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ACID-CATALYZED DEUTERIUM EXCHANGE IN HANTZSCH-TYPE DIHYDROPYRIDINES

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Abstract

An interesting case of the acid-catalyzed deuterium exchange in methanol-d_4 was found for 4-phenyl-1,4-dihydropyridine derivatives that belong to the class of Ca-channel antagonists. Deuterium exchange of the C_α-methyl protons indicates formation of an enamine carbocation that can be described by three mesomeric models.

Introduction

Carbocations produced by interaction of the acid with the carbon-carbon double bond were extensively investigated using experimental and theoretical methods [1]. Carbocations generated from cycloalkene compounds in concentrated acid or super acid solutions are stable species at low temperatures and their structures can be directly determined by NMR spectroscopy. The carbocation formation in addition reactions, when milder conditions are applicable, is generally believed to be the crucial reaction step as demonstrated indirectly by reaction products [2, p141]. Reactivity of enamine derivatives depends on protonation site preference i. e. amine N vs. C_β in many reaction mechanisms. Both protonation sites are implied in the hydrolysis reactions of enamines, the proton transfer to the C_β atom is the reaction rate-determining step [3, 4]. Proton affinity of enamines was also investigated in the gas phase by theoretical and

experimental methods and it was demonstrated that the protonation occured at the C_β atom, the imine ion being more stable than the enammonium ion [5,6]. 1,4-dihydropyridines generally function as enamines [7] and can undergo reaction with electrophiles. On reaction with proton acids the iminium salt is formed by protonation of the dihydropyridine ring at the 3- or 5-position. It can act as a highly eletrophilic species on reaction with another molecule of 1,4-dihydropyridine forming dimeric structures [7, p157, p160] and with nucleophiles such as water [7, p160]. Hantzsch-type dihydropyridines that belong to the Ca-channel antagonists, can also generate iminium species under acid conditions. The reactive intermediate was captured with carbon-carbon double bonds or other internal nucleophiles in sequential cycloaddition reactions producing conformationally rigid 4-phenyl-1,4-dihydropyridines analogues [8, 9, 10, 11].

I have recently observed that strong acids such as benzenesulfonic acid in methanol-d_4 solution trigger regio-specific deuterium exchange in 4-phenyl-1,4-dihydropyridine derivatives. Deuterium exchange of protons of the C_α-methyl group evidences reversible formation of an enamine carbocation. The example is given for amlodipine benzenesulphonate (2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylic acid 3-ethyl 5-methyl ester).

Experimental Part

Samples of amlodipine benzenesulfonate for C-13 NMR mesurements were dissolved in methanol-d_4 and in methanol-d_4 solution containing 1 molar equivalent of benzenesulfonic acid. C-13 NMR spectra were measured immediately after preparation of the samples. Samples for H-1 NMR measurements were prepared by dissolving amlodipine benzenesulfonate in solutions having different ratio of methanol/methanol-d_4 solvents and 1 molar equivalent of benzenesulfonic acid. H-1 NMR measurements were run 24 hrs after preparation of the samples.

H-1 and C-13 NMR measurements were run on a Varian instrument Unity+ at 300 and 75 MHz, respectively. H-1 and C-13 chemical shifts were referenced with regard to internal TMS.

Results and Discussion

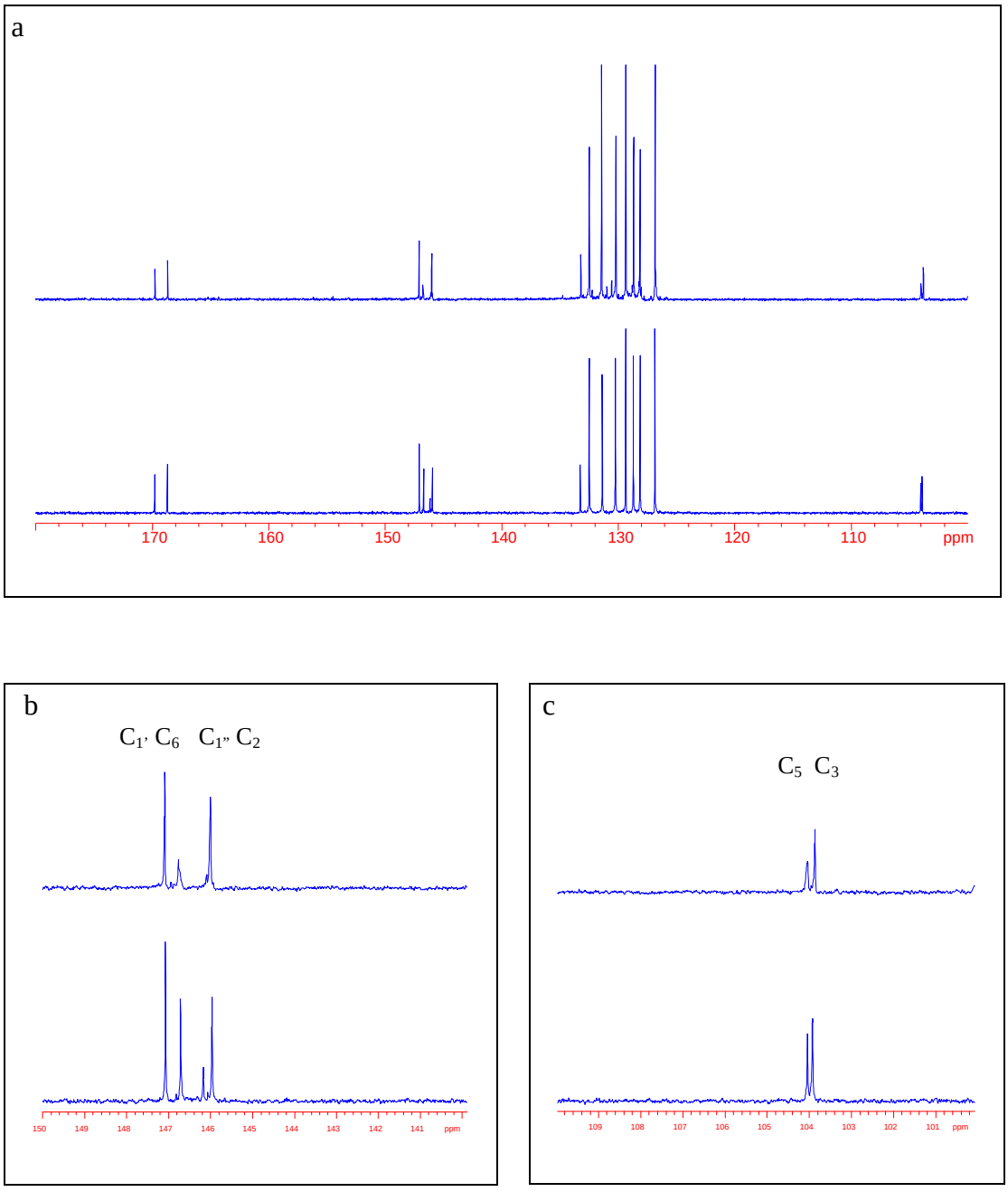


Figure 1. 75 MHz C-13 NMR spectra of amlodipine benzenesulfonate (lower trace) and amlodipine benzenesulfonate with the addition of 1 molar equivalent of benzenesulfonic acid (upper trace) in the range between 100 and 200 ppm (a) and expanded views (b and c).

C-13 NMR spectra of amlodipin benzenesufonate and amlodipin benzenesufonate with 1 molar equivalent of benzenesulfonic acid added demonstrate that the acid significantly alters the signal intensity of C_5 and C_6 (104.1 ppm and 146.7 ppm, respectively, Fig.1) reflecting additional relaxation mechanisms driven by the acid. The interaction of the acid with the double bond carbon atoms of the dihydropyridine ring might imply the formation of a π-complex prior to the proton transfer to the double bond. Such a mechanism is generally characteristic of a specific acid catalysis. General acid catalysis produces carbocations directly in a slow, reaction rate-determining step, without any intervening steps, and was found mostly in water solutions [2, p226].

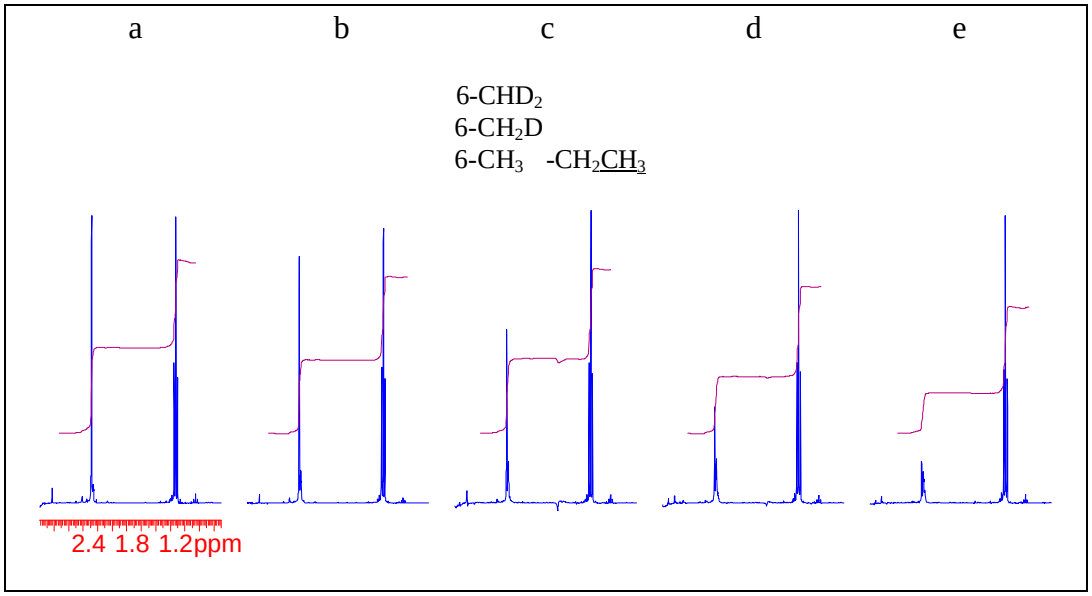
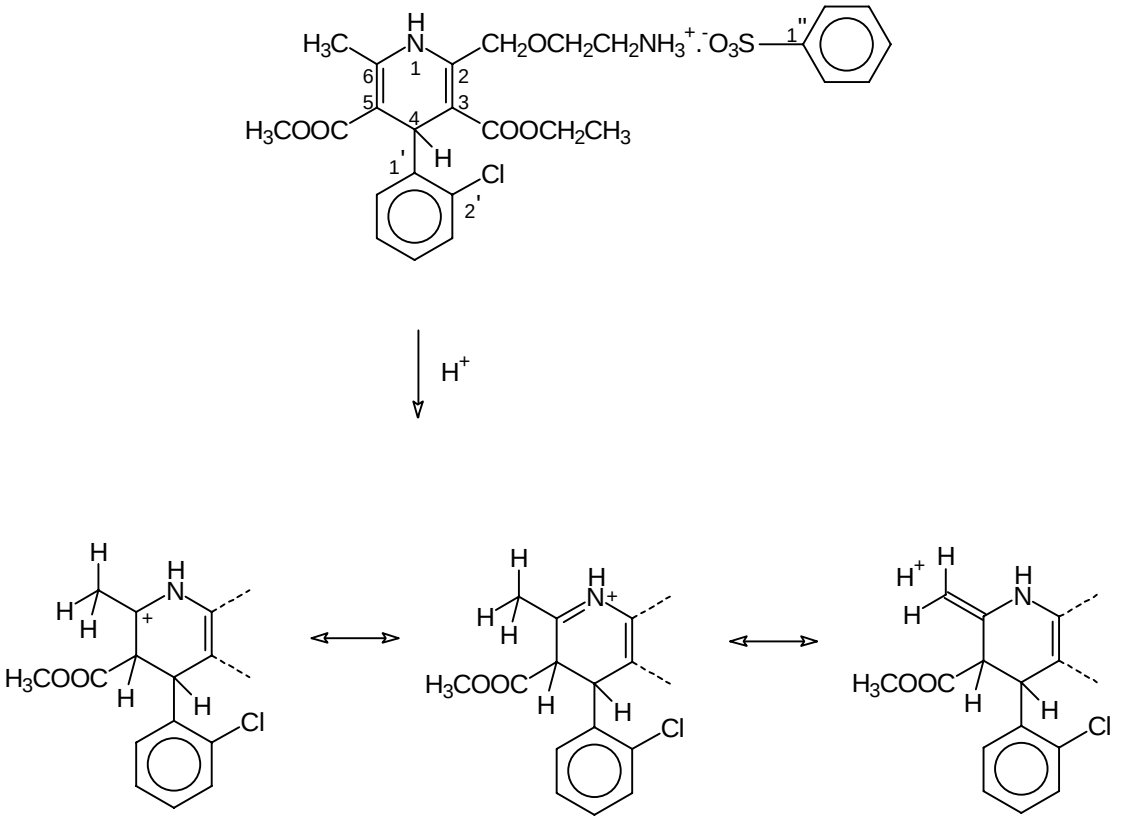


Figure 2. 300 MHz H-1 NMR spectra of amlodipine benzenesulfonate in mixtures of methanol-d_4 and methanol within the ratios: 0.2 (a), 0.5 (b), 1 (c), 2 (d) and 5 (e), with the addition of 1 molar equivalent of benzenesulfonic acid, in the range between 3.0 and 0.5 ppm.

H-1 NMR spectra presented in Figure 2 show variable intensity of the signal of the C_6-methyl group (2.3 ppm) with respect to the signal of the methyl group in the ethyl substituent (1.1 ppm). The intensity of the singlet line (C_6-CH_3) is reduced in direct proportion to the ratio of methanol/methanol-d_4 due to the partial (-CH_2D, -CHD_2) and complete H/D exchange (-CD_3) (Fig.2).

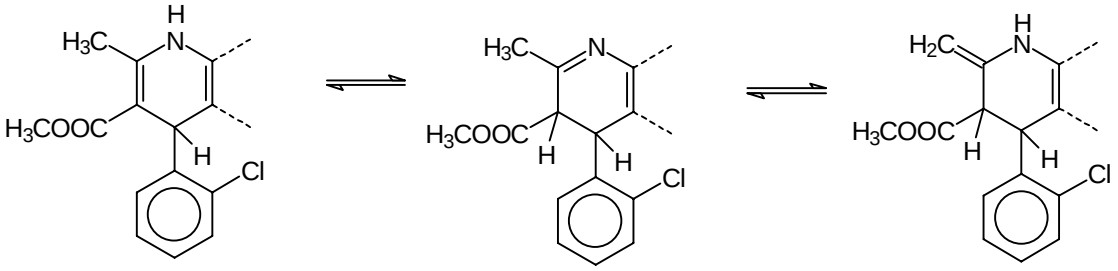


Scheme I

Thus, H-1 NMR spectra provide an indirect evidence for the proton transfer to the C_5 atom. It is transparent that the stabilization of the protonated enamine fragment of the 1,4-dihydropyridine ring brings about the destabilization of the C-H bonds of the methyl

group and, consequently, the isotopic exchange. The C_6-methyl group stabilization of the positive charge includes the hyperconjugative effect, too [1]. The C_β-protonated enamine fragment is normally described as a hybrid of two Lewis models, iminium and carbonium [5]. However, the acid-catalyzed H/D exchange in 1,4-dihydropyridines indicates that the enamine carbocation formed possesses significant contribution of the carbonium type model because of the positive charge delocalization to the C_α-methyl group, and it must be represented by a third model with the formal positive charge on the methyl group (Scheme I).

It is worthwhile to note that there exists a one-to-one correspondence between the three mesomeric models for the protonated enamine fragment and the possible tautomeric forms of the non-protonated enamine fragment (Scheme II).



Scheme II

In this preliminary report I have demonstrated that the enamine fragment of amlodipine benzensulphonate is very amenable toward protonation under an excess of the acid. The resulting enamine carbocation is extensively stabilized by the C_6 methyl group as evidenced by complete deuterium exchange of the methyl group protons. The effect is a general characteristic for 4-phenyl-1,4-dihydropyridine derivatives of the Ca-channel antagonist class [12].

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References

[1]. G. K. Surya Prakash and P. v. R. Schleyer (Eds.), *Stable Carbocation Chemistry*, Wiley, New York, **1996**.
[2] J. March, *Advanced Organic Chemistry*, Wiley, New York, **1985**.
[3] E. J. Stamhuis and W. Maas, *J. Org. Chem*. **1965**, 30, 2156-60.
[4] P. Y. Sollenberger and R. B. Martin, *J. Am. Chem. Soc*. **1970**, 92, 4261-70.
[5] M. R. Ellenberger, D. A. Dixon and W. E. Farneth, *J. Am. Chem. Soc*. **1981**, 103, 5377-82.
[6] R. A. Eades, D. A. Weil, M. R. Ellenberger, W. E. Farneth, D. A. Dixon and C. H. Douglass, *J. Am. Chem. Soc.* **1981**, 103, 5372-77.
[7] R. E. Lyle, in *Pyridine and its Derivatives*, Supplement, Part One, (R. A. Abramovitch, Ed.), Wiley, New York, **1974**, p137-182, and the references cited therein .
[8] G. E. Hartman, B. T. Philips, and W. Halczenko, *J. Org. Chem*. **1985**, 50, 2423-27.
[9] G. T. Hartman, W. Halczenko, and B. T. Philips, *J. Org. Chem*. **1985**, 50, 2427-31.
[10] D. A. Claremone, J. Hirshfield, P. K. Lumma, D. E. McClure, and J. P. Springer, *Synthesis*, **1986**, 144-147.
[11] D. H. Kim, *J. Heterocyclic Chem*. **1986**, 23, 1471-74.
[12] D. Kocjan, *to be published*

Povzetek

Opisan je zanimiv primer kislinsko katalizirane devterijske izmenjave v metanolu-d4 pri 4-fenil-1,4-dihidropiridinski derivatih, ki sodijo v razred Ca antagonistov. Devterijska izmenjava protonov C_α-metilne skupine nakazuje nastanek enaminskega karbokationa, ki ga lahko opi{emo s tremi mezomerni strukturami.