

## CONVENIENT AND RAPID DETERMINATION OF THE CONFIGURATION OF ALDOXIMES AND KETOXIMES BY MEANS OF NOE DIFFERENCE SPECTROSCOPY

Gottfried Heinisch and Wolfgang Holzer\*

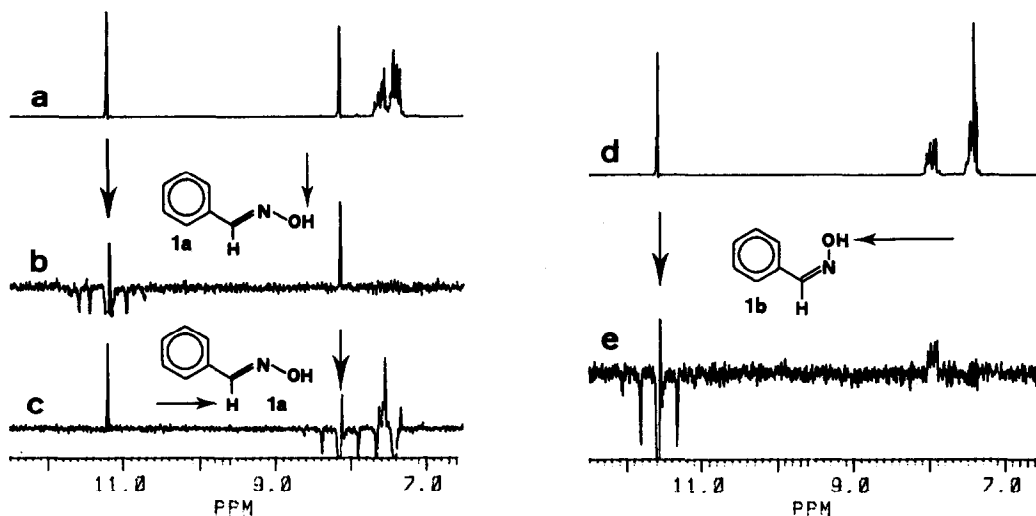
Institute of Pharmaceutical Chemistry, University of Vienna,  
Währingerstraße 10, A-1090 Vienna, Austria

**Abstract:** Based on a through-space connection observed between the hydroxyl proton and the iminyl proton or protons attached to the  $\alpha$ -carbon atom in various types of oximes, homonuclear NOE difference spectroscopy utilizing  $d_6$ -DMSO as solvent is proposed as a simple method for the elucidation of the stereochemistry.

Among numerous methods generally employed for the determination of the stereochemistry of aldoximes and ketoximes, NMR methods play an important role. Thus, for instance, chemical shift differences ( $^1\text{H-NMR}$ :  $\delta_{\text{N-CH}}$ ,<sup>1</sup>  $\delta_{\text{OH}}$ ;<sup>2</sup>  $^{13}\text{C-NMR}$ :  $\delta_{\text{C-}\alpha}$ )<sup>3</sup> of E- and Z-isomers as well as the magnitude of coupling constants [ $^1\text{J}(^{13}\text{C}, ^1\text{H}_{\text{N-CH}})$ ,<sup>4</sup>  $^2\text{J}(^{15}\text{N}, ^1\text{H}_{\text{N-CH}})$ ,<sup>5</sup>  $^3\text{J}(^{15}\text{N}, ^1\text{H})$ ,<sup>6</sup>  $^1\text{J}(^{13}\text{C}, ^{13}\text{C}_{\text{C-N}})$ <sup>7</sup> or  $^1\text{J}(^{15}\text{N}, ^{13}\text{C})$ <sup>8</sup>] have been used for this purpose. There are also reports on the utility of lanthanide shift reagents<sup>9</sup> and on the employment of aromatic solvent induced shift (ASIS) experiments<sup>10</sup> for the assignment of configuration. Most of these methods, however, suffer from certain limitations (e.g. applicability for aldoximes only) and/or experimental difficulties. Methods based on  $^{13}\text{C}$ - or  $^{15}\text{N}$ -NMR spectroscopy often meet with the problem of insufficient solubility, the determination of  $^{13}\text{C}$ ,  $^{13}\text{C}$ - or  $^{15}\text{N}$ ,  $^1\text{H}$ -coupling constants, moreover, requires high-field instruments and is time-consuming.

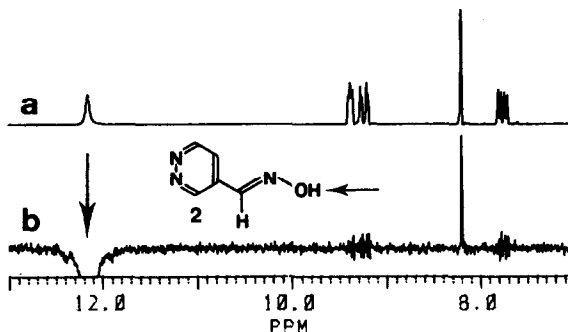
The results previously obtained in this laboratory in attempts to elucidate the configuration of pyridine- and pyridazine-derived thiosemicarbazones<sup>11</sup> together with nuclear Overhauser effects (NOE) recently observed with oximes derived from diaryl ketones (enhancement of the signals of aromatic ring protons upon irradiation of the hydroxyl proton)<sup>12</sup> now drew our attention to homonuclear NOE-difference spectroscopy. Here we wish to propose the use of this technique as a convenient tool for the rapid determination of the stereochemistry of aldoximes and ketoximes as well. To the best of our knowledge,<sup>13</sup> this approach so far has not been employed for configurational assignment in the oxime series.

Using the two isomeric benzaldehyde oximes **1a** and **1b** (prepared according to ref.<sup>14</sup> and ref.<sup>15</sup>, respectively) as model compounds, we observed with the E-isomer **1a** a significant enhancement of the signal of the iminyl-H upon irradiation of the hydroxyl proton (see Figure 1). Likewise, a reverse experiment (irradiation of the iminyl-H) revealed a positive NOE (on the OH proton). By contrast, irradiation of the hydroxyl transition in the Z-isomer **1b** did not result in an NOE on the iminyl-H (see Figure 1). In this case, however, the signals of H-2 and H-6 of the benzene ring are enhanced, whereas no NOE on ring protons occurs with **1a** upon perturbation of the OH resonance.



**Figure 1:** a)  $^1\text{H-NMR}$  spectrum of **1a** b) NOE difference spectrum of **1a** resulting from irradiation of OH c) NOE difference spectrum of **1a** resulting from irradiation of the iminyl-H d)  $^1\text{H-NMR}$  spectrum of **1b** e) NOE difference spectrum of **1b** resulting from irradiation of OH

An example of the exploitation of these findings is given in Figure 2. So far, only one isomeric form of 4-pyridazinecarbaldoxime (of unknown configuration) has been described in the literature.<sup>16</sup> The significant through-space connection observed between the hydroxyl-H and the iminyl-H now enabled us to assign E-configuration to this compound.



**Figure 2:** a)  $^1\text{H-NMR}$  spectrum of **2** b) NOE difference spectrum of **2** resulting from irradiation of OH

Applicability of this simple and rapid method is not restricted to configurational assignment in the aldoxime series but can be extended also to the discrimination between E- and Z-isomers of various ketoximes. Several illustrative examples including oximes derived from acetophenone **3a**,<sup>17</sup> **3b**,<sup>18</sup> methyl 2-pyridyl ketone **4**,<sup>19</sup> and methyl 4-pyridazinyl ketone **5**<sup>20</sup> (the configuration of which hitherto was unknown) are given in Figures 3 and 4. Irradiation of the methyl protons of E-acetophenone oxime (**3a**) and of **4** results in a significant enhancement of the OH signal. A similar observation with methyl 4-pyridazinyl ketoxime **5** gives rise to the unequivocal assignment of E-configuration.

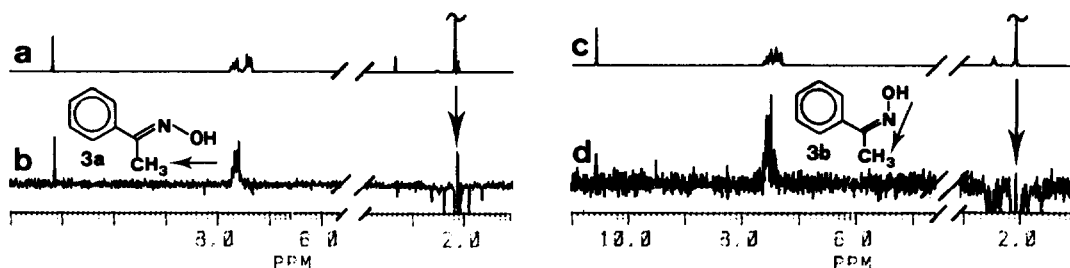


Figure 3: a)  $^1\text{H-NMR}$  spectrum of **3a** b) NOE difference spectrum of **3a** resulting from irradiation of the methyl protons  
c)  $^1\text{H-NMR}$  spectrum of **3b** d) NOE difference spectrum of **3b** resulting from irradiation of the methyl protons

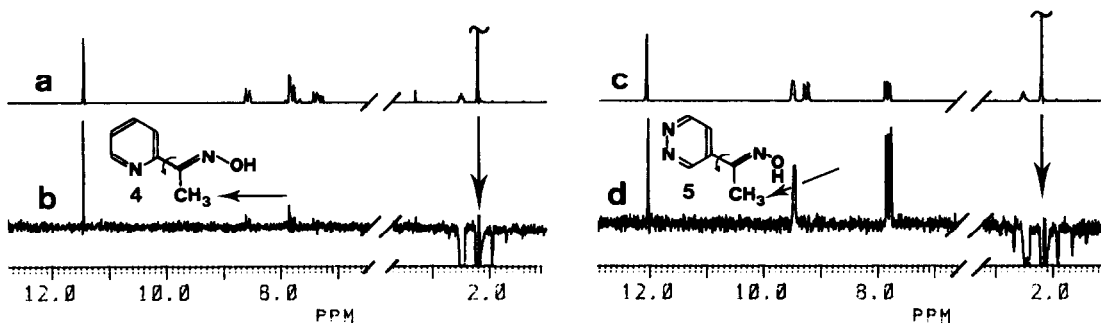
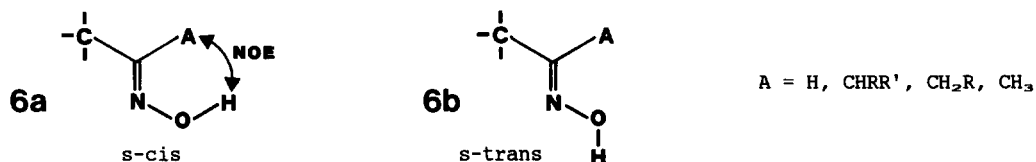


Figure 4: a)  $^1\text{H-NMR}$  spectrum of **4** b) NOE difference spectrum of **4** resulting from irradiation of the methyl protons  
c)  $^1\text{H-NMR}$  spectrum of **5** d) NOE difference spectrum of **5** resulting from irradiation of the methyl protons

Throughout this study,  $d_6$ -DMSO was used as the solvent in order to obtain narrow OH signals facilitating the NOE experiments. Moreover, the strong hydrogen bonding capability of this solvent is known to prevent the predominance of a *s-trans* orientated species **6b**<sup>21</sup> which (due to lone-pair interactions and self-association)<sup>21</sup> represents the generally favoured conformation of an oxime in solution. Without any doubt, *s-trans* conformation, as indicated in formula **6b**, would lead to considerably smaller through-space interaction.



In summary, one may consider such homonuclear NOE-difference experiments as a versatile tool for the elucidation of the stereochemistry of a wide variety of oximes as represented by the general formula **6**. Thus, this method should be applicable not only to aldoximes but also to oximes derived from alkyl aryl ketones and dialkyl ketones characterized by the presence of at least one hydrogen atom attached to the  $\alpha$ -carbon atom, provided that selective irradiation of this proton is possible. Even if only one isomer is at hand, the observation of a significant NOE calls for a configuration as given in formula **6a**, whereas the lack of such an effect at least provides a strong hint for the presence of a species with reverse configuration.

Investigations aimed at the exploitation of differences in nuclear Overhauser enhancements for configurational assignment to E- and Z-isomers of additional types of compounds containing a C=N double bond (oximes derived from diaryl ketones, O-substituted oximes, hydrazones, semicarbazones) are in progress.

NOE-Difference spectra were recorded from non-degassed solutions (approx. 0.2 M) on a Bruker AC-80 spectrometer (80.131 MHz) equipped with an Aspect 3000 computer. Acquisition parameters: 8 K data points; spectral width: 1365 Hz; acquisition time: 3 s; digital resolution: 0.33 Hz / point; pulse width: 2  $\mu$ s (56°); relaxation delay: 3 s; irradiation time: 3 s; irradiation power: 46 - 48 I; number of scans: 160 - 320; temperature: 30°C.

#### REFERENCES AND NOTES

1. a) W. D. Phillips, *Ann. N. Y. Acad. Sci.* **70**, 817 (1958); b) E. Lustig, *J. Phys. Chem.* **65**, 491 (1961); c) G. J. Karabatsos, R. A. Taller, and F. M. Vaine, *J. Am. Chem. Soc.* **85**, 2326 (1963); d) G. J. Karabatsos and R. A. Taller, *Tetrahedron* **24**, 3347 (1968); e) B. Unterhalt, *Arch. Pharm.* **301**, 573 (1968); f) R. Haller and W. Ziriakus, *Arch. Pharm.* **305**, 741 (1972).
2. G. G. Kleinspahn, J. A. Jung, and S. A. Studniarz, *J. Org. Chem.* **32**, 460 (1967).
3. a) G. E. Hawkes, K. Herwig, and J. D. Roberts, *J. Org. Chem.* **39**, 1017 (1974); b) G. C. Levy and G. L. Nelson, *J. Am. Chem. Soc.* **94**, 4897 (1972); c) Z. W. Wolkowski, E. Vauthier, B. Gonbeau, H. Sauvaitre, and J. A. Musso, *Tetrahedron Lett.* **565** (1972); d) C. A. Bunnell and P. L. Fuchs, *J. Org. Chem.* **42**, 2614 (1977); B. Unterhalt and H. Koehler, *Arch. Pharm.* **311**, 366 (1978).
4. T. Yonezawa and I. Morishima, *J. Mol. Spectrosc.* **27**, 210 (1968).
5. a) D. Crepaux and J. M. Lehn, *Org. Magn. Reson.* **7**, 524 (1975); b) D. Crepaux, J. M. Lehn, and R. R. Dean, *Mol. Phys.* **16**, 225 (1969).
6. J. E. Oatis Jr. and H. P. Schultz, *Org. Magn. Reson.* **11**, 40 (1978).
7. L. B. Krivdin, G. A. Kalabin, R. N. Nesterenko, and B. A. Trofimov, *Tetrahedron Lett.* **25**, 4817 (1984).
8. a) R. L. Lichter, D. E. Dorman, and R. Wasylshen, *J. Am. Chem. Soc.* **96**, 930 (1974); b) G. W. Buchanan and B. A. Dawson, *Can. J. Chem.* **54**, 790 (1976); c) *ibid* **55**, 1437 (1977), d) *ibid* **56**, 2200 (1978).
9. a) Z. W. Wolkowski, *Tetrahedron Lett.* **825** (1971); b) K. D. Berlin and S. Rengaraju, *J. Org. Chem.* **36**, 2912 (1971); c) R. R. Fraser, R. Capoor, J. W. Bovenkamp, B. V. Lacroix, and J. Pagotto, *Can. J. Chem.* **61**, 2616 (1984).
10. a) L. Cavalli, *J. Chem. Soc. B* 1453 (1968); b) M. Zinic, M. Stromar, M. Malnar, and D. Kolbah, *Croat. Chem. Acta*, **46**, 45 (1974); c) N. Kalyanam and S. Setish, *Indian J. Chem. B* **21B**, 353 (1982).
11. J. Easmon, G. Heinisch, and W. Holzer, *Heterocycles* **29**, 1399 (1989).
12. W. Holzer and W. von Philipsborn, *Magn. Reson. Chem.* **27**, 511 (1989).
13. Comprehensive reviews (ref. 22, 23) on NOE difference spectroscopy do not reveal any relevant references nor did a computer-assisted search of Chemical Abstracts (1967 - November 1989) using as keywords "oximes, (determination of) configuration of".
14. A. I. Vogel, "Practical Organic Chemistry", 3rd edition, Longman, London 1956, p. 719.
15. G. Zvilichovsky and L. Heller, *Synthesis* 563 (1972).
16. G. Heinisch, E. Luszczak, and M. Pailer, *Monatsh. Chem.* **104**, 1372 (1973).
17. Gattermann - Wieland, "Die Praxis des organischen Chemikers", 43. Auflage, de Gruyter, Berlin - New York, 1982, p. 348.
18. J. H. Smith and E. T. Kaiser, *J. Org. Chem.* **39**, 728 (1974).
19. B. Emmert and K. Diehl, *Chem. Ber.* **62**, 1738 (1929).
20. G. Heinisch, *Monatsh. Chem.* **104**, 953 (1973).
21. H. Moehrl, B. Wehefritz, and A. Steigel, *Tetrahedron* **43**, 2255 (1987); and references cited therein.
22. a) J. H. Noggle and R. E. Schirmer, "The Nuclear Overhauser Effect", Academic Press, New York and London, 1971; b) D. Neuhaus and M. Williamson, "The Nuclear Overhauser Effect in Structural and Conformational Analysis", Verlag Chemie, Weinheim, 1989.
23. J. K. M. Sanders and J. D. Marsh, *Prog. Nucl. Magn. Reson. Spectrosc.* **15**, 353 (1982).