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Theoretical studies on acid-base interactions in the substituted 4-nitropyridines and their *N*-oxides systems

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Abstract

Acid–base equilibrium constants, involving acidity constants of cationic acids formed by substituted 4-nitropyridines and its *N*-oxides and cationic homoconjugation constants of the bases studied with conjugate cationic acids (protonated bases) have been studied by ab initio methods. The calculations were carried out in the gaseous phase and after consideration of solvation energy in solutions of a polar protophobic aprotic solvent, acetone. The energies and Gibbs free energies were calculated at the RHF, MP2 and PCM levels and compared to the pK_a^{AC} and $\log K_{BHB^+}^{AC}$ values which were determined experimentally using potentiometrical method. It was found that the calculated energies, ΔE_{prot}, and Gibbs free energies, ΔG_{prot}, of protonation for the systems studied correlate very well with the acid dissociation constants (expressed as pK_a^{AC}) of protonated pyridines and their *N*-oxides. On the other hand the calculated energies, ΔE_{BHB+}, and Gibbs free energies, ΔG_{BHB+}, of homoconjugation do not correlate with the cationic homoconjugation constants values (expressed as $\log K_{BHB^+}^{AC}$) determined in acetone.

Keywords: Ab initio calculations; Acid–base equilibria; Homoconjugation; N–H–N; N–H–O and O–H–O hydrogen bonds; Acetone

1. Introduction

Acidity constants of cationic acids (Eq. (1a) and (1b)) conjugated with substituted pyridines (see Fig. 1a) and their *N*-oxides (see Fig. 1b) in various non-aqueous media including polar aprotic solvents have been determined [1] by the potentiometric method for compounds of different acid–base properties. The solvents were both protophobic (acetone, acetonitrile, benzonitrile, propylene carbonate and nitromethane), as well as protophilic ones (dimethyl sulfoxide and dimethylformamide). Due to their strong differentiating and weak acid–base properties the protophobic solvents allow us to study subtle properties of solutions such as cationic homo- (2a, 2b) and heteroconjugation (3):

$$BH^+ + \rightleftarrows B + SH_2^+ \qquad K_{BH^+} = \frac{[B][SH_2^+]}{[BH^+][SH]} \tag{1a}$$

$$B_1H^+ + SH \rightleftarrows B_1 + SH_2^+ \qquad K_{B_1H^+} = \frac{[B_1][SH_2^+]}{[B_1H^+][SH]} \tag{1b}$$

$$BH^+ + B \rightleftarrows BHB^+ \qquad K_{BHB^+} = \frac{[BHB^+]}{[BH^+][B]} \tag{2a}$$

$$B_1H^+ + B_1 \rightleftarrows B_1HB_1^+ \qquad K_{B_1HB_1^+} = \frac{[B_1HB_1^+]}{[B_1H^+][B_1]} \tag{2b}$$

$$BH^+ + B_1 \rightleftarrows BHB_1^+ \qquad K_{BHB_1^+} = \frac{[BHB_1^+]}{[BH^+][B_1]} \tag{3}$$

Cationic homo- and heteroconjugation take place in the solution together with acid dissociation equilibria (1a) and (1b) but cannot be investigated in water and other amphiprotic solvents. The extent of protolytic equilibria in aqueous solutions is largely restricted due to high polarity and proton exchange capacity of the solvent molecules. The former property is responsible for the high dissociation degree of the compounds studied and the other property is favourable for establishing conjugation equilibria both in the homo- and hetero-systems.

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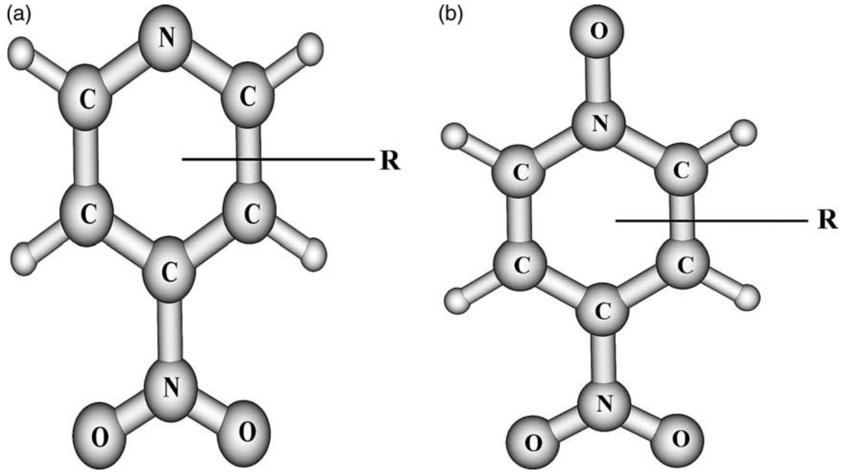

Fig. 1. Structures of the substituted 4-nitropyridine (a) and its *N*-oxide (b). *R* denotes: 2-methylamino-6-methyl, 2-etylamino-6-methyl, 2-methylnitroamino-6-methyl and 2-ethylnitroamino-6-methyl substituents.

The conjugation equilibria in symmetric homo-systems have been the main objective of our interest. The present contribution is a continuation of both experimental [1] and theoretical [2] studies on acid-base equilibria carried out by our research team. Our experience gained in studies of acid–base equilibria by using both theoretical and experimental approaches has led to a general conclusion that best results can be achieved by utilizing those two approaches together.

The substituted 4-nitropyridines and their *N*-oxides covered a wide range of basicities and inherent tendencies towards cationic homoconjugation. Other reasons for using this family of compounds in the present study were their bioactivity [3–6] and interesting physicochemical properties [7–13]. The substituted 4-nitropyridines and their *N*-oxides are able to form several hydrogen bonded systems [10–13]. Oszust et al. [10] have found that 2-amino-4-nitropyridine can form very strong hydrogen bond between two nitrogens in amino group with a distance of 3.011 Å. They also observed that the other N–H bonds of the amino groups were involved in the hydrogen bonding with the oxygen atoms of the nitrogen group forming N–H–O distance of 3.054 Å. The intramolecular interactions were experimentally investigated for the 2-bromo- [11] and 2-iodo-4-nitropyridine *N*-oxide [12]. In the case of the 2-bromo derivative it was found that the ion is coplanar with the pyridine ring. For both derivatives [11,12] the authors observed several of =C–H⋯O intramolecular bonds. Moreno-Fuquen et al. [13] have found a very strong O⋯H⋯O hydrogen bond between an 1:1 complex formed by 4-nitropyridine and 3-hydroxybenzoic acid. The experimentally found O⋯H⋯O distance was 2.642 Å [13]. Dipole moments of 2-alkylamino and 2-alkylaminonitro-3(or 5)-methyl-4-nitroaminopyridines and their *N*-oxides were obtained by Pawelka et al. [14] with experimental and theoretical methods, as well. Their theoretical calculations were carried out with the restricted Hartree-Fock method with the 3-21G basis set. Generally, they have found that theoretically obtained dipole moments were in good agreement with corresponding experimental values. The 4-nitropyridine *N*-oxide was also used as a solvatochromic indicator for the hydrogen-bond donor ability of many solvents (mostly organic) [15]. The UV/VIS spectroscopy showed [15] that the solvatochromic effect for the 4-nitropyridine *N*-oxide is located in the long wavelenght ultraviolet region (330–350 nm).

The main purpose of this work was to calculate energetic parameters for reactions of the protonation and cationic homoconjugation of substituted 4-nitropyridines and their *N*-oxides. These calculations were carried out in the gaseous phase and after consideration of solvation energies in solution. The energies and Gibbs free energies of protonation and formation of homocomplexed cations were calculated by ab initio method at the RHF, MP2 and PCM levels. The calculated energy values were subsequently correlated with the pK_a and $\log K_{BHB^+}$ values obtained experimentally to gain a full picture of acid–base properties of the systems studied.

Theoretical studies were done for the following substituted pyridines (their abbreviations in parentheses): 2-methylamino-6-methyl-4-nitro- ($2MeNH6Me4NO_2Py$), 2-etylamino-6-methyl-4-nitro- ($2EtNH6Me4NO_2Py$), 2-methylnitroamino-6-methyl-4-nitro- ($2N'N'MeNO_26$-$Me4NO_2Py$), 2-ethylnitroamino-6-methyl-4-nitropyridine ($2N'N'EtNO_2-6Me4NO_2Py$), and their *N*-oxides: 2-methylamino-6-methyl-4-nitro- ($2MeNH6Me4NO_2PyO$), 2-ethylamino-6-methyl-4-nitro- ($2EtNH6Me4NO_2PyO$), 2-methylnitroamino-6-methyl-4-nitro ($2N'N'MeNO_26$-$Me4NO_2PyO$), and 2-ethylamino-6-methyl-4-nitropyridine *N*-oxide ($2N'N'EtNO_26Me4NO_2PyO$).

2. Methods

All the systems studied were optimized by the ab initio methods at the RHF (Restricted Hartree Fock) level using