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The Use of $^{1}H-^{15}N$ Coupling Constants for the Investigation of Tautomeric Equilibria of Azines

Short Communication

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$^{15}N-^{1}H$ coupling constants can be measured over a large range by means of the Broadband-INEPT NMR-technique. These coupling constants are used to determine the positions of tautomeric equilibria of 2-(acetylmethyl)-azines with high accuracy.

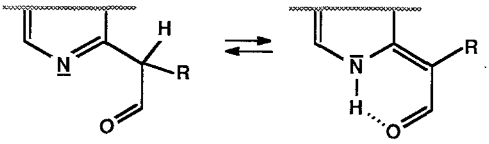
(Keywords: Azine tautomerism; Broadband-INEPT, ^{15}N *NMR)*

Die Anwendung von $^{1}H-^{15}N$*-Kopplungskonstanten bei Untersuchungen von Tautomerengleichgewichten von Azinen (Kurze Mitteilung)*

Mittels der Breitband-INEPT NMR-Technik können $^{15}N-^{1}H$-Kopplungskonstanten über einem weiten Bereich gemessen werden. Aus diesen Kopplungskonstanten kann die Lage der Tautomerengleichgewichte von 2-(Acylmethyl)-azinen mit großer Genauigkeit bestimmt werden.

The tautomerism of nitrogen containing heterocycles is of considerable interest both in synthetic drugs and naturally occurring systems. Among the various investigation methods employed NMR-spectroscopy takes a leading place. We wish to report here a novel NMR approach to the study of tautomeric azine-ylidene equilibria of 2-(acylmethyl)-azine

Scheme 1



derivatives (Scheme 1) based on the measurement of heteronuclear $^{15}\mathrm{N}-{}^{1}\mathrm{H}$ coupling constants.

Previous studies of these equilibria were based on ^{1}H-NMR [1, 2] as well as on ^{13}C [2] and ^{17}O [3, 4] chemical shifts. ^{15}N shifts proved useful for the investigation of tautomeric equilibria in polypyrrolic compounds [5] and hydrogen bonding in pyridine complexes [6]. However all methods relying on the interpretation of chemical shifts suffer from the fact that the shielding does not solely depend on the tautomeric structure but to a major extent on the electronic effects of the intra- and intermolecular environment. It is therefore difficult to interpret chemical shift data quantitatively in terms of equilibrium position, if only exchange averaged signals can be observed and the shift positions for the individual tautomers are unknown.

We found that the determination of heteronuclear coupling constants which vary over a large range is greatly simplified by a variant of an NMR-method recently introduced by *Wimperis* and *Bodenhausen* [7]: Broadband-INEPT (BB-INEPT).

While with the normal INEPT pulse technique [8] optimum signal enhancement is obtained only for a relatively narrow range of coupling constants, the compensation scheme used in BB-INEPT gives a broad maximum for the transfer coefficients as a function of the heteronuclear coupling constants. This is of particular advantage if the coupling constants themselves are subject of the investigation and therefore usually unknown. The pulse sequence

$$\begin{array}{ccccccccc}
\left(\frac{\pi}{2}\right)_x - & \left(\frac{\tau}{2}\right) - & (\pi)_y - & \left(\frac{\tau}{2}\right) - & \left(\frac{2\pi}{3}\right)_y - & (\tau) - & (\pi)_y - & (\tau) - & \left(\frac{\pi}{6}\right)_y \ldots {}^{1}\mathrm{H} \\
- & - & (\pi)_x & - & - & - & (\pi)_x & - & \left(\frac{\pi}{2}\right)_y \text{-acquisition} \ldots {}^{15}\mathrm{N}
\end{array}$$

uses the BB-INEPT compensation scheme during proton precession and yields proton coupled anti-phase ^{15}N-multiplets after *Fourier*-transform of the FID. Neglecting relaxation the theoretical dependence of the transfer coefficient f on J_{NH} for this pulse sequence has been derived as [7]:

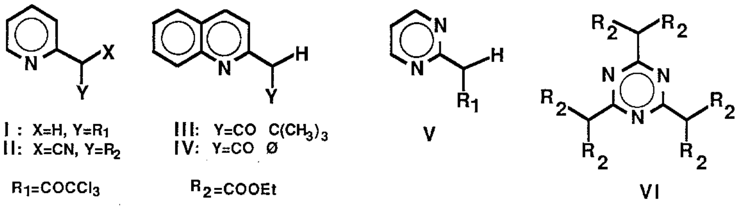
$$f = \frac{1}{4}\sin(\pi J \tau)\cos(2\pi J \tau) - \frac{1}{2}\cos(\pi J \tau)\sin(2\pi J \tau) - \frac{3}{4}\sin(\pi J \tau)$$

For the corresponding ordinary INEPT-experiment [8],

$$\begin{array}{ccccc}
\left(\frac{\pi}{2}\right)_x - & \left(\frac{\tau}{2}\right) - & (\pi)_y - & \left(\frac{\tau}{2}\right) - & \left(\frac{\pi}{2}\right)_y \ldots {}^{1}\mathrm{H} \\
- & - & (\pi)_x & - & \left(\frac{\pi}{2}\right)_y \text{-acquisition} \ldots {}^{15}\mathrm{N}
\end{array}$$

the transfer coefficient is simply $-\sin(\pi J \tau)$. As a consequence, for example, if τ deviates 75% from the optimum value of $(2J)^{-1}$, in BB-INEPT 43% more signal intensity than in the standard procedure is obtained. The only drawbacks are the longer duration of the pulse sequence, which may lead to signal loss through proton relaxation, and—depending on the spectrometer—the more critical implementation of the pulse sequence. As no phase shifting capabilities for angles deviating from multiples of $\pi/2$ were available on our instrument, the $\alpha = \pi/6$ and $\alpha = 2\pi/3$ pulses were not substituted by the superior $(\pi/2)_{\pi}(\pi/2)_{\alpha}$ composites. The $\pi/2$ pulses were 24.0 and 36.1 µs for ^{15}N and ^{1}H, respectively, on the selective 10 mm probehead of a Bruker WM-360 NMR-spectrometer. A single value of $\tau = 4$ ms was used for all experiments. Between 1 000 and 20 000 free induction decays were accumulated for the spectra.

Scheme 2



The compounds **I–VI** used as test cases for this method were prepared by established procedures [1]; details will be given elsewhere [9]. Their choice was determined by the wish to cover a broad range of equilibrium positions and consequently coupling constants. The ^{15}N chemical shifts and $^{15}N-^{1}H$ coupling constants are given in Table 1. Assuming linear dependence of the apparent splitting on the relative amounts of tautomers present, the fraction of the N−H forms and the equilibrium constants have been calculated. There is a rough correlation between the shifts and the coupling constants. However, the equilibrium constants calculated from the coupling constants are believed to be of higher accuracy than those based on nitrogen chemical shifts or on the ^{1}H and ^{17}O chemical

Table 1. ^{15}N *chemical shifts* ∂ *(ext. ref.* $NaNO_3$*)*, $^{1}J_{^{15}N^{1}H}$ *measured at 308 K in* $CDCl_3$ *solution.* For the tautomeric equilibrium $N=C-CH-C=O \rightleftarrows HN-C=C-C=O$ of compounds **I–VI** the fractions of ylidene forms and the equilibrium constants calculated from the coupling constants (assuming 100% ylidene form for **VI**)

Compound	∂ (ppm)	J (Hz)	%NH	K
I	−197.83	71.7	75.2	33.0
II	−224.50	92.9	97.5	39.0
III	−231.70	79.5	83.4	5.0
IV	−228.64	77.5	81.3	4.3
V	−87.83	13.2	13.9	0.16
VI	−273.15	95.3	100.0	∞

shifts reported earlier for related compounds [1–4] for the reasons given above. Care must however be exercised in the case of small apparent coupling constants (e. g. compound **V**) since one cannot *a priori* distinguish between small values of $^1J_{NH}$ and $^{2,3}J_{NH}$ of similar magnitude by this type of experiment.

By overcoming the selectivity limitations of previous methods Broadband-INEPT is a versatile tool in the arsenal of organic NMR spectroscopy for the determination of heteronuclear coupling constants not only for questions of the type discussed here but also for other nuclei or stereochemical investigations.

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