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The influence of steric hindrance on kinetics and isotope effects in the reaction of 2,2-bis(4-dimethylaminophenyl)-1-nitro-1-(4-nitrophenyl)ethane with DBU base in acetonitrile

Iwona Nowak *, Arnold Jarczewski

Department of Chemistry, A. Mickiewicz University, ul. Umultowska 89b, 61-614 Poznań, Poland

HIGHLIGHTS

- The pK_a value for $(dmap)_2$ equal to 25.11 has been determined in acetonitrile.
- The low energy conformers of C-acids have been determined by PM6 and DFT methods.
- The influence of steric hindrance on the stability of the TS has been discussed.

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ABSTRACT

The pK_a value for 2,2-bis(4-dimethylaminophenyl)-1-nitro-1-(4-nitrophenyl)ethane, $(dmap)_2$ (pK_a = 25.11) has been measured spectrophotometrically using buffer solutions of a few strong amine bases: 1,8-diazabicyclo[5.4.0]undec-7-ene, (DBU); 1,1,3,3-tetramethylguanidine, (TMG); 1,5,7-triazabicyclo[4.4.0]dec-5-ene, (TBD); 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene, (MTBD) and their salts. The low energy conformers of nitrophenyl nitroalkanes have been determined using the semiempirical PM6 methods, (B3-LYP) density functional theory (DFT) together with the 6-31G(d,p) basis set. The participation of the low energy conformer in the proton transfer reaction to DBU base has been discussed. The kinetic data for proton transfer reactions between $(dmap)_2$ and DBU in acetonitrile (MeCN) at pseudo-first order conditions have been presented. The influence of steric hindrance brought by reacting C-acid and organic base on the stability of the transition state has been discussed. The rates of second-order rate constants for series of nitrophenyl nitroalkanes, $NO_2PhCHRNO_2$ (R = Me; Et; *i*Pr; dimethylaminophenyl = $(dmap)_2$) are presented and discussed.

Introduction

One of the important issues in proton transfer reactions is the role of steric effects. Generally, due to the small size of the hydrogen atom and its outermost position in the donor molecule, and thus a large sensitivity to nucleophilic attack, proton detachment reactions are not particularly demanding from the viewpoint of steric hindrance. However, if the environment of the reaction center makes it difficult to access the proton the spatial factors visibly influence the reactivity of the compounds in the process of proton transfer. Discussion on steric hindrance and its effect on the kinetic of reaction is complex [2–10,35]. The bulk substituents may not only lead to a desolvation of the transition-state or increased demands on the mutual orientation of molecules in an activation complex, but also affect other parameters determining the value of the kinetic isotope effects, KIE such as ΔG°. There are many studies which revealed that the steric effects caused by volume substituents in the base molecule lead to large values of KIE [3,11–16]. Although there are few examples of lower KIE due to steric hindrances present in the amine molecule [4,17]. Also the decrease in the value of KIE with increasing steric hindrance in the molecule of a C-acid in the reaction of series of proton detachment from nitrophenyl nitroalkanes by DBU in tetrahydrofurane and chlorobenzene was present [5]. In turn, the same reaction systems examined in the polar acetonitrile, did not show a similar trend [18]. So, this effect seems to be complex and worth recognition.

Thus, there is still a need to systematize the influence of steric effects both introduced by acid and base molecule on kinetic isotope effects (see Fig. 1). In our previous papers [19,20] we found widely diverse kinetics behavior in the proton transfer reactions between strong amine bases and nitroalkanes differing by electron withdrawing groups and by the bulk of substituents on the acidic

* Corresponding author.

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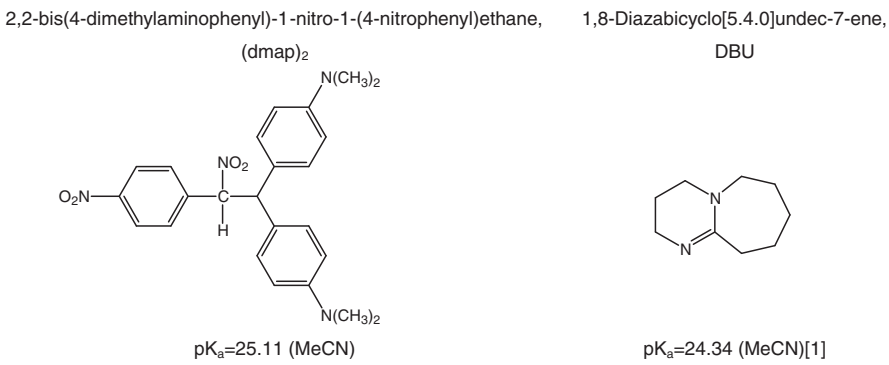


Fig. 1. The C-acid and organic base used in kinetic experiment.

carbon atom, but having similar acidity in acetonitrile. The appearance of two commercially available very strong [21,22] cycling guanidine bases TBD (1,5,7-triazabicyclo[4.4.0]dec-5-ene) and MTBD (7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene) with similar equilibrium constants ($pK_{a\ (TBD)} = 26.03$ [1], $pK_{a\ (MTBD)} = 25.49$ [1]) in MeCN but differing in the presence of the frontal methyl group close to the reaction center had opened up new experimental possibilities and allowed to expand research on this subject. Our research found that the secondary reaction rate constants were always higher in the ionization process of TBD by nitrophenyl nitroalkanes with increasing steric hindrance ($k_{TBD}/k_{MTBD} = 120–290$ in THF and $k_{TBD}/k_{MTBD} = 48–147$ in MeCN) [19]. Furthermore, we found weak dependence of the reaction rate involving TBD on the size of the alkyl substituent at the C-acid. Thus, we concluded that stronger nucleophilic properties [21] of TBD with similar thermodynamic properties of both bases indicate a different reaction mechanism. Hence, the unique TBD reactivity is a result of the presence of additional stabilizing hydrogen bond in the transition state, whilst the kinetic properties of MTBD are controlled primarily by steric effects due to the presence of a methyl group at one of the nitrogen atoms.

The idea was, that the rate constants of the proton transfer carried out in low polar solvents has to be less dependent on the repolarization of solvents molecules accompanied of the motion of the proton since lower dielectric constants of the solvent molecules of the environment. However, we have unexpectedly found a weak dependence of the reaction rate constants on the polarity of the solvent used [19,20]. The reaction rate constants measured with TBD were approximately the same both in a solvent of high and low dielectric constant. This effect is typical for reactions running through cyclic transition state. In turn, for reactions with MTBD rate constants measured in acetonitrile were greater than those measured in THF, suggesting that the reaction proceeds via a polar transition state characterized with a lower charge separation comparing with the product.

Presented research is a continuation of the studies of the impact of steric hindrance on kinetic isotope effects in proton transfer reactions. For this purpose the 1,8-diazabicyclo[5.4.0]undec-7-ene, DBU has been used. The DBU provides convenient conditions to observe steric effects [23,24]. The title compound $(dmap)_2$ belongs to the group of C-acids activated by nitro group. It is characterized by the extended bulk substituent on the acidic carbon atom compare to the previous tested C-acids [4,18–20]. The reactions were carried out in the polar aprotic solvent, acetonitrile (MeCN). In our former papers we stated that in polar solvents most of the products of reactions between C-acids and strong amine bases were largely dissociated into free ions (Scheme 1) [9,18,20,25,26].

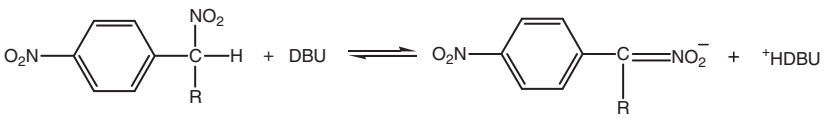
Although the general mechanism of proton transfer reactions is considered to be relatively simple in the acetonitrile, however it has to be taken into account that the possible uncontrolled changes in $[BH^+]$ concentration during a kinetic run may lead to fairly complicated analysis. To ensure pseudo-first order kinetics the concentration of used base is at least ten-fold larger than the concentration of C-acid. Since some amount of $[BH^+]$ can be brought up to the system with the base the additional concentration of $[BH^+]$ may be comparable with concentration of C-acid. In such a case the initial $[BH^+]$ is unknown and it changes with the base concentration. Although the plot of k_{obs} vs. [base] remains close to the straight line it may results in distorted k_f and an intercept of no physical meaning. For that reasons the rates of proton transfer reactions for reactions with not very large equilibrium constant should be measured in buffer solutions BH^+/B, with $[BH^+]$ being kept on constant by using well dissociated amine salt [25]. Otherwise the kinetic studies performed without addition of amine salt, especially when strong amine bases such as an amidine or guanidine are used, can give overlooked deviations from first order kinetics [19,25,2,27]. However, we found also that the use of large concentration of amine base cation could cause some negative salt effects [25], and could lead to anion association manifested by a blue shift in electronic spectra [20,26,28].

The values of kinetic isotope effects determined for various bases and nitroalkanes differing by electron withdrawing groups and by the bulk of substituents on the acidic carbon atom have been reported by us previously in polar as well as nonpolar medium [4,18–20]. In this paper we report the kinetic studies of the reaction of proton transfer in acetonitrile involving DBU and 2,2-bis(4-dimethylaminophenyl)-1-nitro-1-(4-nitrophenyl)ethane, $(dmap)_2$.

Results and discussion

The equilibrium measurements

The knowledge of potentiometric pK_a's values of some strong amine bases [1] in acetonitrile creates possibility of making equi-



Scheme 1. The scheme of proton transfer reaction between nitrophenyl nitroalkanes and DBU in MeCN.

librium measurements leading to the determination of $(dmap)_2$'s pK_a (Table 1). The measurements were carried out in appropriate buffer solutions [29].

The product of the reaction of strong amine bases with relatively strong carbon acids in polar acetonitrile is mostly dissociated into free ions. In this case, the equilibrium can be presented by eq. $K = f^2[BH^+][A^-]/[B][AH]$. Buffer consists of a base and its salt ($[BH^+]/[B]$), so that the concentration of BH^+ can be controlled and maintained at a constant level. When the $[BH^+]$ is constant a Benesi–Hildebrandt equation is followed: $c_{AH}/Abs = 1/\varepsilon + 1/(\varepsilon\ K_{Ben}\ c_B)$, where *Abs* is the absorbance of the product in λ_{max}, ε is the molar extinction coefficient, and K_{Ben} the pseudo equilibrium constant by the Benesi–Hildebrandt method. The plot of c_{AH}/Abs *vs.* $1/c_B$ at a constant c_{AH} and $[BH^+]$ gives K_{Ben} that could be converted into K using following eq. $K = K_{Ben}\ f^2\ [BH^+]$ [30]. In this paper, a few amine bases were used (Table 1). As a result the pK_a values of $(dmap)_2$ were determined as ($pK_a = -\log K + pK^+_{BH}$) and the average value was calculated $pK_{(dmap)2} = 25.11 \pm 0.11$.

Table 1
Equilibrium constants of the proton transfer reaction between 2,2-bis(4-dimethylaminophenyl)-1-nitro-1-(4-nitrophenyl)ethane and strong bases in MeCN at 25 °C and C-acid's pK_a values evaluated using Leito's [1] pK^+_{BH}.

Base	K	pK	pK^+_{BH}	$pK_{a'}$ $(dmap)_2$
DBU	0.187 ± 0.002	0.73	24.34	25.07
	0.13 ± 0.03[a]	0.87[a]		25.21[a]
TMG	0.0138 ± 0.0004	1.86	23.37	25.23
MTBD	2.82 ± 0.06	−0.45	25.49	25.04
TBD	~10	−1	26.03	25.03

[a] Calculated using homoconjugation constant of DBU $K_{HOMO} = 35 \pm 6$ [28].

Table 2
Equilibrium constants, λ_{max} and molar extinction coefficients for the products of the reaction of 1-nitro-1-(4-nitrophenyl)alkanes with DBU in MeCN in 25 °C.

C-acid	pK_a (MeCN)	K_{BH} (M^{-1})	λ_{max} (nm)	ε_{BH} ($M^{-1}\ cm^{-1}$)	Ref.
H	20.7	–	496	26,900	[50]
Me	23.2	48,000 ± 8 000	508	24,200 ± 100	[18]
Et	23.9	35,000 ± 3000	514	25,900 ± 100	[18]
*i*Pr	25.9	900 ± 40	515	16,800 ± 200	[18]
$(dmap)_2$	25.11	0.173 ± 0.009	510	16,500 ± 100	

$$DBUH^+ + DBU- > (DBU)_2H^+$$

$$K_{HOMO} = \frac{[(DBU)_2H^+]}{[DBUH^+][DBU]}$$

$$[PiDBU] = [(DBU)_2H^+] + [DBUH^+]$$

$$PiDBU] = K_{HOMO}[DBUH^+][DBU] + [DBUH^+]$$

$$[DBUH^+] = \frac{[PiDBU]}{(K_{HOMO}[DBU]) + 1}$$

Scheme 2.

For the reaction of $(dmap)_2$ with strong guanidine base DBU in acetonitrile the spectrophotometric titration was carried out at 15, 20, 25, 30, 35 °C. Measurements were run at the maximum absorption band, $\lambda_{max} = 510$ nm, of the product and its molar absorption coefficient of about $\varepsilon = 16{,}500\ dm^3\ mol^{-1}\ cm^{-1}$) was determined (Table 2). The C-acid solution concentration was 2.478×10^{-5} M. The DBU picrate as the salt component of the buffer was used. The small concentration of salt $[BH^+] = 1 \times 10^{-3}$ M was applied to minimize the possible ion-association effect [26]. Due to the fact that there are some reports of extensive dimerization of the DBU base ($K_{HOMO} = 35 \pm 6$) [28,31]. (Scheme 2) the range of base concentration used varied from 3.26×10^{-3} to 0.223 M and should not affect our results. In order to ascertain the accuracy of measurements a correction to homoconjugation to a calculation of equilibrium constant has been used (Scheme 3).

As shown in Table 1 the effect of possible formation of dimmers by DBU is trifling, not exceeding 1% of pK_a value of $(dmap)_2$. The reaction shows the thermodynamic parameters $\Delta H^\circ = -24 \pm 2$ kJ mol^{-1} and $\Delta S^\circ = -94 \pm 8$ J $mol^{-1}\ deg^{-1}$), respectively.

For the next, the equilibrium measurements for a pair of TMG and $(dmap)_2$ reactants in MeCN were carried out. Nevertheless, there are some reports of extensive dimerization of TMG base [32], it was showed elsewhere [28] that there was no essential homoconjugation up to 1 M of TMG base. For that reason the absorbencies were measured in the TMG base concentration range from 1.60×10^{-3} to 0.323 M at 25 °C. The used concentrations of the C-acid and salt were: $[(dmap)_2] = 4.923 \times 10^{-5}$ M, $[PiTMG] = 1.009 \times 10^{-3}$ M, respectively. In this way $K = 1.38 \times 10^{-2} \pm 0.0004$ and $\varepsilon = 17{,}400 \pm 300\ dm^3\ mol^{-1}\ cm^{-1}$ were determined.

At the end, two bicyclic guanidine bases MTBD and TBD as proton acceptors were used. With respect to homoconjugation, it was interesting to compare the equilibrium results for the proton transfer reaction between $(dmap)_2$ and bases of similar basicity (about 0.5 ΔpK_a), very similar structure, differing only in the presence of steric hindrance near the center of the reaction, moreover not having tendency to form dimmers ($K_{HOMO} = 0$ [26,28,33]) in both entries.

In the reaction with MTBD base the equilibrium parameters were measured as follows: $[PiMTBD] = 4.02 \times 10^{-4}$ M, $[(dmap)_2] = 4.92 \times 10^{-5}$ M, $[MTBD] = 7.114 \times 10^{-4}$ to 1.865×10^{-2} M. The resulting equilibrium constant was equal to $K = 2.82 \pm 0.06$ and was about three times lower than the constant estimated for the reaction involving TBD base $K \cong 10$, $\varepsilon \cong 16{,}400\ dm^3\ mol^{-1}\ cm^{-1}$. The last has been evaluated from the reaction of TBD (1.5×10^{-3} M) and $(dmap)_2$ (4.92×10^{-5} M) without addition of $TBDH^+$ ion. The exact determination of the equilibrium constant has failed because the equilibrium experiment

where the [PiDBU] is the concentration of DBU picrate entered to the reaction system.

In turn, the expression for the equilibrium constant is:

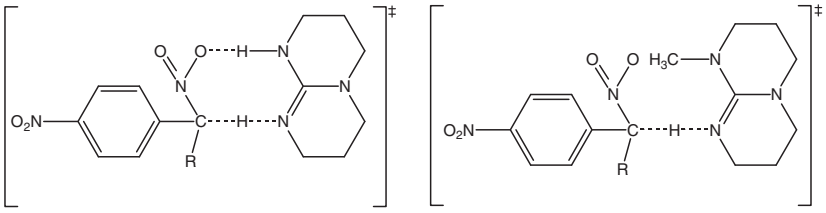
$$DBU + AH \Leftrightarrow DBUH^+ + A^-$$

$$K = \frac{[DBUH^+][A^-]}{[DBU][AH]}$$

Hence,

$$K^* = \frac{[PiDBU]}{[DBU](K_{HOMO}[DBU] + 1)} \frac{[A^-]}{[AH]}$$

Scheme 3.



Scheme 4. Structures of the transition state for the proton transfer between nitrophenyl nitroalkanes and TBD and MTBD bases in acetonitrile solvent.

with TBD base and $(dmap)_2$ in MeCN in the presence of guanidine salt took an unexpected course. During the spectrophotometric titration the mixture of a C-acid and a guanidine salt was titrated by a solution of a base at 25 °C as usual. For the relatively high equilibrium constant ($K = [A^-][BH^+]/[AH][B] \cong 10$) the concentration of the common salt, to ensure a 50 percent degree of a reaction $[A^-]/[AH] = 0.5$, must have been at least 20 times larger $[BH^+]/[B] = 20$ than the concentration of a base. For this purpose, we used a solution of picrate TBD [PiTBD] = 1.5×10^{-2} M while the base concentration was very low and varied from 3.696×10^{-4} to 5.972×10^{-2} M. In turn, the C-acid concentration was equal to 4.92×10^{-5} M. Surprisingly, we noticed that until the concentration of added base solution was twice lower than the concentration of a guanidine salt no band derived from the product of the reaction was present on a visible spectrum. Beyond the half concentration of the guanidine salt the absorbance of the product at 436 nm appeared. We presumed that the observed, broad, of low intensity absorption band, with a maximum about 70 nm less than for free nitronate ion (λ_{max} = 510 nm) belongs to the ion pair product ($[BH^+A^-]$). The effect of a shift to a shorter wavelengths with addition of a common ion is well known and was observed for other nitroalkanes measured in polar MeCN [26]. We noticed, that the absence of the absorption band till the half of the concentration of BH^+ was common for the reaction with addition of $TBDHClO_4$ as well. Furthermore, the change of a C-acid to (2-methyl-1-(4-nitrophenyl)-1-nitropropane) showed the same effect.

In such circumstances, we decided to conduct an analogous experiment with MTBD base using $MTBDHClO_4$ as a source of common cation and 2-methyl-1-(4-nitrophenyl)-1-nitropropane (5×10^{-5} M) as a proton donor. For this purpose we used very low concentration of the MTBD base, that is crucial in our opinion, ranged from 3.88×10^{-4} M to 2.592×10^{-2} M while the $[MTBDH^+]$ was equal 1.562×10^{-2} M. In this case the lack of the expected absorbance on UV–Vis spectrum until the half concentration of BH^+ was also recorded. Based on the experiments described above, we conclude that the lack of the reaction to the half concentration of $[BH^+]$ is not exclusive only for MTBD but also for TBD base. Furthermore, similar phenomenon is observed independently for chlorate and picrate salts and also when a different C-acid from nitroalkanes family is used. On this bases, we suspect, that at the very low concentration of a base in the presence of a common cation the ion pair of an unknown stoichiometry is formed (*e.g.* $B(BH^+)_2A_2^-$). Measurements made by ESI-MS did not confirm our conjecture. Unfortunately, we haven't managed to answer the question how the alleged ion pair looks like, so far. The query is still opened, very interesting and requires further study. In spite of all, the difficulties described above did not prevent determination of the $(dmap)_2$'s pK_a, what was the main purpose of that study, because in most cases listed in Table 1 there was no need to use base concentrations of less than 1×10^{-4} M.

Kinetics

The reactions of proton transfer in acetonitrile solvent between C-acids and amine bases give colored product that predominantly exists as free ions illustrated by Scheme 1. Due to the relatively low equilibrium constant of the reaction of DBU with $(dmap)_2$ in MeCN the discussed proton transfer reactions were carried out in the addition of well dissociated DBU picrate (PiDBU) by using it in the concentration of about 1×10^{-3} M. In all cases the conditions of the reactions lead to completion and the colored nitronate anion of λ_{max} = 510 nm was observed. The plots of k_{obs} *vs* base concentration were all good straight lines (Figs. 2 and 3 and Table 3). The equilibrium constant determined at 25 °C from kinetic measurements $K = k_2/k_{-1}\cdots[BH^+]f^2$ was equal 0.183 and was in a good agreement with the corresponding constant obtained in the equilibrium measurements described in this article.

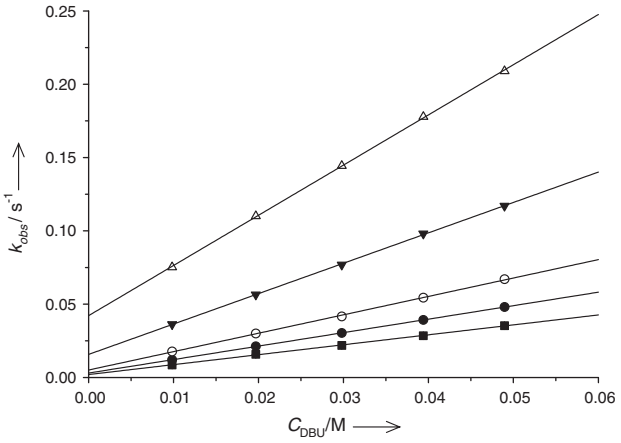


Fig. 2. The plot of pseudo-first order rate constants k_{obs} *vs.* c_{DBU} for the proton transfer reaction of 2,2-bis(4-dimethylaminophenyl)-1-nitro-1-(4-nitrophenyl)ethane with DBU in MeCN solvent at 15, 20, 25, 35 and 45 °C.

The rate constants and kinetic isotope effects are collected in Table 3. The second-order rate constants for the forward reaction

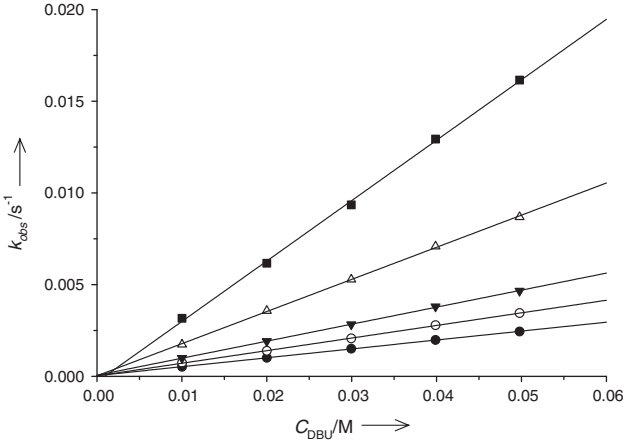


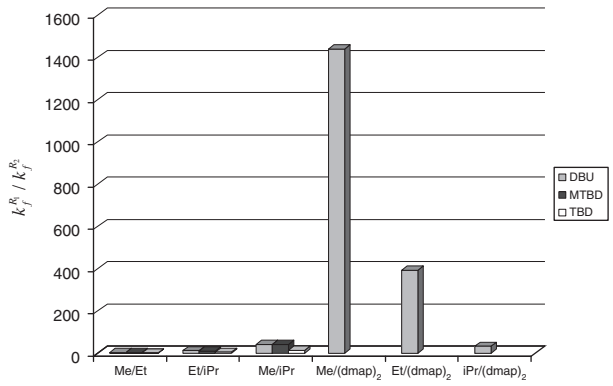
Fig. 3. The plot of pseudo-first order rate constants k_{obs} *vs.* c_{DBU} for the deuteron transfer reaction of 2,2-bis(4-dimethylaminophenyl)-1-nitro-1-(4-nitrophenyl)ethane with DBU in MeCN solvent at 15, 20, 25, 35 and 45 °C.

Table 3
Rate constants for proton and deuteron transfer reactions of 2,2-bis(4-dimethylaminophenyl)-1-nitro-1-(4-nitrophenyl)ethane with DBU base in MeCN solvent.

T (°C)	c_{DBU} (10^{-2} M)	k_{obs} (10^{-3} s^{-1})	k_f (10^{-3} M^{-1} s^{-1})	R^2	RESSD (10^{-4})	k_H/k_D
H						
15	0.983–4.90	8.490–35.33	680 ± 10	0.9991	3.62	
20	0.983–4.90	12.00–48.03	919 ± 3	0.9999	0.988	
25	0.983–4.90	17.71–67.03	1260 ± 20	0.9992	6.28	
35	0.983–4.90	36.25–117.0	2070 ± 20	0.9998	5.56	
45	0.983–4.90	75.18–209.0	3420 ± 30	0.9998	7.80	
D						
15	1.00–4.98	5.146–24.43	48.56 ± 0.04	0.9998	0.115	14.0 ± 0.3
20	1.00–4.98	7.286–34.45	68.73 ± 0.02	0.9997	0.207	13.4 ± 0.1
25	1.00–4.98	9.885–46.56	92.82 ± 0.06	0.9997	0.295	13.5 ± 0.3
35	1.00–4.98	17.35–86.85	175.25 ± 0.03	0.9996	0.658	11.8 ± 0.2
45	1.00–4.98	31.65–161.6	329.6 ± 0.3	0.9990	0.185	10.4 ± 0.2

Table 4
Kinetic isotope effects for the reaction of series of 1-(4-nitrophenyl)-1-nitroalkanes with DBU, TBD and MTBD in MeCN in 25 °C.

C-acid	$pK_{a\ (MeCN)}$	DBU ($pK_{a\ (MeCN)}$ = 24.34)		MTBD ($pK_{a\ (MeCN)}$ = 25.49)		TBD ($pK_{a\ (MeCN)}$ = 26.03)	
		k_H/k_D	k_f (M^{-1} s^{-1})	k_H/k_D	k_f (M^{-1} s^{-1})	k_H/k_D	k_f (M^{-1} s^{-1})
H	20.7	–	–	–	–	–	–
Me	23.2	12.1 ± 0.2[18]	1820[18]	12.5 ± 0.5[19]	317[19]	9.9 ± 0.5[19]	15,200[19]
Et	23.9	12.6 ± 0.3[18]	496[18]	10.8 ± 0.7[19]	86[19]	11.2 ± 0.4[19]	5300[19]
*i*Pr	25.9	13.0 ± 0.2[18]	43[18]	6.9 ± 0.6[19]	7.6[19]	12.6 ± 0.5[19]	1120[19]
$(dmap)_2$	25.11	13.5 ± 0.3	1.26	–	–	–	–



Scheme 5. The ratios of rate constants $k_f^{R_1}/k_f^{R_2}$ for the proton transfer reactions of 1-(4-nitrophenyl)-1-nitroalkanes with DBU, TBD and MTBD in MeCN in 25 °C.

k_f for protonated and deuterated compounds are listed in column 4 of the Table 3. The values of k_f's measured for the series of nitrophenyl nitroalkanes with increased steric hindrance with DBU and two guanidine bases TBD and MTBD are collected in Table 4.

In two cases (DBU and MTBD), there has been a decline of k_f in the order of magnitude with increasing steric hindrance of the reacting C-acid (Table 4). It is also noteworthy that the response of the steric hindrance in the C-acid on the reaction rate with DBU and MTBD bases is almost the same (Scheme 5) while the corresponding values for the TBD base outlier, specially when the small methyl substituent in the C-acid is changed into more bulky isopropyl. On the other hand, the introduction of $(dmap)_2$ to the vicinity of the reaction center results in the outstanding slowing down the reaction with DBU.

The influence of the type of substituents on the rates of C-acids ionization is closely associated with the durability of a carbanion being formed. In the case of a benzyl anion one should expect competing effects of two factors. Firstly, the tendency to adopt a pyramidal configuration with the maximum participation of orbital s in the distribution of the free electron pair, and secondly, the tendency to relocate the free electron pair that is possible but only in the case of a flat configuration of carbanions. It is well known that the electron pair delocalization causes a significant stabilization of this type of anions [35–37]. For example, replacement of hydrogen atoms with another phenyl group increases the acidity by 9, 13 and 15 pK_a units. This means that the triphenylmethyl anion is about 21 kcal mol^{-1} more stable ($RT \ln 10^{15}$) than the analogous methyl anion. Further substitutions of the hydrogen atoms reduce this effect. Therefore, the prerequisite of the optimal relocation is coplanarity of the system. The more phenyl groups, the harder it is to comply with the requirements. Consequently, triphenylmethyl anion has a geometry of propeller type and this is the result of a compromise between the factors countermeasure itself hyperconjugation and steric interactions.

On the other hand, if the carbon atom in the carbanion is in the immediate vicinity of π bond binding carbon atom with oxygen or nitrogen and the latter are more distant from the negative center, the carbanion can be more stable. Therefore, in such systems as enolate anions, α-nitrocarboanions, α-cyjanocarboanions it is expected that the largest negative charge density will be on oxygen or nitrogen atoms, due to their higher electro negativity. As a consequence, the pK_a values of this systems are generally much lower compared with CH_3NO_2, pK_a = 10.2; CH_3COCH_3, p*K*a = 20; $CH_3SO_2CH_3$, p*K*a = 23; CH_3CN, p*K*a = 25; CH_3CO_2Et, p*K*a = 25 [38].

The effect of alkyl substituents on the rate of exchange of α protons was discussed by Belanger and co-workers [39] for the proton exchange reactions of carboxylic acid salts in alkaline D_2O. They reported the kinetic data for a series of α-substituted (H, Me, Et, *i*Pr) sodium phenyl acetates. The authors stated that the presence of a methyl group near the center of the reaction reduced the rate of exchange by the factor of 270 in comparison with benzoic acid. In turn, an ethyl group reacts 2 300 times slower than phenyl acetate whereas with isopropyl group the exchange was 42,000 times slower. Belanger and co workers deem that observed decreases in the rates of exchange are caused by steric effects which hinder the formation of a carbanion in the rate determining step in two ways. Firstly, the presence of a bulky hydrophobic group precludes the approach of the base to the α-proton and decreases the stabilization of the carbanion by the solvent shell. Secondly, the severe

interaction between the bulky α-alkyl group and the ortho-hydrogens as the carbanionic character develops contributes the steric effects by destabilization of the carbanion preventing coplanarity with the ring thus hindering delocalization of the π electrons.

Bordwell and co workers studied the alkyl effects on equilibrium acidities of carbon acids in protic and dipolar aprotic media [40–43]. They examined the effect of hydrogen and alkyl groups in disubstituted nitroalkanes $R_1R_2CH_2NO_2$ in the series CH_3NO_2 (pK_a = 11.11; 17.20), $CH_3CH_2NO_2$ (pK_a = 9.63; 16.72), $(CH_3)_2CHNO_2$ (pK_a = 9.99; 17.01) on the equilibrium in two solvents: 50% MeOH–H_2O and DMSO, respectively. They stated that the second methyl effect is acidifying, but less so that the first. They assumed that the lesser effect was due to a saturation of the hyperconjugative effect, or to steric hindrance to solvation. Also the increasing size of the second substituent in RCH_2NO_2 led to acid weakening: $MeCH_2NO_2$ (pK_a = 9.63), iPrCH$_2$NO$_2$ (pK_a = 10.38) what was in a good agreement with the anticipated effect. However, surprisingly substitution of H for iPr in iPrCH$_2$NO$_2$ (pK_a = 10.38) caused also a slight acid-weakening effect, since the examination of a model of iPrC = NO_2^- did not indicate much interaction between the iPr groups but rather there is the severe crowding in iPrCHNO$_2$ (pK_a = 11.0) which is reduced by formation of the anion. In such a case one might have expected the steric effect to be acid-strengthening. The conclusion was that the steric hindrance to solvation in the anion could be the most likely cause for the acid-weakening effect observed.

In the field of our research, the effect of introduction of the phenyl group to the vicinity of the reaction center is also significant. From the above cited Bordwell data it can be seen that the substitution of an α hydrogen atom in CH_3NO_2 (pK_a = 17.20) by phenyl group PhCH$_2$NO$_2$ (pK_a = 12.20) results in acid-strengthening equal to ΔpK_a = 5 units in DMSO. What's more, the substitution of the para H in a phenyl group by NO_2 in PhCH$_2$NO$_2$ leads to a further increase in the acidity for the O_2NPhCH$_2$NO$_2$ ($pK_a \cong 8.2$ [29,44] (DMSO), 20.3 [29] (MeCN)) owing to the stabilizing effects present in a forming carbanion.

The influence of the alkyl substituents on equilibrium acidities of nitrophenyl nitroalkanes (O_2NPhCHRNO$_2$) can be easily trace in a series of nitrophenyl nitroalkanes along with the growing bulk of the R substituent. The rule of acidic properties decrease with increasing steric hindrance close to the reaction center is also fulfilled for the following C-acids (Table 3): R = H (pK_a = 20.7); Me (pK_a = 23.2); Et (pK_a = 23.9); iPr (pK_a = 25.9) [29]. It is noteworthy, that in these C-acid's series there are two abrupt changes of pK_as values, the first when going from small H atom to more bulky methyl group (ΔpK_a = 2.5) and the second when ethyl is substituted by isopropyl group (ΔpK_a = 2.0). The exchange of Me to Et weakens the acidity of only about 0.7 ΔpK_a. Moreover, as can be seen from our studies, introduction of potentially even greater steric hindrances near the reaction center, as it happens in the $(dmap)_2$ compound, the acidity changes only of about 0.77 ΔpK_a and in the direction of lower pK_a values. It indicates that the steric factors play an important role specially when the planarity of a carbanion and increased steric inhibition of all different structure of the complex of the transition state are concerned.

In our previous paper we proposed two different structures for the transition states and products for the proton transfer between some C-acids and TBD and MTBD bases in acetonitrile [19]. The proposed structures were also confirmed using computational methods by other authors [45]. It was shown that there is a distinct reaction mechanism which is caused by the mono and double-hydrogen bonded complexes of the transition states and products for the series of nitroalkanes and TBD and MTBD bases. We admit that the stabilization of the transition state by two hydrogen bonds (Scheme 4) is responsible for the significant acceleration of the proton transfer reaction for the TBD base [19]. In turn, the similarity of the ratio values of the rate constants (e.g. k_f^{Me}/k_f^{Et}) obtained for the reactions of MTBD and DBU arise from the similar structure of the active complex characterized by one hydrogen bond.

The stabilization of the TS of the TBD reaction by hydrogen bonding gives relatively good access to the C-acid even to the most crowded C-acid what accounts for the week sensitivity of these reactions to the steric hindrance Scheme 5.

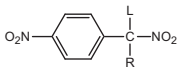
The different mechanism for reactions of DBU and MTBD is reflected in the values of activation parameters collected in Table 5. There are large negative activation entropies $\Delta S^{\ddagger}$ and the moderate activation enthalpies $\Delta H^{\ddagger}$ for all entries. It is well known that the large negative $\Delta S^{\ddagger}$ values are characteristic for bimolecular ionogenic proton transfer reactions and indicate a more structured than the reactants and of a considerable arranging transition state, TS. As shown in Table 5 in the case of the reaction with TBD the negative $\Delta S^{\ddagger}$ values are the same within the limits of experimental error for all C-acids, whereas in the reaction with DBU are increasing with increasing steric hindrance for Me, Et reaching the highest value for the C-acid with iPr substituent. Hydrogen bonds formed in a transition state [45] in the reaction with TBD make that TBD molecule has a relatively easy access to the C-acid even to the most crowded iPr. Actually, molecular models (Table 6) predict that there is not much steric hindrance for hydrogen bonding of TBD with all three acids. Furthermore, the steric hindrance in iPr forces the exocyclic nitro group into position suitable for hydrogen bonding. This accounts for the week sensitivity of TBD reactions to the steric hindrance in C-acids. With regard to the DBU base, lower $\Delta S^{\ddagger}$ values for more bulky substituents indicates more structured TS relative to the substrates, particularly in the case of iPr. However, the introduction of $(dmap)_2$ results in a decrease in the negative value of $\Delta S^{\ddagger}$ pointing to a worsening of conditions for the arranging the active complex.

Analysis of the $\Delta H^{\ddagger}$ shows the same values within the experimental error for the reaction with TBD and MTBD (for Me and Et) and increasing trend along with steric hindrance in the reaction with DBU. Wherein in $(dmap)_2$ and DBU reaction nearly twofold increase of $\Delta H^{\ddagger}$ was observed compared to iPr. A weak dependence of $\Delta H^{\ddagger}$ on the size of the substituent provides almost equal proton transfer distance in reactions of Me, Et and iPr with DBU and TBD and Me, Et with MTBD. This suggests that the proton transfer distance is primarily determined by the interactions along the axis of the linear activated complex, and not by the size of the substituent. The steric hindrance is than evident for the reaction of iPr and $(dmap)_2$ with DBU and iPr and MTBD base, while in other cases the increase in the bulk of the alkyl substituent enforces some sterical restraints but repulsive interactions can be avoided (Scheme 5, Table 5) [20].

The simultaneous increase of enthalpy of activation $\Delta H^{\ddagger}$ and negative values of entropy of activation $\Delta S^{\ddagger}$ along with increasing steric hindrance of the reacting molecules cause a rise in Gibbs energy $\Delta G^{\ddagger}$. The absence of the compensating effect entails that the changes of $\Delta S^{\ddagger}$ are determined by restriction of the free motion within the active complex rather than desolvation of the transition state. The level and trend of changes in Gibbs energy $\Delta G^{\ddagger}$ along with increasing steric hindrance is of the same order of magnitude as previously found by other authors [3,18,45–47] regardless of whether crowding into the reaction center was introduced by the reacting base or is caused by alkyl group present in the C-acid molecule. The overall value of the Gibbs energy is therefore the result of the considerable steric effects as well as the solvation effects taking place in the reaction way.

As it is known, some nitrophenyl nitroalkanes (Table 6) may exist in form of various conformers characterized by unequal accessibility to the reaction center of the base molecule. We showed in our previous papers [19,20], that for the nitophenyl nitromethane substituted by iPr group the most stable conformer

Table 5
Activation parameters and kinetic isotope effects for proton and deuteron transfer reactions between DBU [18], MTBD [19] and TBD [19] bases and 1-(4-nitrophenyl)-1-nitroalkanes in MeCN solvent



; R = Me; Et; *i*Pr; $(dmap)_2$-(2,2-bis(4-dimethylaminophenyl)); L = H, D.

R	DBU				
	$\Delta H^{\ddagger}$ (kJ mol^{-1})	$\Delta S^{\ddagger}$ (J mol^{-1}K^{-1})	$\Delta H^{\ddagger}_D - \Delta H^{\ddagger}_H$ (kJ mol^{-1})	$\Delta G^{\ddagger}$ (kJ mol^{-1})	$\Delta G^{\ddagger}_{iPr} - \Delta G^{\ddagger}_{Me}$ (kJ mol^{-1})
L = *H*					
Me	15.4 ± 0.6	−131.0 ± 2.0		55 ± 2	
Et	17.8 ± 0.7	−134.0 ± 2.0		58 ± 2	
*i*Pr	19.9 ± 0.5	−147.0 ± 2.0		64 ± 2	9.3
$(dmap)_2$	38.4 ± 0.6	−114.0 ± 2.0		72 ± 2	
L = *D*					
Me	22.4 ± 0.6	−128.0 ± 2.0	7.0 ± 0.8	61 ± 2	
Et	25.2 ± 0.5	−130.0 ± 2.0	7.4 ± 0.9	64 ± 2	
*i*Pr	27.5 ± 0.2	−142.8 ± 0.5	7.6 ± 0.5	70 ± 1	9.3
$(dmap)_2$	45.9 ± 0.6	−111.0 ± 2.0	7.5 ± 0.8	79 ± 2	
	MTBD				
L = *H*					
Me	25.1 ± 1.6	−113.0 ± 5.5		58.8 ± 5.5	
Et	22.1 ± 1.0	−133.9 ± 3.6		62.0 ± 3.6	
*i*Pr	33.2 ± 1.0	−117.0 ± 3.2		68.1 ± 3.2	9.3
L = *D*					
Me	33.3 ± 2.0	−106.4 ± 10.1	8.2 ± 2.6	65.0 ± 10.1	
Et	28.8 ± 1.4	−131.1 ± ± 4.6	6.7 ± 1.7	67.9 ± 4.6	
*i*Pr	40.5 ± 3.6	−109.1 ± 12.3	7.3 ± 3.7	73.0 ± 12.3	8.0
	TBD				
L = *H*					
Me	17.2 ± 1.9	−107.4 ± 6.5		49.2 ± 6.5	
Et	20.2 ± 1.7	−106.1 ± 5.8		51.8 ± 5.8	
*i*Pr	19.4 ± 3.0	−121.5 ± 10.3		55.6 ± 10.3	6.4
L = *D*					
Me	22.1 ± 2.2	−109.4 ± 7.3	4.9 ± 2.9	54.7 ± 7.3	
Et	27.0 ± 1.2	−103.3 ± 4.1	6.8 ± 2.1	57.8 ± 4.1	
*i*Pr	30.7 ± 1.6	−104.8 ± 5.3	11.3 ± 3.4	61.9 ± 5.3	7.2

is the one with antiperiplanar position of hydrogen atoms. This is confirmed by both the H–H coupling constant J_{H-H} found in NMR spectrum and the heat of formation calculated using PM6 geometry and Hartree–Fock method, density functional theory (DFT) at the B3LYP/6-31G(d,p) level of theory (Table 6).

In the case of $(dmap)_2$ the situation seems to be similar. The computational studies showed that there are three possible conformers of $(dmap)_2$ obtained by rotation of $-CH_2(dmap)_2$ group (Table 6). The most stable conformer is the conformer A depicted in Scheme 5 whose heat of formation shows distinctive stability confirmed by the H–H coupling constant J_{H-H} found in NMR spectrum.

It is worth noting that we failed to optimize the structure of conformer D (Table 6). Initially we assumed, that the arrangement of substituents in the conformer D seemed to create good conditions for the approximation of the base. It turned out, however, that sterical restraints not allow the existence of this structure.

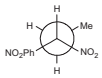
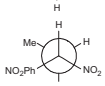
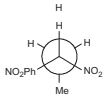
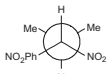
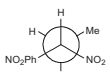
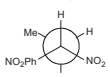
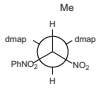
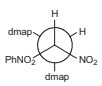
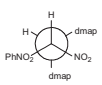
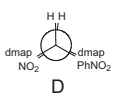
In our previous paper [19] we have shown that there is a direct relationship between the value of dihedral angle HCNO (Scheme 4) in the TS complex and the rate of proton transfer reaction when TBD base is considered. We stated that along with growing bulk of substituent R in the C-acid, a decrease in HCNO angle is found, which in practice means that the exocyclic nitro group is coplanar with the proton transfer axis. This arrangement of the nitro group favors the formation of the double hydrogen bonded cyclic structure in the TS (Scheme 4). The detailed analysis of the HCNO angles (Table 6) showed that for almost all of C-acids the most stable conformers is the one with the most coplanar NO_2 with proton transfer axis. However, in the case of $(dmap)_2$ this rule was not confirmed. The low-energy conformer A is characterized by a small but not the smallest HCNO angle. We also noticed that both dmap groups are pointed toward the approaching base molecule hindering its access to the reaction center more than it did in the case of conformer C and C-acid substituted by isopropyl group. The conformer C, in turn is characterized by more coplanar NO_2 group with proton transfer axis and additionally only the *ortho*-hydrogen atom of the nitrophenyl ring is directed to the approaching base. Thus, due to steric reasons conformer C seems to be most advantageous for the proton exchange reaction.

It is also worth comparing the values of $\Delta_f H$ for anions (Table 6). The values for C-acids: H, Me, Et, and *i*Pr varied from −256.274 to −306.725 kJ mol^{-1}, respectively. Generally, the larger the substituent the lower the heat of formation and the more stable C-acid. In the case of $(dmap)_2$ the $\Delta_f H$ energy is many times higher (−19.05 kJ mol^{-1}) but the change of $\Delta\Delta_f H$ in the transition from the neutral, most stable C-acid to an anion is in the trend for the rest of the C-acids and is equal about 263.31 kJ mol^{-1}, while for the remaining compounds is equal to 294.36, 275.46, 278.45 and 271.86 kJ mol^{-1}, respectively.

The results of the computational study indicate that $(dmap)_2$ is the compound of the highest energy, and a benefit resulting from the creation of anion is the smallest in this group of compounds. It can be concluded that the steric hindrance is responsible for a significant slowdown of the proton transfer reaction between DBU and $(dmap)_2$ described in this project.

The effect of steric hindrance on the value of the kinetic isotope effect is consistent with our earlier observations. In previous

Table 6
Electronic energies, Hartree and heats of formation, $\Delta_f H$ of nitrophenyl nitroalkanes and their anions calculated using PM6 and DFT methods.

R	Conformation of a C-acid	$\Delta_f H$ (kJ mol^{-1}) (PM6)		Hartree (a.u.) (DFT)	HCNO (°) (PM6)	δ_H (ppm)	J_{H-H} (Hz)
		C-acid	Anion	C-acid			
H	–	38.087	−256.274	−680.56943379	–	–	–
Me	–	11.773	−263.685	−719.89007443	6.4	5.73 (90 MHz) [4] 1H, q, $CHNO_2$	6.95 (90 MHz) [4]
Et		−7.465	−285.917	−759.20643162	6.2	5.49 (90 MHz) [4] 1H, m, $CHNO_2$	–
		−7.427 (0.038)[a]		−759.20643221 (6×10^{-7})[b]	9.0		
		−1.474 (5.991)[a]		−759.20331104 (3.1206×10^{-3})[b]	9.4		
*i*Pr		−34.863	−306.725	−798.52339642	4.3	5.18 (90 MHz) [4] 1H, d, $CHNO_2$	10.94 (90 MHz) [4]
		−33.059 (1.804)[a]		−798.52024818 (3.1483×10^{-3})[b]	3.6		
		−30.417 (4.446)[a]		−798.51989942 (3.497×10^{-3})[b]	3.4		
$(dmap)_2$	 A	244.258	−19.050	−1449.94491375	9.0	6.26 (300 MHz) 1H, d, $CHNO_2$	12.09 (300 MHz)
	 B	255.813 (11.255)[a]		−1449.94075059 (4.163)[b]	60.8		
	 C	256.400 (12.142)[a]		−1449.93880404 (6.109)[b]	1.7		
	 D	Minimum not found		Minimum not found	–		

[a] The energy difference relatively to the most stable conformer (kJ mol^{-1}).
[b] The energy difference relatively to the most stable conformer (a.u.).

papers, we noticed that the KIE values increase when the TS is less product-like (Scheme 5). In the case of $(dmap)_2$ we found the KIE value similar to that obtained for the C-acid substituted by *i*Pr (KIE = 13.5 ± 0.3) in the reaction with DBU (Tables 3 and 4, Scheme 6). The assumption is that bulky dimethylaminophenyl substituents affects the distance along the axis of the linear reaction complex ($\Delta H^{\ddagger}$ is doubled relative to the value obtained for *i*Pr) and this is the main result of steric hindrance present in $(dmap)_2$. It is different if compared with the series of C-acids with Me, Et, *i*Pr substituent, where the $\Delta H^{\ddagger}$ can be considered as almost identical and tends to indicate rather equal proton transfer distance for all compounds. As far as $\Delta S^{\ddagger}$ is concerned the obtained highest value for $(dmap)_2$ indicates an important role of steric effects in the difficulties of stabilization of the active complex. It is consistent with the rather high KIE value which is greatly influenced by the factor resulting from the structure of the transition state formed with hydrogen bond between a base and oxygen atom of nitro group of reacting C-acid and it shows weak similarity of the active complex to the product. It can therefore be concluded that the KIE has a direct relationship with the structure of the TS and increase when its structure is described by a larger level of energy.

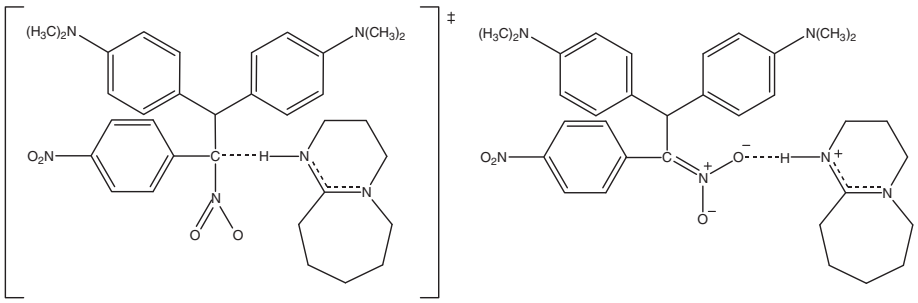
Experimental section

Acetonitrile (MeCN)

The commercial acetonitrile anhydrous, 99.9%, inhibitor free, purchased from Aldrich, was used. The solvent was handled under positive pressure of argon.

2,2-Bis(4-dimethylaminophenyl)-1-nitro-1-(4-nitrophenyl)ethane, $(dmap)_2$

2,2-Bis(4-dimethylaminophenyl)-1-nitro-1-(4-nitrophenyl)ethane, $(dmap)_2$ was obtained in the three step procedure. First, the Michler's Hydrol Blue (MHB) was obtained by reduction of commercial Michler's Ketone (MK) according to procedure previously described [48]. Then, the MHB was transformed into its benzhydrylium salt. To this end, 1.88 g (7 mmol) MH was dissolved in 40 mL of anhydrous THF and 0.95 mL (7 mmol) $HBF_4 \times OEt_2$ was added. A dark blue precipitate appeared and 10 mL of pentane was added to the reaction mixture. The precipitate was filtered



Scheme 6. Structures of the transition state and the product for the proton transfer between $(dmap)_2$ and DBU base in acetonitrile solvent.

under reduced pressure. It was washed twice with pentane and then with one portion of diethyl ether. The product was next dried over P_2O_5 in desiccator under reduced pressure. The crude product (97.6% yield) was used to the next step without further purification. The reaction of nitroalkyl anions with benzhydrylium salts in water was carried out according to the procedure of Bug et al. [49]. 2,2-Bis(4-dimethylaminophenyl)-1-nitro-1-(4-nitrophenyl)ethane was obtained as a light orange precipitate [50] in 26.4% yield after recrystallization from MeCN. The ^1H NMR spectrum and the melting point were in accordance to the literature data [49]. The purified orange product dissolved in MeCN gave green solutions due to a week absorption band at 604 nm.

Nitrophenyl nitroalkanes

Nitrophenyl nitroalkanes and its deuterated analogues were prepared according to the procedures already published [4].

1,8-Diazabicyclo[5.4.0]undec-7-ene, (DBU)

The commercial product of DBU purchased from Aldrich, was dried over potassium hydroxide pellets and then fractionally distilled under reduced pressure. The middle fraction was collected and used. The base was protected against moisture and CO_2 with argon and stored in desiccator over potassium hydroxide pellets.

7-Methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene, (MTBD)

A commercial product of MTBD from Aldrich was used without further purification.

Kinetic measurements

Kinetic measurements of proton transfer reactions were performed with a stopped-flow spectrophotometer (Applied Photophysics), while deuteron transfer reaction were followed using a HP 8452A diode-array spectrophotometer fitted with thermo stated cell at λ_{max} of the product. In order to ensure the adequacy of stopped-flow and diode-array techniques, the slowest of the proton transfer reaction studied (15 °C, [DBU] = 1×10^{-2} M, 1000 s) was performed both using stopped-flow and diode-array spectrophotometer. Measurements were repeated three times and there were no differences in the observed reaction rate constants. The solutions of base were prepared directly before measurements and its concentrations varied from ca. 1×10^{-2} to 0.1 M. The concentration of C-acid was from 2 to 3.5×10^{-5} M. The concentration of picrate 1×10^{-4} M.

Computationals details

The calculations were carried out using Gaussian 03 suite of programs [51]. In particular, we study the semiempirical PM6 method; density functional theory (DFT) approach B3LYP. The standard 6-31G(d,p) basis sets were used.

Conclusions

The present work is motivated by the important role that the steric effects play in proton transfer reactions. The current study provides the experimental data, which reports how the expansion of the alkyl substituent present in the molecule in either the C-acid and an organic base influence the kinetic of the proton transfer reaction.

In this paper the pK_a value of 2,2-bis(4-dimethylaminophenyl)-1-nitro-1-(4-nitrophenyl)ethane $(dmap)_2$ in polar aprotic solvent, acetonitrile has been determined and presented.

We have chosen to study $(dmap)_2$ as representative of nitrophenyl nitroalkanes characterized by the bulky group near the reaction center. The observed effects allow us to say that the effects of alkyl groups in the tested reactions do not cause the increase of the KIE with the expansion of the substituent but mainly amount to reduce the molecular orientation favoring the reaction of the C-acid and the DBU, reducing the freedom of movement and the transition state desolvation. Furthermore, as the proton transfer distance is concerned it is independent of the size of the alkyl group in the reaction with TBD and MTBD base with each of the C-acid discussed in this paper, but for the reaction with DBU base and $(dmap)_2$ the distance increase which is reflected in the relatively large negative value of $\Delta H^{\ddagger}$, and low negative value of $\Delta S^{\ddagger}$. The reaction studied proceeds via the polar transition state characterizing much less charge separation than the reaction product.

The outcome of this paper concerns the structure of the most stable conformer of $(dmap)_2$ and its participation in the examined proton transfer reaction. The kinetic, as well as the NMR study, calculations using the PM6 geometry as well as DFT method allow us to conclude that the $(dmap)_2$ conformer involved in the tested reaction with DBU is the one with periplanar arrangement of the hydrogen atoms.

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