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Toward extension of the gas-phase basicity scale by novel pyridine containing guanidines

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Dedicated to the memory of Professor Detlef Schroeder.

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ABSTRACT

The gas-phase basicities (GB) and proton affinities (PA) of six novel guanidine derivatives were measured by the entropy corrected kinetic method. The proton affinities of the dimethylaminopropyl and methoxypropyl guanidine derivatives **8**–**12**, as described earlier in Ref. [5], were refined employing a new set of reference bases and were found to be in good agreement with previously published values. Their GB values were also evaluated. In this way a useful set of potential reference bases with GBs in the range of 1037–1079 kJ mol^{-1} was developed allowing their use in further measurements of more basic compounds. The experimentally determined gas-phase basicities correlate well with the pK_{HB} values of the hydrogen bond accepting functional groups within the heteroalkyl side-chain(s). Trends in the changes in the measured GB and PA values for the set of 25 nitrogen bases including the investigated ones were compared with the computed data arrived with the following methods: B3LYP/6-311+G(2df,p)//B3LYP/6-31+G(d,p), MP2/6-311+G(d,p)//B3LYP/6-31+G(d,p), BMK/6-311+G(d,p)//B3LYP/6-31+G(d,p) and M06-2X/6-311+G(d,p)//B3LYP/6-31+G(d,p). It is shown that the B3LYP and BMK functionals slightly overestimate the experimental values for 2-(2-pyridyl)ethyl substituted bases, while the M06-2X, and in particular the MP2 results, are in much better agreement with the absolute GB values.

1. Introduction

Guanidine derivatives occupy a prominent role in the design of strong non-ionic organic bases of interest for organic chemists; this is primarily due to their high catalytic potential in a number of synthetically important reactions [1,2], to mention only the transesterification of vegetable oils [3,4], which is a key-step in the production of Biodiesel. Consequently, considerable attention has been paid to molecular modifications of the parent molecule leading to an enhancement of its basicity. This was achieved through electronic effects by changing the nature and the site of attachment(s) of substituents, substitution by flexible heteroalkyl chains which are capable of forming intramolecular hydrogen bonds (IMHB) [5,6], implementing structural rigidity as in proton sponges [7], enlargement of the guanidine framework leading to polyguanides [8], etc. Particularly interesting in this regard are guanidines substituted with more than one flexible heteroatom containing side-chains. This effect provides additional stabilization which is more pronounced in the protonated forms and hence giving rise to significantly higher basicities [9,10] compared to the basicity of the parent base. In a recent paper [5], we demonstrated that the formation of intramolecular hydrogen bonds significantly contributes to the basicity of 3-dimethylaminopropyl and 3-methoxypropyl guanidines, with the effect being most pronounced for the species bearing three such substituents. Their gas phase proton affinities ranged from 1051 to 1105 kJ mol^{-1} what is by 67–121 kJ mol^{-1} higher than the proton affinity of the parent guanidine [11]. On the other hand, measurements of their basicity in acetonitrile showed a significant increase in the pK_a values for the dimethylaminopropyl substituted guanidines, but not for their methoxypropyl congeners [12]. Based on these results and hydrogen-bond energy calculations we concluded that only 3-dimethylaminopropyl derivatives form sufficiently stable IMHBs that are preserved in acetonitrile and most likely in other less polar solvents. This conclusion was also confirmed by NMR, IR and X-ray measurements [13], as well as by quantum chemical calculations [14]. In line with its high pK_a value (pK_a(**BH**$^+$) = 27.15 [12]), *N*,*N*′,*N*″-*tris*-(3-dimethylaminopropyl)guanidine proved to be a very good catalyst in transesterification of the vegetable oils by methanol [4]. In order to provide more insight into the importance of intramolecular hydrogen bonding in tailoring this type of bases, herein we

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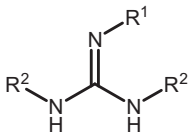
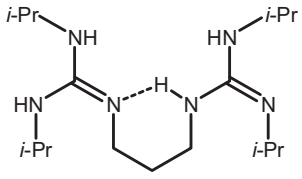


Measured bases

1 R^1 = 2-(2-pyridyl)ethyl; R^2 = methyl
2 R^1 = 2-(2-pyridyl)ethyl; R^2 = isopropyl
3 R^1 = *i*-Pr ; R^2 = 2-(2-pyridyl)ethyl
4 R^1 = R^2 = 2-(2-pyridyl)ethyl
5 R^1 = 3-dimethylaminopropyl; R^2 = isopropyl
6 R^1 = 3-thiomethoxypropyl; R^2 = isopropyl

Reference bases

8 R^1 = 3-dimethylaminopropyl; R^2 = propyl
9 R^1 = propyl; R^2 = 3-dimethylaminopropyl
10 R^1 = 3-methoxypropyl; R^2 = propyl
11 R^1 = propyl; R^2 = 3-methoxypropyl
12 R^1 = R^2 = 3-methoxypropyl



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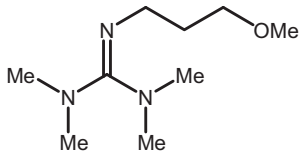

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Scheme 1. Schematic representation of the studied guanidine derivatives.

report an extension of our previous work to new representatives of this intriguing class of compounds. Our primary goal in undertaking this study was to achieve an expansion of available guanidine bases by modifying the nature of the side-chain(s). For this purpose a series of hitherto unknown guanidine derivatives **1**–**4** substituted with 2-(2-pyridyl)ethyl groups (Scheme 1), in which the N-atom of the pyridine ring is involved in intramolecular hydrogen bonding, was prepared and their gas phase basicities and proton affinities were assessed. This was carried out using the kinetic method [15], which is based on the competitive dissociation of a proton bound complex $[R_i{-}H\cdots B]^+$, where B is the base of interest and R_i is a reference base. From the ratio of the abundances of the product ions R_iH^+ versus BH^+ the appropriate thermochemical data can be derived. In addition, the effects caused by the attachment of 3-dimethylaminopropyl (**5**), 3-thiomethoxypropyl (**6**) or 3-($N^{1'}$,$N^{3'}$-diisopropylguanidin-$N^{2'}$-yl)propyl (**7**) group to the imino nitrogen of N^1,N^3-diisopropylguanidine will be discussed.

Our second goal was to apply these compounds as reference bases in refining existing proton affinities of previously measured dimethylaminopropyl and methoxypropyl guanidines. This is of considerable importance since the choice of available reference bases that were used in Ref. [5] was rather limited, allowing in some cases only the measurements against 1–2 reference bases. This is not regarded as sufficient according to the generally accepted Vekey's recommendation which requires that at least three reference bases are necessary for obtaining reliable results [16]. The experimental work is complemented by testing the performance of two (BMK [17] and M06-2X [18]) computational methods and their comparison with more frequently used B3LYP [19] and MP2 approaches in calculating GB and PA values for the considered classes of compounds. BMK and M06-2X density functionals were recommended by Truhlar and coworkers for the study of thermochemistry and kinetics of molecules containing main-group atoms [18], however, their reliability in calculating gas phase basicities has not been widely explored [20]. We are particularly interested in testing the performance of the M06-2X method due to its claimed ability to be successful in treating nonbonding interactions [18b].

2. Experimental and theoretical details

2.1. Synthesis

The target guanidine derivatives were synthetized either by addition of the corresponding amine to diisopropyl carbodiimide (guanidines **2** and **5**–**7**) [12] or using the isothiouronium method (for compounds **1**, **3** and **4**) [12]. The former approach was conducted by using microwave heating under solvent-free conditions. The slight excess of diisopropyl carbodiimide was removed under high vacuum and the products were obtained in high yields without need for additional purification. Details of the synthetic procedures are given in Supplementary data. Compounds **7**–**12** were prepared according to previously published procedures [12,21]. Compounds **1**, **2** and **8**–**12** were redistilled prior to mass spectrometric measurements. 7-Methyl-1,5,7-triazabicyclo-[4.4.0]dec-5-ene (MTBD, for its structure, see Scheme 2 in Section 3.2), which was used as the reference base in measuring the basicity of guanidine derivatives **1**, **6** and **10**, was commercially available.

2.2. Instrumentation

All measurements were performed on VG BIO-Q triple quadruple MS instrument equipped with an electrospray ionization (ESI) system. The experimental setup and the instrument characteristics were identical to those described earlier [5]. Briefly, VG BIO-Q instrument consists of an electrospray source combined with tandem mass spectrometer of QHQ configuration (Q, quadrupole; H, hexapole). The ESI source was adjusted to cone voltage of 5 V, i.e. soft ionization conditions were applied, using nitrogen as the nebulizing and drying gas at a source temperature of 80 °C. Typically, a mmolar solution of a 1:1 mixture of two bases was introduced to the ESI source via syringe pump (at 4 μL/min). The target proton bound heterodimer was mass-selected using Q1 and fragmented in the hexapole by collision-induced dissociation (CID) using xenon as the collision gas under single-collision conditions (2×10^{-4} mbar). The internal energy of the precursor proton bound heterodimer was varied by nominally setting E_{lab} to 0, 2, 4, 5, 6, 8, 10 and 15 eV