Theoretical Study of Proton Affinities of Some *N*-Bases of Biological Importance

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Ab initio SCF (MINI-1 base) and AM1 methods have been used to calculate the vapour phase proton affinities of substituted methylamines. Our calculations have shown that the MINI-1 proton affinities are superior to those calculated using another minimum basis set (STO-3G). As regards the AM1 results, the absolute values of the proton affinities are about 5 % lower than the corresponding vapour phase experimental enthalpies. However, the agreement with experiments is much better for the AM1 method in comparison with the MINI-1 *ab initio* calculations. Moreover, the AM1 quantum-chemical method has been used for the determination of the proton affinities of some local anaesthetics.

Many pharmacologically important drugs (*e.g.* local anaesthetics, antiarrhythmics, neuroleptics, antihistaminics) possess a basic amino group [1] which can add a proton to form a cation. At physiological pH those drugs can occur in positively charged and uncharged forms. In order to better understand the intrinsic basicities of biologically active amines, and with respect to the fact that the experimental proton affinities (PA) of these drugs are as yet not available, we investigated the PA of some local anaesthetics using the theoretical AM1 method.

The initial calculations were carried out with the simpler models of the amino group of those drugs — substituted methylamines. For the sake of comparison of the results of several theoretical methods with the experimental data some calculations were also performed by means of the *ab initio* SCF method using minimal basis sets. Those *ab initio* methods are, with respect to the size of drug molecules, most frequently used in quantum pharmacology.

CALCULATION METHOD

The theoretical calculations for the substituted methylamines were performed using the *ab initio* MINI-1 [2] basis and the AM1 method [3]. The geometries of bases and their cations were completely optimized. (The precise geometry specification used in this paper may be obtained from the present author by request.) For the calculations of the proton affinities of local anaesthetics we used the X-ray geometries of procaine [4], cocaine [5], lidocaine [6], dyclonine [7], heptacaine [8], mexiletine [9] chlorides and phenacaine bis(*p*-nitrophenyl) phosphate monohydrate [10].

The proton affinity of a base B from the *ab initio* calculations was determined as the negative ΔE_p value of the exothermic reaction

$$B(g) + H^+(g) \rightarrow BH^+(g) \qquad (A)$$

i.e. the difference between the energies of the neutral and protonated species

$$\Delta E_p = E_B - E_{BH+} \qquad (1)$$

The semiempirical quantum-chemical AM1 method allows the calculation of the standard formation enthalpies [11] $\Delta H^\circ_{f,298}$. The proton affinity of base PA(B) can be computed by the equation

$$PA(B) = \Delta H^\circ_{f,T}(H^+, g) + \Delta H^\circ_{f,T}(B, g) - \Delta H^\circ_{f,T}(BH^+, g) \qquad (2)$$

$\Delta H^\circ_{f,T}$ represents the heat of formation of the species stated between parenthesis. For $\Delta H^\circ_{f,298}(H^+, g)$ the experimental value 1537.1 kJ mol^{-1} is taken [12].

The *ab initio* calculations were carried out using the GAUSSIAN 80 program [13] and the AM1 calculations were conducted using AMPAC [14].

RESULTS AND DISCUSSION

Proton Affinities of the Substituted Methylamines

The basicity of ammonia and methylamines in gas phase follows a regular ordering [15] (it increases in the order NH_3, $MeNH_2$, Me_2NH, Me_3N). In order to test the ability of the AM1 method to correctly describe the effect of alkyl substitution on the val-

ues of the calculated PA of the substituted amines we computed PA of the substituted methylamines. Proton affinities for the protonation of methylamines are given in Table 1. Also reported, for the sake of comparison, are the differences in energy ΔE_p (eqn (*1*)), representing the electronic contribution to the proton affinity, obtained from our minimal basis set (MINI-1) *ab initio* SCF calculations, as well as the STO-3G results taken from the literature [16]. The STO-3G calculated PA are considerably higher than those obtained using the MINI-1 basis set (Table 1). This observation is in accordance with the conclusion of the recent investigations [17—19] that the MINI-1 proton affinities are far superior to the STO-3G proton affinities which are considerably overestimated.

Table 1 shows that the calculated proton affinities increase in the order $PA(NH_3)$, $PA(MeNH_2)$, $PA(Me_2NH)$, $PA(Me_3N)$. Using the regression analysis with PA_{exp} as the independent variable the following regression equations were obtained

$$PA_{AM1} = 78.775 + 0.870\ PA_{exp}\ (r = 0.9802) \quad (3)$$

$$PA_{MINI\text{-}1} = -53.143 + 1.197\ PA_{exp}\ (r = 0.9986) \quad (4)$$

$$PA_{STO\text{-}3G} = 254.451 + 0.969\ PA_{exp}\ (r = 0.9997) \quad (5)$$

where r is the correlation coefficient. These equations show that the better correlation is obtained for the *ab initio* SCF results. The AM1 results are in much better agreement with the experiments since they are only about 5 % too low. However, for the sake of clarity, it is necessary to stress that the *ab initio* SCF ΔE_p energies represent the electronic contribution to the proton affinity only. The experimentally determined proton affinity at 298 K (Table 1) includes zero-point vibrational terms as well as thermal, translational and rotational contributions, making direct comparison with ΔE_p imprecise; nevertheless the experimental values do serve as a valuable point of reference. On the other hand, the Dewar's AM1 method, with respect to its semiempirical nature and the fact that it was directly designed to mimic the experimental enthalpies of compounds, gives better agreement with the experiment. Similarly a very good agreement between AM1 calculated and experimental PA of substituted pyridines has been observed by *Voets et al.* [11].

Table 1. Calculated and Experimental Values (kJ mol^{-1}) for the Proton Affinities of Methylamines in Gas Phase

Compound	ΔE_p		$\Delta H^\circ_{f,298}$	ΔH°_{298}
	MINI-1	STO-3G[a]	AM1	exp[b]
NH_3	972.7	1085.8	821.3	858.1
CH_3NH_2	1021.1	1123.5	863.3	896.2
$(CH_3)_2NH$	1054.3	1149.9	888.4	923.0
$(CH_3)_3N$	1074.9	1169.1	893.7	944.4

a) Ref. [16]; *b*) Ref. [15].

Proton Affinities of Local Anaesthetics

At pH of physiological medium local anaesthetics studied can occur in their ionized and nonionized form [20, 21]. The protonation site is the amino group. The protonation—deprotonation equilibrium is characterized by the experimental pK_a value (in aqueous system). This parameter is often related to anaesthetic potency and action [21]. The pK_a parameters are, however, not proportional to the electron density at the nitrogen atom of the base. A quantity which is related to the electron densities at the nitrogen atoms is the proton affinity in the gaseous state [25]. Table 2 summarizes the AM1 calculated proton affinities of local anaesthetics. For reasons of investigation of the effect of geometry optimization on the calculated PA, in the case of the mexiletine, also the computations using the AM1 fully optimized geometry of B and BH^+ were carried out. Full geometry minimization resulted in the neglecting of the decrease of the PA (less than 0.5 %) (Table 2).

Table 2. AM1 Calculated Proton Affinities in Gas Phase and Experimental pK_a Values of Local Anaesthetics

Compound	$\Delta H^\circ_{f,298}$/(kJ mol^{-1})	pK_a(exp)
Procaine	942.6	8.56[a]
Cocaine	930.1	8.5[b]
Lidocaine	882.8	7.25[a]
Dyclonine	889.9	–
Phenacaine	993.3	–
Heptacaine	912.9	7.6[c]
Mexiletine	926.4 (922.6)[e]	8.8[d]

a) Ref. [22]; *b*) Ref. [23]; *c*) Ref. [20]; *d*) Ref. [24]; *e*) PA calculated using the optimized geometry of B and BH^+.

It has been previously reported [26, 27] that the pK_a data of the *N*-containing biologically active compounds correlate strongly with calculated electronic parameters (protonation energy, molecular electrostatic potential, energy of the HOMO's) and a good correlation was found within a homogeneous series of compounds. Since local anaesthetics studied by us do not belong to the single chemical type we do not expect very good correlation of calculated PA and experimentally determined pK_a values. The AM1 calculated PA were submitted to regression analyses against available pK_a (Table 2) with the following results

$$pK_a = -15.827 + 0.026\ PA\ (r = 0.8810) \quad (6)$$

Thus there is only a qualitative correlation between

theoretical proton affinities (corresponding to the vapour state) and experimentally determined pK_a (in the solvated state).

In summary, the present results indicate that the AM1 calculations seem to be much better than the minimal basis set *ab initio* calculations in predicting the PA of amines. Thus the AM1 method can be successfully applied for the calculations of PA of the *N*-basic drugs.

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