MAGNETIC RESONANCE IN CHEMISTRY
Magn. Reson. Chem. 2005; **43**: 27–30
Published online 24 September 2004 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/mrc.1497

Substituent effects on ^{15}N NMR chemical shifts in selected *N*-alkylthiohydroxamic acids. A comparative study

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Received 2 December 2003; Revised 2 August 2004; Accepted 10 August 2004

The ^{15}N NMR spectra of three *N*-alkyl-*δ*-carbomethoxyvalerothiohydroxamic acids (2) and six synthesized *N*-isopropylbenzothiohydroxamic acids (3) were measured and compared with appropriate spectra of structurally similar hydroxylamines (1), benzohydroxamic acids (4), benzamides (5) and thiobenzamides (6). The analysis of the chemical shifts of the thiohydroxamic acids under investigation indicates that the inductive effect of the hydroxyl group rather than steric hindrance is responsible for non-additivity of the effect of substituents. Additionally, *N*-hydroxyl diminishes the effect of aromatic ring substituents on the ^{15}N chemical shifts in the thiohydroxamic acids 3 which is approximately half that in the respective thiobenzamides 6. The chemical shift values correlate best with Brown's σ^+ parameter. Copyright © 2004 John Wiley & Sons, Ltd.

KEYWORDS: NMR; ^{15}N NMR; chemical shifts; gHMQC; thiohydroxamic acids; hydroxylamine derivatives

INTRODUCTION

Owing to their biological activity, widespread application in chemical analysis, industry, and technology and especially in organic synthesis (so called Barton esters), thiohydroxamic acids (THAs) provide a very interesting subject of studies.[1] To our knowledge, this class of compounds has not been investigated earlier by means of ^{15}N NMR. An issue that requires consideration is that even the chemical shift of the most popular representative of this class of compounds, i.e. *N*-hydroxypyridine-2-thione, is unknown.

We synthesized selected aliphatic thiohydroxamic acids (**2**) from the corresponding *S*-thioacyl dithiophosphates while investigating the chemoselectivity of these new thioacylating agents.[2] Aromatic thiohydroxamic acids (**3**) were obtained by direct thionation of hydroxamic acids, specifically for the spectroscopic study described in this paper. Moreover, our knowledge of the chemical shift values of some of the thiohydroxamic acids proved indispensable in continuing the investigation of the mechanism of reaction of benzohydroxamic acids with Lawesson's reagent.[3] Considering all the above, we present here ^{15}N NMR resonance data for selected aliphatic and aromatic representatives of *N*-alkyl-THAs and the determination of the susceptibility of their ^{15}N chemical shifts to electronic effects.

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Contract/grant sponsor: Polish State Committee for Scientific Research (KBN); Contract/grant number: T09A 06116.

RESULTS AND DISCUSSION

If we take into account both the data on chemical shifts of thioamides, whose spectra show signals at higher frequency values than those of the corresponding amides, and the data on hydroxamic acids, whose signals appear at even higher frequency values,[4] the shifts for thiohydroxamic acids can be expected at still higher δ values. It is well known that as the substituent-induced electron deficiency on the nitrogen atom increases, the ^{15}N chemical shift becomes more positive. Let us consider the transmission of substituent-induced electronic effects and the substituent chemical shifts of (thio)amide nitrogen in the analogs of benzohydroxamic acids, i.e. benzamides and thiobenzamides. As expected, in both cases the presence of an electron-accepting group on the aromatic ring results in a higher frequency shift of the resonance signal of the nitrogen atom. The observed shift range ($\Delta\delta_{NO_2-OCH_3}$) measured in DMSO for *para*-substituted primary thiobenzamides is 7.85 ppm, which is almost twice that for the corresponding benzamides (4.59 ppm).[5] This is probably due to the fact that the lone electron pair on the N atom conjugates more effectively with a thiocarbonyl than with a carbonyl group.[6]

As we will show below, the data on ^{15}N chemical shifts presented in this paper are in accordance with the general rule that the nitrogen nucleus is deshielded in amides and their derivatives.

The structures of all compounds investigated are shown in Scheme 1. Apart from *N*-alkyl-*δ*-carbomethoxyvalerothiohydroxamic acids (**2**) and ring-substituted *N*-isopropylthiobenzhydroxamic acids (**3**), for comparison we also recorded and analyzed the spectra of the hydroxylamines **1** and