products look more complex (Fig. 3). According to both ^{29}Si and ^{15}N NMR spectra, both end groups are silylated solely in their hydroximic form. The number of the observed lines is easily interpreted as a superposition of the spectra of all three possible combinations of end group configurations. Taking into account that if the two end groups have the same configuration the corresponding nuclei are chemically equivalent and that the configuration of one end group affects the shifts in the other, we get for the combinations *Z–Z* and *E–E* two lines in the ^{29}Si NMR spectrum and one in the ^{15}N spectrum for each combination, and for *Z–E* combination four ^{29}Si and two ^{15}N lines. In total we should see eight and four lines in ^{29}Si and ^{15}N NMR spectra, respectively. While this agrees with the picture observed (Fig. 3) we have not yet been able to assign the observed lines to the individual combinations of configurations. The most difficult to solve is the silylation product of dihydroxamoxalic acid. According to NMR spectra (two ^{29}Si lines at $\delta = 26.28$ and 22.22, one ^{15}N line at $\delta = -62.8$) the product is a derivative of dihydroximoxalic acid but its configuration is difficult to determine because of symmetry (the two CN carbons are equivalent), absence of hydrogens etc. Because of experimental requirements we have not yet been able to measure the $^{3}J(^{15}\text{N}–^{13}\text{C})$ coupling constant which could resolve this ambiguity. We only assume that the product takes the *Z–Z* configuration as it is less sterically crowded than the *E–E* combination and it is unlikely that ^{29}Si and ^{15}N shifts would both accidentally degenerate in the *E–Z* configuration.

NMR spectra of ring-substituted silylated benzhydroximic acid derivatives

For a study of NMR properties we have prepared a series of ring-substituted benzhydroxamic acids and silylated (trimethylsilylated and t-butyldimethylsilylated) them as described above. In the course of preparation of the parent hydroxamic acids we have come across of some errors in the fundamental papers; these are briefly described in the Appendix. The detailed NMR data have been published[22,23] but we shall mention here briefly only some interesting results concerning simple Hammett-type correlations; a more complicated treatment (DSP) can be found in the references cited.[22,23]

Linear correlation of ^{15}N chemical shifts with Hammett substituent constants in the silyl derivatives of benzhydroximic acids studied confirms the hydroximic structure, as the slope (TMS derivatives; $b = 7.73$, $n = 12$, $r = 0.966$) is intermediate between those found in analogous correlations for *N,N*-dimethylbenzamides (C—N; $b = 3.79$, $n = 12$, $r = 0.951$) and benzonitriles (C≡N; $b = 10.5$, $n = 7$, $r = 0.993$).

Similar correlations also hold for ^{13}C chemical shifts in the C═N moiety but the slopes are negative and in absolute value smaller then in methyl benzoates, benzonitriles and *N,N*-dimethylbenzamides. Considering the polarizability of the groups involved and the properties of Si–O bonds, these findings are in agreement with the model in which the C═N double bond behaves as an isolated unit polarized by the distant substituent.[22]

Excellent correlations between the ^{29}Si chemical shifts in TMS and TBDMS derivatives on one side and Hammett substituent constants on the other (TMS: SiO^1; $r = 0.988$, $n = 12$, $b = 1.96$; SiO^4; $r = 0.977$ $n = 12$, $b = 1.92$; TBDMS: SiO^1; $r = 0.988$, $n = 12$, $b = 1.83$; SiO^4; $r = 0.977$, $n = 12$, $b = 1.96$) confirm the independence of the hydroximic structure on the remote ring substituent. (In contrast, the molecular structure of the parent benzhydroxamic acids or their alkali acids are strongly influenced by the ring substituents.[24–26]) The correlations have surprisingly the same slopes for the two silicon atoms in the molecule irrespective of the fact that one of the silicon atoms (SiO^4) is one bond closer to the benzene ring. We assume that association with the solvent (hydrogen bonding with chloroform) partially compensates the direct substituent effect on the nearer silicon. The substituent effect which increases the silicon shielding also increases the basicity of the oxygen atom in the C–O–Si fragment and hence the hydrogen bond to it is stronger. As such hydrogen bonding reduces the shielding of silicon,[27] it compensates partially the direct substituent effect. Calculations have shown that the oxygen atom in question is solvent-accessible, even in the TBDMS derivatives.

Uniquely, we observed correlations of methyl and quaternary carbons of both t-butyl groups in TBDMS derivatives. Such effects, observed on atoms five and six bonds away from the ring, are rare and difficult to explain.

The correlations described and other details[22,23] indicate that the ring substituent has no significant

effect on the geometry of the hydroximic moiety; its structure and torsion angle with the benzene ring do not vary in the series.

APPENDIX

As mentioned above, in the course of the present study we have come across several errors in fundamental papers on hydroxamic acids. We would like to explain them here as the explanations are instructive. The error described under (i) warns against an indiscriminate trust in accepted reference sources of information; errors (ii) and (iii) can be easily repeated if straightforward logic is used without considering fine details of experiments.

(i) Structure of alkali salts of benzhydroxamic acids

Preparation of alkali salts of benzhydroxamic acid for studies of their structures is usually carried out according to the procedure[28] described (and tested) in *Organic Synthesis*.[29] As a simple complete elemental analysis reveals, the product[29] is not a potassium benzhydroxamate, $K[C_6H_5CONHO]$, but potassium hydrogen benzhydroxamate, $KH[C_6H_5CONHO]_2$. The same product had already been correctly described in 1967 by Maggio *et al.*[30] but their acidimetric study went unnoticed. Our X-ray diffraction studies[24,26] revealed that the structure of these salts is very sensitive to the nature of the cation and phenyl ring substitution; for example whereas benzhydroxamic acid forms acid salts with potassium and lithium, the potassium salt of 4-nitrobenzhydroxamic acid is a normal salt.

(ii) IR spectra of the alkali salts of benzhydroxamic acids

(The absence of a ν(OH-assoc) band (at 2730 cm^{-1}) in the solid-state IR spectra of some alkali salts, as contrasted to the spectra of the parent benzhydroxamic acid, was taken as a proof that the acid was an *O*-acid in these salts which were (incorrectly) assumed to be 'normal' salts. How could the OH band disappear from the spectrum of an acid salt? According to the X-ray structure, the OH…ON bonds in these acid salts are very strong and short (around 2.46 Å)[25] and so, according to the correlation between O…O distances and ν(OH-assoc) frequencies,[31] the band should move from 2730 cm^{-1} to the 1600–700 cm^{-1} region, where it is buried among many other bands.

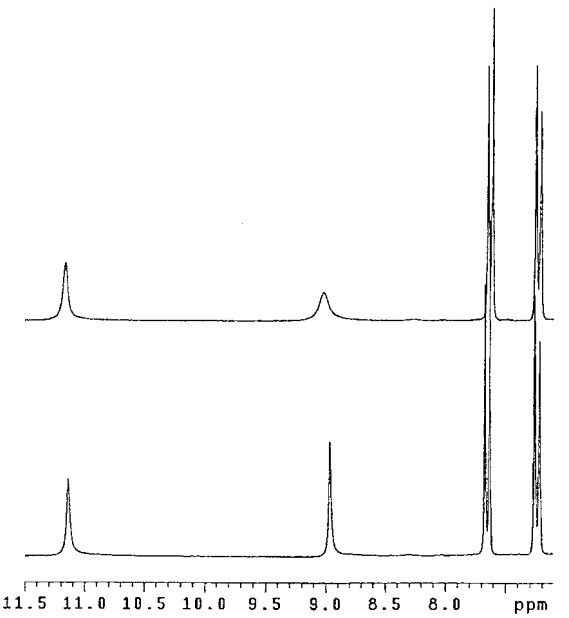


Figure 4 Regions of ^{1}H NMR spectra of 4-methylbenzhydroxamic acid in dry (bottom) and wet (top) dimethyl sulfoxide-d_6.

(iii) Assignment of OH and NH lines in the ^{1}H NMR spectra of hydroxamic acids

(Brown *et al.*[32] assigned the two lines in acetohydroxamic acid (in DMSO) through ^{15}N isotopic substitution unequivocally. Their assignment opposes that derived earlier[33] from the spectra of *N*-phenyl derivatives by straightforward logic: if a peak disappears from the spectrum when NH is replaced by N—C_6H_5, then the peak must be due to the NH proton. Clearly, the authors[33] neglected other factors. Similar mistakes can happen when the hydroxamic acids are measured in wet DMSO (Fig. 4). If the moisture is not monitored, the broader of the two peaks might be erroneously assigned to the NH proton (as if broadened by the quadrupolar ^{14}N nuclei).

CONCLUSIONS

Silylation of hydroxamic acids produces derivatives of the tautomeric hydroximic acids. In the case

of aromatic acids the *Z* conformer is the single product; aliphatic acids yield *E* and *Z* products in an approximate ratio of 2:3. In aliphatic dihydroxamic acids, the two groups are silylated independently as long as they are separated by at least one methylene group.

^{29}Si and ^{15}N NMR chemical shifts can differentiate hydroxamic and hydroximic structures but more data are needed before *E/Z* can be estimated from the chemical shift data. At present, coupling constants are the only option for the latter determination but a suitable coupling must be chosen for each case individually.

The chemical shifts reported for ring-substituted benzhydroximic acids exhibit excellent correlations with Hammett substituent constants, indicating thus that no significant structural change in the hydroximic moiety is induced by the remote substituent.

Acknowledgements The paper is based on the work of Drs V. Blechta, J. Čermák, M. Kvíčalová, R. Řeřicha and L. Soukupová, and advice of Prof. O. Exner. Their collaboration is most gratefully acknowledged and so is the financial support provided by the Granting Agency of the Academy of Sciences of the Czech Republic (grant no. A4072605) and the Granting Agency of the Czech Republic (grant no. 203/99/0132). The project was supplied with subvention by The Ministry of Education of the Czech Republic (Project LB98233).

REFERENCES

1. Bauer L, Exner O. *Angew. Chem., Int. Ed. Engl.* 1974; **13**: 376.
2. Kehl H (ed.). *Chemistry and Biology of Hydroxamic Acids*. S. Karger: Basel, 1982.
3. Schmid GH. *Organic Chemistry*. Moshby: St Louis, MO, 1996.
4. McMurry J. *Organic Chemistry*. Brooks: Pacific Grove, CA, 1992.
5. Lossen H. *Annalen* 1868; **150**: 314.
6. Exner O, Hradil M, Mollin J. *Coll. Czech. Chem. Commun.* 1993; **58**: 1109.
7. Chiu F-T, Chang YH, Özkan G, Zon G, Fichter KC, Phillips LR. *J. Pharm. Sci.* 1982; **71**: 542.
8. King FD, Pike S, Walton DRM. *J. Chem. Soc., Chem. Commun*. 1978; 351.
9. Schraml J. ^{29}Si NMR Spectroscopy of Trimethylsilyl Tags. In: *Progress in Nuclear Magnetic Resonance Spectroscopy*, vol. 22, Emsley JW, Feeney J, Sutcliffe LH (eds). Pergamon, Oxford, 1990; 289–348.
10. Heuchel W, Boldhaus H-M, Bliefert C. *Chem. -Ztg.* 1983; **107**: 69.
11. Kozyukov VP, Feoktistov AE, Mironov VF. *Zh. Obshch. Khim.* 1988; **58**: 1056.
12. Rigaudy J, Lytwyn E, Wallach P, Nguyen KC. *Tetrahedron Lett.* 1980; **21**: 3367.
13. Narula CK, Gupta VD. *Indian J. Chem., Sect. A* 1980; **19**: 1095.
14. Lipczynska-Kochany E, Iwamura H. *J. Org. Chem.* 1982; **47**: 5277.
15. Kalinowski H-O, Berger S, Braun S. *^{13}C-NMR-Spektroskopie*. Georg Thieme: Stuttgart, 1984.
16. Berger S, Braun S, Kalinowski H-O. *NMR-Spektroskopie von Nichtmetallen*. Georg Thieme: Stuttgart, 1992.
17. Bax A, Freeman R, Kempsell SP. *J. Am. Chem. Soc.* 1980; **102**: 4849.
18. Schraml J, Boldhaus H-M, Erdt F, Bliefert C. *J. Organomet. Chem.* 1991; **406**: 299.
19. Werner A. *Berichte* 1893; **26**: 1561.
20. Exner O, Jehlička V, Reiser A. *Collect. Czech. Chem. Commun.* 1959; **24**: 3207.
21. Larsen IK, Exner O. *Chem. Commun.* 1970; 254.
22. Schraml J, Kvíčalová M, Soukupová L, Blechta V, Exner O. *J. Phys. Org. Chem.* 1999; **12**: 668.
23. Schraml J, Kvíčalová M, Soukupová L, Blechta V, Exner O. *J. Organomet. Chem.* 2000; **597**: 200.
24. Řeřicha R, Císařová I, Podlaha J. *Collect. Czech. Chem. Commun.* 1996; **61**: 139.
25. Podlaha J, Císařová I, Soukupová L, Schraml J, Exner O. *J. Chem. Res. Synop.* 1999; 520.
26. Podlaha J, Císařová I, Soukupová L, Schraml J. *Colled. Ozech. Chem. Commun.* 2000; in press.
27. Schraml J, Jakoubková M, Kvíčalová M, Kasal A. *J. Chem. Soc., Perkin Trans. 2* 1994; 1.
28. Renfrow WB Jr, Hauser CR. *J. Am. Chem. Soc.* 1937; **59**: 2308.
29. Hauser CR, Renfrow WB Jr. *Organic Synth.* 1959; Collect. Vol. **II**: 67.
30. Maggio F, Romano V, Cefalu R. *Ann. Chim. Rome* 1967; **57**: 47.
31. Novak A. *Struct. Bonding (Berlin)* 1974; **18**: 177.
32. Brown DA, Glass WK, Mageswaran R, Girmay B. *Magn. Reson. Chem.* 1988; **26**: 970.
33. Shendrovich VA, Ryaboj VI, Kriveleva ED, Ionin BI, Vajnshenker AI, Dogadina AV. *Zh. Obshch. Khim.* 1979; **49**: 1746.

