Pergamon

Tetrahedron: *Asymmetry* 10 (1999) 1861–1865

TETRAHEDRON: *ASYMMETRY*

Stereochemistry of α-(*tert*-butoxycarbonylamino) hydroxylamines: ^{1}H NMR analysis of hydroxylamines derived from 2-pyrrolidinyl nitrones

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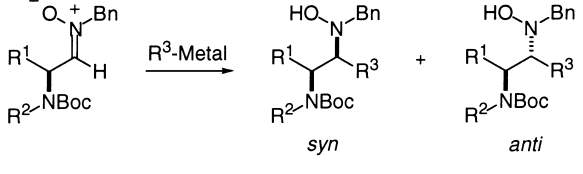
Received 30 April 1999; accepted 18 May 1999

Abstract

Hydroxylamines derived from 2-pyrrolidinyl nitrones can be easily and unambiguously distinguished by ^{1}H NMR spectroscopy. A strong hydrogen bond which can be observed both in the solid state and solution is responsible for the preferred conformation of the title compounds.

Over the last few years we have been concerned with the development of new stereoselective reactions based on nucleophilic additions to chiral nitrones.[1–5] In particular, recent reports from this laboratory[6–9] showed that optically active α-amino nitrones, easily obtained from the corresponding α-amino acids, are extremely suitable substrates for the construction of two different vicinal nitrogenated functionalities which, in turn, can be further used in the synthesis of more elaborate compounds such as 2,3-diamino acids[8] and 1,2-diamines.[9]

When a nucleophilic addition to an α-amino nitrone is carried out as previously described,[9] *syn* and *anti* adducts may be produced. Consequently, we desired a method to ascertain reliably the stereochemical outcome of such reactions. We have found that ^{1}H NMR is an excellent tool for this determination (Scheme 1).



Scheme 1.

In a previous paper,[9] we reported a simple procedure for determining the relative stereochemistry of α-amino monoprotected hydroxylamines (R^2=H). This method was based on three criteria: (i) the

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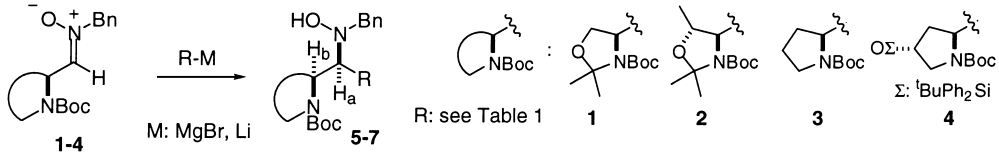
0957-4166/99/$ - see front matter
PII: S0957-4166(99)00202-5

hydrogen-bond interaction existing between the hydroxyl group of the hydroxyamino moiety and the carbonyl group of the carbamate; (ii) the values of the coupling constant of the protons attached to the carbon atoms bearing the nitrogen functionalities (observed even at 55°C), which secured a particular conformation in conjunction with the first criterion; and (iii) the chemical shift correlation of the ^{13}C NMR resonances of the R^1 sp^3 carbons. However, we have found that this method is not applicable in the case of α-amino diprotected nitrones in which the α-amino group forms part of a ring. This is due to: (i) stereochemical constraints, i.e. *syn* adducts cannot adopt the proposed conformation; and (ii) the high *syn* selectivity observed in nucleophilic additions to those nitrones which leads to the isolation of only one isomer; so no comparison of chemical shift values between diastereomers can be made. Since such nitrones are those derived from L-serine, L-threonine and L-proline, among others, we judged of importance the corresponding products obtained after a nucleophilic addition since they lead to polyfunctionalized substrates including interesting optically active pyrrolidines.

We chose the α-amino diprotected nitrones **1**–**4** as model substrates (Scheme 2). In all cases, the *syn* adducts were observed as the only isomers, thus confirming a high diastereoselectivity. A rationale to explain such a selectivity has also been proposed (see the following paper). The *R* groups incorporated as nucleophiles include phenyl, methyl, ethyl, benzyl, vinyl, allyl, cyanide, (trimethylsilyl)ethynyl and (methoxycarbonyl)ethynyl. The resonances and coupling constants that are of interest to us are listed in Table 1.



Scheme 2.

It is worthy of mention that, in all the cases examined, when ^1H NMR spectra were recorded at a low temperature (−40°C) the $^3J_{H,H}$ coupling constants between H_a and H_b were in the range of 9.2–10.7 Hz. This value is in agreement with the depicted *syn* arrangement (Fig. 1) in which protons H_a and H_b adopt an antiperiplanar disposition. Support for that conformation was secured from the observed chemical shifts for the hydroxyamino protons: in all cases they were in the range of 7.0–8.0 ppm, whereas common values for those hydrogens are in the range of 4.5–6.0 ppm. These findings clearly indicate the presence of a strong intramolecular hydrogen bond for those protons.† We did not observe the occurrence of any mixture of rotamers characteristic of *N*-substituted *N*-Boc compounds‡ such as 1,3-oxazolidines derived from L-serine and L-threonine.[10] This is undoubtedly due to the hydrogen-bond interaction which fixes the conformation to that illustrated in Fig. 1. On the other hand, further derivatives of hydroxylamines **5**–**8** (e.g. mono- and diprotected amines) always present complex ^1H NMR spectra as a consequence of the presence of rotamers.

The hydrogen-bonding interaction was also observed in all cases in which single crystals, suitable for an X-ray analysis, could be obtained. Both the distances and dihedral angles α and β observed in solid state for the X-ray analyzed compounds[11] are shown in Table 2.

Additionally, a conformational analysis of *syn* hydroxylamines was carried out. We have taken as a typical case from Table 1 hydroxylamine **7a** and have made a survey of the minimum energy structure.

† The intramolecular character of the hydrogen bond was confirmed by measuring several ^1H NMR spectra at different concentrations, no changes being observed in any case.

‡ Upon cooling to −60°C and −80°C no significant changes of the ^1H NMR coupling patterns were observed, indicating that the solutions contained almost exclusively one single conformer.

Table 1
Selected ^{1}H NMR data for *syn* hydroxylamines **4–6**[a]

entry	nitrone	R	hydroxylamine[b]	δ H_a (ppm)	δ H_b (ppm)	$J_{a,b}$ (Hz)	δ NO*H* (ppm)
1	**1**	methyl	**5a**	2.74	3.90	10.3	7.32
2	**1**	phenyl	**5b**	3.36	3.77	9.2	7.56
3	**1**	benzyl	**5c**	3.00	4.06	10.3	7.30
4	**1**	CN	**5d**	3.50	4.37	10.3	7.90
5	**1**	$Me_3SiC{\equiv}C$	**5e**	3.37	4.18	10.3	7.56
6	**1**	MeO_2C-C≡C	**5f**	3.52	3.97	9.6	7.60
7	**1**	2-thiazolyl	**5g**	4.32	4.42	10.5	7.70
8	**1**	2-furyl	**5h**	3.42	4.45	10.7	7.66
9	**1**	vinyl	**5i**	2.98	4.11	10.2	7.40
10	**1**	MeO_2C-CH=CH	**5j**	3.50	4.53	9.8	7.59
11	**1**	HC≡C	**5k**	3.51	4.20	10.3	7.61
12	**2**	methyl	**6a**	2.74	3.73	10.3	6.80
13	**2**	phenyl	**6b**	3.36	4.46	10.5	7.20
14	**2**	2-thiazolyl	**6c**	4.24	4.31	10.5	7.70
15	**2**	2-furyl	**6d**	3.75	4.30	10.4	7.38
16	**2**	vinyl	**6e**	2.95	3.95	10.0	7.40
17	**3**	methyl	**7a**	2.49	3.86	10.3	7.51
18	**3**	ethyl	**7b**	2.21	3.97	10.3	7.44
19	**3**	phenyl	**7c**	3.35	4.57	10.7	7.80
20	**3**	benzyl	**7d**	2.40	4.80	9.9	7.62
21	**3**	vinyl	**7e**	2.72	4.10	9.9	7.78
22	**3**	allyl	**7f**	2.40	3.95	10.0	7.52
23	**3**	$Me_3SiC{\equiv}C$	**7g**	3.21	4.23	10.0	7.75
24	**3**	MeO_2C-C≡C	**7h**	3.28	4.26	10.1	7.85
25	**4**	methyl	**8a**	2.29	4.05	10.3	7.69
26	**4**	phenyl	**8b**	3.06	4.66	9.9	7.82
27	**4**	vinyl	**8c**	2.40	4.20	10.0	7.55
28	**4**	allyl	**8d**	2.20	4.10	10.1	7.64
29	**4**	$Me_3SiC{\equiv}C$	**8e**	3.00	4.50	10.1	7.79
30	**4**	MeO_2C-C≡C	**8f**	3.14	4.40	10.1	7.81
31	**4**	MeO_2C-CH=CH	**8g**	3.26	4.32	10.3	7.60

[a] ^{1}H NMR spectra were recorded in $CDCl_3$ at –40°C using a Bruker 300 ARX NMR instrument. [b] For characterization of hydroxylamines **5** and **6** see refs. 6-9. For characterization of compounds **7** and **8** see following paper.

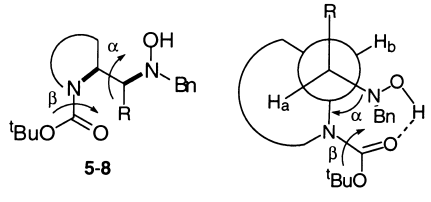


Figure 1. Conformations of hydroxylamines **5–8**

Table 2
Selected X-ray data for hydroxylamines **5–8**

R	hydroxylamine	d(O..O) Å	α (°)	β (°)
CN	**5d**	2.751	58.0	181.5
2-thiazolyl	**5g**	2.712	54.8	180.0
2-furyl	**5h**	2.735	53.0	180.3
2-thiazolyl	**6c**	2.735	53.7	180.4
methyl	**7a**	2.743	50.0	189.4
phenyl	**7c**	2.763	48.0	192.0
vinyl	**8c**	2.768	53.2	181.4

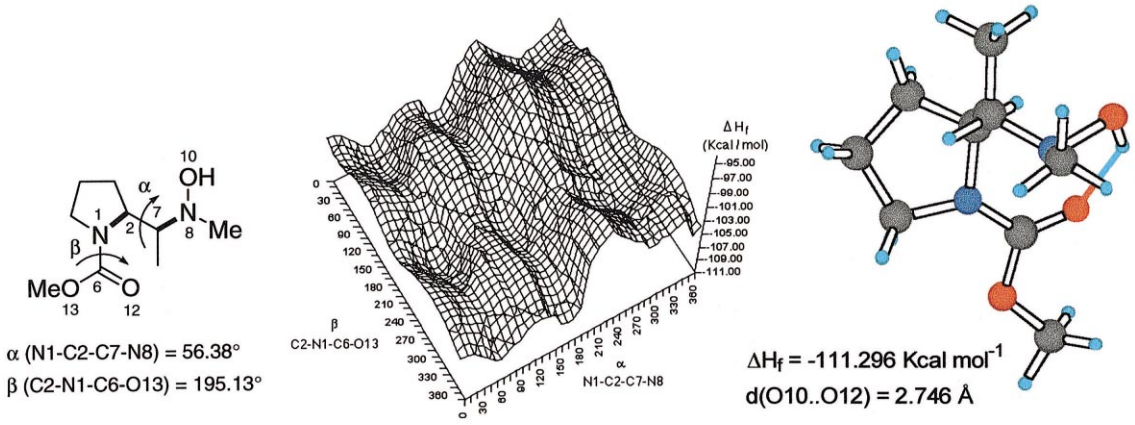


Figure 2. Conformational analysis of **7a** and minimum energy structure data

Input coordinates were taken from X-ray data and they were used for generation of 73×73 (5329) different conformations by stepwise rotation of 5° around both important C2–C7 and N1–C6 bonds, and then they were optimized. The heat of formation (ΔH_f) was calculated[§] for all these conformations and a surface was calculated in which ΔH_f was plotted as a function of dihedral angles α (N1–C2–C7–N8) and β (C2–N1–C6–O13), respectively (Fig. 2). The relative and absolute minima were reoptimized and the minimum energy structure of **7a** corresponded to that shown in Fig. 2; it was almost identical to the general model illustrated in Fig. 1 and in good agreement with solid state data.

Interestingly, from the analysis of the conformational model for **7a**, a deshielding effect for H_b can also be deduced, as a consequence of the carbonyl group's cisoid orientation. This effect, pointed out by Misiti and Zappia,[12] could be observed in all hydroxylamines studied (see Table 1).

Similar conformational analyses carried out for hydroxylamines **5a**, **6a** and **8a** showed identical results, thus supporting the hydrogen-bonded structure as the preferred conformation for hydroxylamines **5**–**8**.

In conclusion, we have assigned the relative configuration of hydroxylamines **5**–**8**, with inspection of only one diastereomer; the high value of $^3J_{a,b}$ (>9 Hz) is only compatible with a *syn* relative configuration, taking into account the presence of a strong intramolecular hydrogen bond. These assignments are a useful tool for the analysis of mixtures of hydroxylamines derived from 2-pyrrolidinyl nitrones, as evidenced in the above examples.

Acknowledgements

The authors gratefully acknowledge the financial support by the Direccion General de Enseñanza Superior (Project PB97-1014, MEC, Madrid, Spain).

§ All calculations were carried out at a semi-empirical level (PM3) using MOPAC 97 as implemented in the ChemOffice™ package of programs (CambridgeSoft Corporation, Cambridge, MA, USA). *N*-Benzyl and *O*-^{t}butyl groups were changed to methyl groups.

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