



A DFT Model Reaction and a Procedure for Predicting the Nucleofugality of Tertiary Heterocyclic Amines

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Abstract: A previously described procedure for estimating the nucleofugality of substituted pyridines in terms of N_f^{calc} parameters has now been applied to various tertiary heterocyclic amines. Geometries of conformers of some 4,4'-bis(dimethylamino)benzhydryl substituted ammonium ions, bearing tertiary heterocyclic amines as leaving groups, and of corresponding heterolytic transition-state conformers have been optimized at the M06-2X/6-311+G(2d,p) level of theory with the IEFPCM implicit solvation model for acetonitrile. Taking into account the existence of multiple parallel paths connecting corresponding conformers of the two states (that is, ground state and transition state), free energies of activation for the model heterolysis of the cationic substrates ($\Delta G^{\ddagger\text{model}}$) were derived from computed free energies of conformers at 25 °C. Very good correlation between the $\Delta G^{\ddagger\text{model}}$ values and corresponding experimental free energies of activation (ΔG^{\ddagger}) taken from the literature indicates that both the applied DFT model reaction and the described procedure provide very good bases for evaluating N_f^{calc} nucleofugality parameters of various tertiary heterocyclic amines.

Keywords: DFT, free energy of activation, heterocyclic amines, heterolysis, IEFPCM, leaving group, M06-2X, nucleofugality, nucleofuge.

INTRODUCTION

It is well-known that quaternary ammonium salts exhibit antibacterial, antifungal, and antiviral activities.^[1,2] Due to their antimicrobial properties, this class of compounds have a broad application as biocides, antiseptics, disinfectants, sanitizers and cleaners in industry, medicine and agriculture. As active ingredients, they are also present in household and various consumer products. Expectedly, the increased use of quaternary ammonium salts in recent years has begun to attract more interest in their environmental impact and fate.^[2]

Although commercially employed quaternary ammonium salts are generally considered as stable compounds,^[1] the fact is that quaternary ammonium ions, like some other classes of substrates (e.g., alkyl halides and benzoates), are composed of an electrofuge (that is, an alkyl moiety) and a nucleofuge (that is, a leaving group), which renders them subject to nucleophilic displacement reactions at C(sp³) centers and C(sp³)–leaving group

heterolyses.^[3–6] It can be expected that the structural features of the constituents of quaternary ammonium ions determine the reactivity of the ions over a wide range of reactivity. For example, as previously shown, the solvolysis of only monosubstituted pyridinium ions (bearing a common benzhydryl electrofuge in the series) in 80 % ethanol at 25 °C covers a reactivity range of approximately eight orders of magnitude.^[7] Cationic substrates from the same series undergo heterolysis in dichloromethane at 20 °C in a similar reactivity range.^[8] Due to limitations of conventional techniques of kinetic measurements, it is impossible to perform the measurements in such wide reactivity ranges and, consequently, to compare contributions of the substrate constituents (e.g., substituted pyridine leaving groups) to the overall reactivity in a certain solvent.

In order to overcome the above-mentioned difficulties and to provide the possibility to predict rates of solvolyses and heterolyses for various classes of substrates in different solvents, Mayr and coworkers have proposed a

simple LFER approach based on Equation (1), in which k is a first-order rate constant for solvolysis of some substrate at 25 °C. In this equation, contributions of an electrofuge (alkyl moiety) and a nucleofuge (leaving group) to the overall solvolytic reactivity of a substrate are separated.^[5] Thus, the N_f parameter represents the nucleofugality of a leaving group in combination with some solvent, whereas E_f is a parameter that quantifies the reactivity of an electrofuge (that is, a parameter that defines electrofugality).

$$\log k = s_f(E_f + N_f) \quad (1)$$

There are two practical applications of this LFER approach. First, it enables determination of nucleofugalities (N_f) of various types of leaving groups in a wide range of reactivity, which further enables a direct comparison of heterolytic reactivities of leaving groups. Secondly, rates and reaction times for solvolyses (in protic solvents and mixtures) and heterolyses (in aprotic solvents) of substrates consisting of any combination of an electrofuge and a nucleofuge can be estimated in some solvent at 25 °C using Equation (1) and corresponding reactivity parameters.^[5,9] According to Equation (1), nucleofuge-specific parameters N_f and s_f for some combination of a leaving group and a solvent can be determined by correlating logarithms of solvolysis rate constants of a series of substituted benzhydryl substrates (containing a leaving group of interest) with corresponding electrofugalities of reference benzhydryl electrofuges. Negative intercepts on the abscissa of $\log k$ versus E_f plots yield N_f values, whereas slopes, which are usually about unity, yield s_f values. The N_f nucleofugality scale so far covers a reactivity range of 15 orders of magnitude.^[5,7–9] Although only reference benzhydryl electrofuges spanning a reactivity range of 18 orders of magnitudes are used to determine nucleofuge-specific parameters,^[5] E_f values of other electrofuges are also available in the literature.^[10] In previous studies, we have demonstrated that DFT/PCM computations can be employed to estimate nucleofugality parameters of both charged^[9,11] and neutral leaving groups.^[7,8] The procedure for estimating reliable N_f values is based on very good correlations between measured free energies of activations for solvolyses and heterolyses of substrates containing the same functionality (e.g., aryl/alkyl carbonates or quaternary pyridinium ions) in a certain solvent and free energies of activations calculated by a DFT method for corresponding model reactions (that is, ΔG^\ddagger versus $\Delta G^\ddagger_{\text{model}}$ correlations).

In this study, we investigate the possibility of applying the above mentioned ΔG^\ddagger versus $\Delta G^\ddagger_{\text{model}}$ correlation in predicting both heterolytic reactivities of various heterocyclic quaternary ammonium ions in an aprotic solvent (that is, acetonitrile) and nucleofugalities of corresponding tertiary amines using available kinetic data

from the literature (ΔG^\ddagger)^[5,6] and calculated free energies of activations for model reactions ($\Delta G^\ddagger_{\text{model}}$).

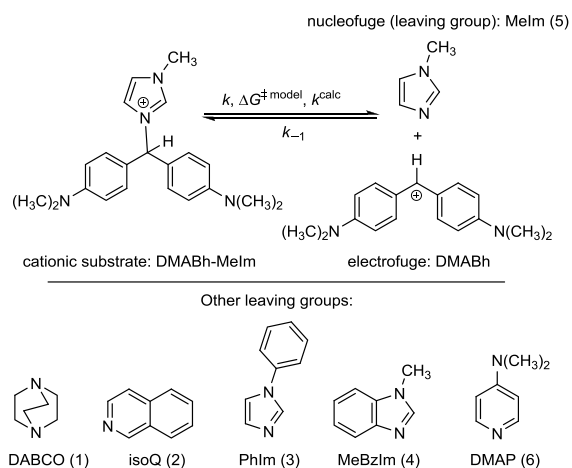
COMPUTATIONAL METHODS

All computations were carried out with the GAUSSIAN 16 (A.03) suite of programs.^[12] Cationic substrate conformers and corresponding transition-state conformers were fully optimized using the M06-2X^[13] DFT method, 6-311+G(2d,p) basis set and the IEFPCM^[14] model with acetonitrile as a solvent. The implicit solvation model was used with default parameters in GAUSSIAN 16 (A.03). The ultrafine grid and tight convergence criteria were applied in all computations. Frequency calculations were performed upon all optimized geometries at the mentioned level of theory to compute thermal corrections at 298.15 K. Coordinates of optimized geometries and corresponding energies (Table S1) are given in the Supporting Information. Vibrational analysis was used to confirm stationary points as either a minimum (no imaginary frequencies) or a transition-state structure (one imaginary frequency).

RESULTS AND DISCUSSION

Experimental kinetic data for heterolyses of various benzhydryl substituted ammonium ions in aprotic solvents as well as N_f values for corresponding tertiary heterocyclic amines have been previously published.^[5,6] Since in recent studies on the heterolysis of *N*-alkyl-*X*-pyridinium ions the 4,4'-bis(dimethylamino)benzhydryl electrofuge (DMABh electrofuge) had been chosen as a reference electrofuge and, consequently, *N*-[4,4'-bis(dimethylamino)benzhydryl]-*X*-pyridinium ions had been reference substrates,^[7,8] published kinetic data for the heterolysis of six reference 4,4'-bis(dimethylamino)benzhydryl substituted ammonium ions, bearing tertiary heterocyclic amines as leaving groups, in acetonitrile at 20 °C were used for correlation in this study (Scheme 1). N_f values of the heterocyclic amines, $\log k$ values and corresponding free energies of activations (ΔG^\ddagger) for the heterolysis of the reference cationic substrates are listed in Table 1.

It appears that transition structures for the pure heterolysis of neutral substrates cannot be located either in the gas phase or in a solvent using implicit solvation models.^[11] On the other hand, we had previously managed to optimize transition structures for the heterolysis of various *N*-benzhydryl-*X*-pyridinium ions using the M06-2X method in combination with the IEFPCM solvation model for both ethanol and dichloromethane.^[7,8] Now, employing the M06-2X/6-311+G(2d,p) level of theory and the IEFPCM solvation model for acetonitrile, we have optimized all accessible conformers of the six 4,4'-bis(dimethylamino)benzhydryl substituted ammonium ions bearing tertiary heterocyclic



Scheme 1. Heterolysis of quaternary ammonium ions containing the 4,4'-bis(dimethylamino)benzhydryl electrofuge and some tertiary heterocyclic amines as leaving groups.

amines as leaving groups and corresponding transition-state conformers according to the model reaction given in Scheme 1. To obtain thermal corrections to free energies of the conformers at 25 °C, frequency calculations have been performed upon the all optimized geometries. Energies

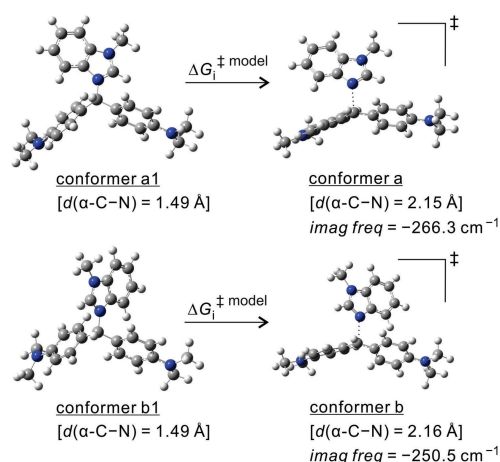


Figure 1. Geometries of some conformers of 1-[4,4'-bis(dimethylamino)benzhydryl]-3-methyl-benzimidazol-1-ium ion and geometries of corresponding heterolytic transition-state conformers optimized at the M06-2X/6-311+G(2d,p) level of theory by using the IEFPCM solvation model for acetonitrile.

(Table S1), some geometries (Figure S1) and coordinates of the conformers are given in the Supporting Information.

Table 1. Experimental (ΔG^\ddagger), DFT-model ($\Delta G^\ddagger_{\text{model}}$) and predicted ($\Delta G^\ddagger_{\text{calc}}$) free energies of activation and corresponding logarithms of first-order rate constants for the heterolysis of some quaternary ammonium ions containing the 4,4'-bis(dimethylamino)benzhydryl electrofuge (DMABh) and some tertiary heterocyclic amines as leaving groups along with corresponding nucleofugality parameters and mean absolute errors of predictions

No.	Cationic substrate	Leaving group	$N_f^{(a)}$	$\log k^{(b)}$	$\Delta G^\ddagger^{(c)}$	$\Delta G^\ddagger_{\text{model}}^{(d)}$	$\Delta G^\ddagger_{\text{calc}}^{(e)}$	$\log k^{\text{calc}}^{(f)}$	$N_f^{\text{calc}}^{(g)}$
1	DMABh–DABCO	diazabicyclo[2.2.2]octane	-1.00	3.84 ^(h)	12.00	11.39	11.95	3.89	-0.95
2	DMABh–isoQ	isoquinoline	-3.04	1.61	14.99	15.30	15.11	1.52	-3.32
3	DMABh–PhIm	1-phenylimidazole	-5.59	-0.82	18.26	18.83	17.97	-0.61	-5.45
4	DMABh–MeBzIm	1-methylbenzimidazole	-6.01	-1.40	19.03	19.91	18.85	-1.26	-6.10
5	DMABh–Melm	1-methylimidazole	-6.29	-1.45 ^(h)	19.10	20.24	19.11	-1.46	-6.30
6	DMABh–DMAP	4-dimethylaminopyridine	-6.29	-1.45 ^(h)	19.10	20.46	19.29	-1.59	-6.43
MAE ⁽ⁱ⁾									
							0.17 ^(j)	0.13	0.14

^(a) Experimental nucleofugality parameters of leaving groups in acetonitrile at 20 °C. Values were taken from Ref. 5.

^(b) Logarithms of first-order rate constants for heterolyses of the cationic substrates in acetonitrile at 20 °C (Scheme 1). Unless noted otherwise, rate constants for heterolysis were calculated from an experimental equilibrium constant K and a second-order rate constant for the reverse reaction (k_{-1}) by $k = k_{-1} / K$. Values and details are given in Ref. 5.

^(c) Experimental free energies of activation (in kcal mol⁻¹) for heterolyses of the cationic substrates in acetonitrile at 20 °C (Scheme 1). Derived from corresponding rate constants (k) by the Eyring equation.

^(d) Free energies of activation (in kcal mol⁻¹) for the model heterolysis of the cationic substrates in acetonitrile at 25 °C (Scheme 1) calculated at the M06-2X/6-311+G(2d,p) level of theory with the IEFPCM solvation model for acetonitrile.

^(e) Predicted free energies of activation (in kcal mol⁻¹) for heterolyses of the cationic substrates in acetonitrile at 20 °C derived from the ΔG^\ddagger versus $\Delta G^\ddagger_{\text{model}}$ plot given in Figure 2.

^(f) Logarithms of predicted heterolytic first-order rate constants at 20 °C calculated from the corresponding $\Delta G^\ddagger_{\text{calc}}$ values by using the Eyring equation.

^(g) Predicted nucleofugalities derived from Equation 1 and the corresponding $\log k^{\text{calc}}$ values. An s_f value of 1.00 and an E_f value for the DMABh electrofuge of 4.84 were taken from Ref. 5.

^(h) Derived from Equation 1 and the corresponding experimental N_f values. An s_f value of 1.00 and an E_f value for the DMABh electrofuge of 4.84 were taken from Ref. 5.

⁽ⁱ⁾ Mean absolute error of predictions.

^(j) in kcal mol⁻¹.

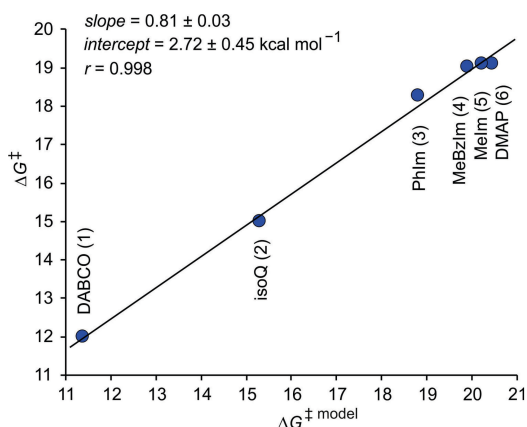


Figure 2. Plot of experimental free energies of activation (in kcal mol⁻¹) for the heterolysis of some quaternary ammonium ions containing the 4,4'-bis(dimethylamino)-benzhydryl electrofuge and some heterocyclic amines as leaving groups at 20 °C versus free energies of activation for the corresponding model heterolysis of the ions at 25 °C calculated at the M06-2X/6-311+G(2d,p) level of theory with the IEFPCM solvation model for acetonitrile (Table 1).

Since the geometry of the two dimethylamino substituents attached to benzhydryl rings is pyramidal, at least four conformers are optimized for each cationic substrate (1–4). On the other hand, the geometry of the dimethylamino substituents in optimized transition structures is planar due to strong charge delocalization in the 4,4'-bis(dimethylamino)benzhydryl moiety. However, in some cases, rotation around the α -C–N bond (that is, the electrofuge—nucleofuge bond) gives rise to the existence of additional conformers (a, b, etc.) of both cationic substrates and transition structures (Figures 1 and S1). Thus, for each orientation of a heterocyclic amine leaving group in a substrate (a, b, etc.) there are four conformers (1–4) due to rotation of dimethylamino substituents, whereas the number of transition-state conformers is determined solely by the orientation of a leaving group. As can be seen in Figures 1 and S1, the orientation of the leaving groups in the cationic substrate conformers (e.g., a1–a4) is analogous to that in the corresponding transition-state conformer (e.g. a).

The existence of substrate conformers, which are in equilibrium in the ground state, and transition-state conformers implies that heterolyses and solvolyses, as well as other reactions,^[15] proceed by multiple parallel paths connecting corresponding conformers of the two states. Depending on the number of conformers, the pattern of the heterolysis path can be more or less complex. To calculate free energies of activations for the model heterolysis ($\Delta G^{\ddagger \text{model}}$) of DMABh-substituted ammonium ions, we have used a procedure applied in previous studies.^[7,8] Williams has described and tested transition-

state theory procedures for evaluating $\Delta G^{\ddagger \text{model}}$ values for heterolyses of cationic substrates, however, as reported, all these procedures afford similar results.^[16]

Assuming that the heterolysis of each cationic substrate conformer (e.g., conformers a1–a4) proceeds through the corresponding (that is, analogous) conformer of the transition state (e.g., conformer a), as shown in Figures 1 and S1, free energies of activation for the model heterolysis ($\Delta G^{\ddagger \text{model}}$) given in Scheme 1 have been obtained from weighted individual free energy barriers ($\Delta G_i^{\ddagger \text{model}}$) according to Equation (2). Statistical weights of conformers of some cationic substrate at 25 °C (χ_i) were calculated from the Boltzmann distribution of the conformers. Accordingly, χ_i represents the mole fraction of the i^{th} substrate conformer in the ground-state conformer population. Calculated $\Delta G^{\ddagger \text{model}}$ values are shown in Table 1, while $\Delta G_i^{\ddagger \text{model}}$ and χ_i values are tabulated in Table S1.

$$\exp\left(-\frac{\Delta G^{\ddagger \text{model}}}{RT}\right) = \sum_i \chi_i \exp\left(-\frac{\Delta G_i^{\ddagger \text{model}}}{RT}\right) \quad (2)$$

As mentioned above, the heterolytic ΔG^{\ddagger} values were obtained from kinetic measurements performed at 20 °C (Table 1) while the $\Delta G^{\ddagger \text{model}}$ values were derived for model heterolyses at 25 °C; thus, these values cannot be directly compared. In addition, the values also cannot be compared when solvolysis measurements are conducted in aqueous mixtures.^[7,11] In order to obtain predicted free energies of activation ($\Delta G^{\ddagger \text{calc}}$) that can be compared with corresponding experimental values at 20 °C, the ΔG^{\ddagger} values were correlated with the $\Delta G^{\ddagger \text{model}}$ values of corresponding model heterolyses (Scheme 1). A correlation coefficient of 0.998 and a slope of 0.81 for the plot given in Figure 2 indicate a very good correlation between the two series of activation free energies. The quality of $\Delta G^{\ddagger \text{model}}$ values and the given correlation, as well as their applicability in predicting free energies of activation, can further be assessed by comparing the $\Delta G^{\ddagger \text{calc}}$ values (Table 1) derived from the correlation with the corresponding experimental values ΔG^{\ddagger} (also shown in Table 1). A mean absolute error (MAE) of predictions (that is, $\Delta G^{\ddagger \text{calc}}$ values) of 0.17 kcal mol⁻¹, which refers to a reactivity range of about 7 kcal mol⁻¹, validates the procedure for estimating heterolytic free energies of activation. Accordingly, $\Delta G^{\ddagger \text{model}}$ values obtained at the IEFPCM-M06-2X/6-311+G(2d,p) level of theory, along with the described procedure, can further be employed for predicting free energies of activation of heterolyses of DMABh-substituted ammonium ions bearing other tertiary heterocyclic amines as leaving groups in acetonitrile at 20 °C with the above presented reliability. Of course, the inclusion of a larger set of experimental data could further increase the reliability of the given procedure.

Using the Eyring equation, the $\Delta G^\ddagger_{\text{calc}}$ values were converted into first-order rate constant (k^{calc}). Logarithms of the predicted rate constants ($\log k^{\text{calc}}$) are shown in Table 1 and can be compared with corresponding $\log k$ values obtained from the experimental kinetic data (also shown in Table 1). Considering the previous reports,^[7,8,11] MAE of 0.13 for the six $\log k^{\text{calc}}$ values spanning a reactivity range larger than 5 orders of magnitude represents an acceptable error in the following prediction of nucleofugality parameters.

Finally, predicted nucleofugality parameters (N_f^{calc}) for the six heterocyclic amines (Scheme 1) in acetonitrile at 20 °C were obtained using Equation (1). Each N_f^{calc} value was calculated from the corresponding $\log k^{\text{calc}}$ value, a predefined electrofugality parameter (E_f) for the DMABh electrofuge of 4.84^[5] and a previously reported s_f parameter for these heterolyses of 1.00.^[5] The N_f^{calc} values given in Table 1 can now be compared with the corresponding experimental N_f values. Similarly as in the case of $\log k^{\text{calc}}$ values, MAE for predicted nucleofugality parameters (N_f^{calc}) is 0.14, which represents an acceptable error for a range that covers more than 5 units (that is, orders of magnitude in reactivity) on the nucleofugality scale.

CONCLUSION

As shown for other leaving groups and substrates in previous studies,^[7,8,11] the N_f^{calc} parameters obtained by the above-described procedure can reliably be used to predict reactivities of quaternary ammonium ions bearing various tertiary heterocyclic amines as leaving groups in acetonitrile at 20 °C according to Equation (1). However, to apply the described procedure to heterolyses and solvolyses of quaternary ammonium ions on a larger scale, it is necessary to provide sets of measured reference data for various solvents and aqueous mixtures beforehand.

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Supplementary Information. Supporting information to the paper is attached to the electronic version of the article at: <https://doi.org/10.5562/cca3976>.

PDF files with attached documents are best viewed with Adobe Acrobat Reader which is free and can be downloaded from [Adobe's web site](https://www.adobe.com/acrobat).

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