A Study on the Activation of Carboxylic Acids by Means of 2-Chloro-4,6-dimethoxy-1,3,5-triazine and 2-Chloro-4,6-diphenoxy-1,3,5-triazine

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Received November 4, 1997

Activation of carboxylic function by means of 2-chloro-4,6-disubstituted-1,3,5-triazines **1** and **2** leading to triazine esters was found to be a multistep process with participation of quarternary triazinylammonium salts **3**−**6** as the intermediates, with the rate of reaction strongly dependent on the structure of the tertiary amine. The studies on alkylation of tertiary amines with CDMT revealed the two-step process $A_N + D_N$, and zwitterionic addition product **9** was identified by ^{1}H NMR spectroscopy. Semiempirical modeling of the reaction as well as measured nitrogen and chlorine isotope effects also support this mechanism.

Introduction

The efficiency of 2-chloro-4,6-disubstituted-1,3,5-triazines in formation of the peptide bond,[1] especially between sterically hindered substrates,[2] prompted us to undertake a systematic study on the reaction of chloro-*s*-triazines with carboxylic acids. The previous investigations documented the role of 2-acyloxy-4,6-disubstituted-1,3,5-triazines[3] as powerful acylating intermediates due to the fact that they contain an excellent leaving group strongly inclined for acyl-transfer reaction facilitated by intramolecular catalysis involving nitrogen atoms of triazine ring (triazine "superactive esters").[4] However, the details of the activation step leading from the carboxylic acid to 2-(acyloxy)-4,6-disubstituted-1,3,5-triazines, which results in the substitution of the chlorine atom in the triazine ring by a carboxylic group, remain unknown.

Our preliminary observations have shown that the successful activation of carboxylic acids by means of 2-chloro-4,6-disubstituted-1,3,5-triazines requires the presence of a tertiary amine in the reacting medium. Thus, the sodium, silver, or quaternary ammonium salts of carboxylic acids, otherwise considered as good sources of carboxylate anion, do not react with 2-chloro-4,6-disubstituted-1,3,5-triazines at all, or else react extremely slowly.[3] We concluded, therefore, that the reaction proceeds with the participation of an intermediate, formed in the first step, involving amine as the obligatory component. Just recently, we further confirmed this mechanism in the process of activation of a carboxylic group achieving highly enantioselective activation of racemic carboxylic acids in the presence of chiral amines.[5] These new, strongly stereodifferentiating effects of amines acting as a chiral auxiliary prompted us to study all stages of activation of the carboxylic function in the process involving the substitution of chlorine in the triazine ring with carboxylate anion.

Results and Discussion

Generally, we found that the reaction of amine with chloro-*s*-triazine could be considered as erratic because only a few of all tertiary amines respond to treatment with chloro-*s*-triazines. Moreover, the borderline between reactive amines (pK_a in aqueous solutions at 25 °C are presented in brackets) *N*,*N*,*N*′,*N*′-tetramethylguanidine (TMG)[6] [13.6], *N*-methylpiperidine[7] [10.13], trimethylamine[8] [9.81], 4-(*N*,*N*-dimethylamino)pyridine (DMAP)[9] [9.61], *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA)[10] [8.1], *N*-methylmorpholine (NMM)[11] [7,42], 4-picoline[9] [6.25], pyridine [5.19[12]], and inactive amines: triethylamine[13] [10.87], tributylamine[14] [10.63], *N*-ethylmorpholine[15] [7.8], *N*,*N*-diethylaniline[14] [6.61.], and *N*,*N*-dimethylaniline[14] [5.06] does not correlate with the basicity of amines in polar solvents.

It has been found that all amines involved in activation of the carboxylic function are prone to the formation of

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S0022-3263(97)02020-3 CCC: $15.00
Published on Web 06/05/1998

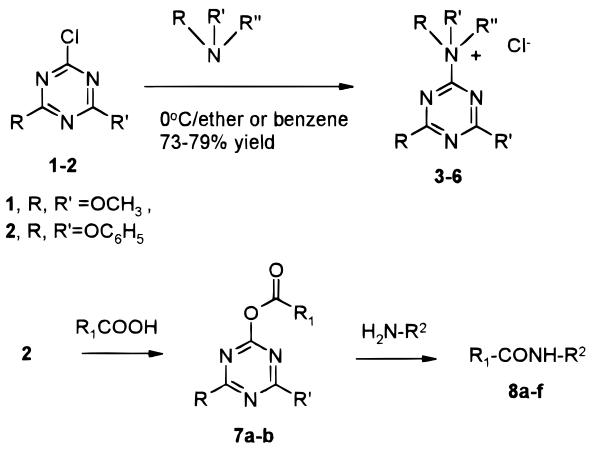
Table 1. Synthesis of Quaternary Ammonium Salts of 2-Chloro-4,6-disubstituted-1,3,5-triazines 3−6

	amine	triazine	formula	yield (%)	C, found (calcd)	H, found (calcd)	N, found (calcd)
2	NMM	CDMT	$C_{10}H_{17}N_4O_3Cl$ (276.72)	79	43.18 (43.40)	6.20 (6.19)	20.46 (20.45)
3	NMM	CDPT	$C_{20}H_{21}N_4O_3Cl$ (400.87)	62	59.85 (59.93)	5.30 (5.28)	13.98 (13.98)
4	TMG	CDMT	$C_{10}H_{19}N_6O_2Cl$ (290.75)	83.5	41.08 (41.31)	6.87 (6.59)	28.12 (28.90)
5	TMG	CDPT	$C_{20}H_{23}N_6O_2Cl$ (414.90)	35	57.63 (57.90)	5.80 (5.59)	18.62 (20.26)

Table 2. Activation of Carboxylic Acids by Means of 3

	triazine	product	yield (%)	mp (°C)	lit. mp (°C)
7a	CDMT*NMM	$(CH_3)_3CCOODMT$	44	47−49	50−52[3]
7b	CDMT*NMM	p-$O_2NC_6H_4COODMT$	92	118−120	122−24[3]
8a	CDMT*NMM	CH_3CONHc-C_6H_{11}	17	102−104	102−103[26]
8b	CDMT*NMM	C_6H_5CONHc-C_6H_{11}	47	144−146	144−146[27]
8c	CDMT*NMM	m-ClC_6H_4CONHc-C_6H_{11}	58	145−147	121[28]
8d	CDMT*NMM	o-$O_2NC_6H_4CONHc$-C_6H_{11}	73	147−149	151−2[29]
8e	CDMT*NMM	m-ClC_6H_4CONH-C_6H_5	63	125−127	121[28]
8f	CDMT*NMM	o-$O_2NC_6H_4CONH$-C_6H_5	67	149−150	151−152
8g	CDMT + TEA	$C_6H_5CONHC_6H_5$	0		163[30]

Scheme 1



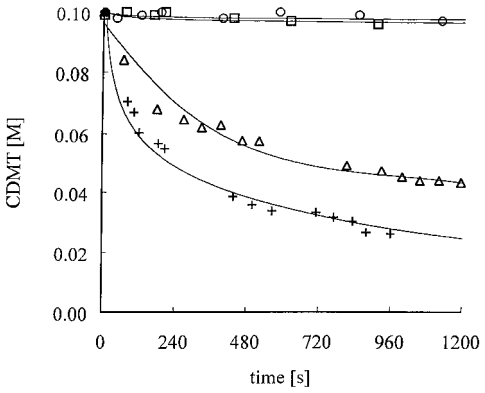


Figure 1. Rate of activation of trimethylacetic acid in acetonitrile-d_3 solution by means of **1** relative to the structure of the tertiary amine: for *N*-methylomorpholine (− + − + −); *N*,*N*′-tetramethylethylenediamine (−Δ−Δ−); triethylamine (−○−○−); *N*,*N*-dimethylaniline (−□−□−).

intermediate products **3**−**6** when treated with chlorotriazine. In most cases, isolated intermediates decompose rapidly at room temperature, but derivatives of *N*-methylmorpholine and tetramethylguanidine were found to be sufficiently stable to be studied by spectroscopic methods and elemental analysis (Table 1).

On the basis of spectroscopic data and elemental analysis, structures of quaternary morpholinium salts **3** and **4** and appropriate guanidinium salts **5** and **6** have been determined (Scheme 1).

The participation of morpholinium salt **3** in the activation step was confirmed by the synthesis of 2-(acyloxy)-4,6-dimethoxy-1,3,5-triazines **7a**,**b** and amides **8a**−**f**, directly from **3**, under conditions typical for the activation of carboxylic acids by means of CDMT (see Table 2). In all experiments, we found noticeably lower yields as compared to the standard procedure involving CDMT,[16] which is probably due to the prolonged activation procedure caused by the poor solubility of **3** and the formation of appropriate carboxylic acid anhydrides as byproducts during the reaction course.

In our further experiments, we attempted to study the ability of amines to activate carboxylic acids by means of CDMT (see Figure 1). The rate measurements of activation of trimethylacetic acid and benzoic acid by means of 2-chloro-4,6-dimethoxy-1,3,5-triazine (**1**) revealed that the ability of tertiary amines to promote the activation of carboxylic dramatically decreased with the increase of steric hindrance of amine substituents. Thus, triethylamine, which did not form a quarternary ammonium salt in the reaction with CDMT, was entirely incapable of activating benzoic acid (compare Table 3, last entry and Figure 1).

Moreover, the addition of a tertiary amine, which otherwise is inactive toward CDMT, has a negligible influence on the rate of activation of carboxylic acids. Thus, the presence of *N*,*N*-dimethylaniline, added in amounts equal or even exceeding the amounts of NMM, does not influence the reaction rate (as evidenced by entries 4−6 in Table 3).

The Structure of Morpholinium Salt 3. Morpholinium salt **3** can exist as a mixture of conformers with triazine ring in axial **3a** or in an equatorial position **3e**.

Attempts to establish the preferred conformation of substituents in the morpholine ring were performed by means of ^1H and ^{13}C NMR spectroscopy. For all solvents, only a single set of signals of *N*-methyl, $-CH_2O$, and $-CH_2N$ groups, respectively, was observed (Table 4). Also, the low-temperature experiments revealed no splitting of the above-mentioned signals upon lowering the temperature from 25 to −55 °C. Thus, taking into consideration the separation of the methylene hydrogen signals in the less substituted, and therefore probably more flexible, ring of NMM observed below −25 °C, we postulate that **3** is characterized by the presence of one dominant conformer rather than a fast equilibrating mixture of conformers in the chloroform solution.

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Table 3. Rate Constants of Activation of 2,2-Dimethylpropionic Acid by Means of 1 in Acetonitrile-d_3 in the Presence of Tertiary Amines

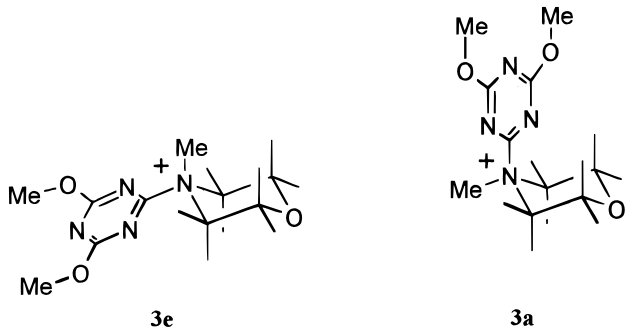
	C_{PivA}[a] (M)	C_{CDMT} (M)	C_{NMM} (M)	$C_{additive}$ (M)	T (K)	$k^{III} \pm \Delta k$ (M^{-2} s^{-1})
1	0.1	0.1	0.1		299.5	0.333 ± 0.038
2	0.1	0.1	0.1		305	0.663 ± 0.073
3	0.05	0.05	0.05		310	0.972 ± 0.13
4	0.05	0.05	0.05		303.5	0.723 ± 0.046
5	0.05	0.05	0.05	DMA; 0.05	303.5	0.740 ± 0.043
6	0.05	0.05	0.05	DMA; 0.10	303.5	0.621 ± 0.045
7	0.1	0.1		TMEDA; 0.1	303.5	0.185 ± 0.013

[a] 2,2-Dimethylpropionic acid.

Table 4. ^{1}H and ^{13}C NMR (δ) Data of 3

solvent	NCH_3	NCH_2CH_2O	OCH_3	triazine
^{1}H NMR, ($CDCl_3$)	3.02	3.71 (d, 2H, J = 4.4 Hz); 3.76(t, 2H, J = 3.4 Hz), 3.85 (t, 2H, J = 3.3 Hz), 3.87 (d, 2H, J = 4.4 Hz)	3.95	
^{1}H NMR (DMSO-d_6)	3.03	3.60 (bt, J = 4.5 Hz), 3.70 (bt, J = 4.5 Hz)	3.81	
^{13}C NMR (DMSO-d_6)	27.03	44.43, 66.63	54.98	167.10, 172.77

Chart 1



3e **3a**

The rigid conformation, however, should yield a 0.5−1.0 ppm downfield chemical shift of axial compared to equatorial hydrogens. Such a differentiation of chemical shift of axial and equatorial hydrogens was observed in the case of NMM[17,18] for both NCH_2− and OCH_2− at −45 °C and for NCH_2-hydrogens in the more rigid *N*-methyl-*N*-phenylpiperidinium iodide at room temperature.[19] No such differentiation was observed for the chemical shifts of axial and equatorial signals of **3**. We believe that this can be explained by the deshielding effect of triazine in the axial position **3a** (see Chart 1), but further studies on the conformation of morpholinium salts[20] are required.

Mechanism of Quaternization of *N*-Methylmorpholine. The established relation between the structure of amine and its ability to react with 2-chloro-4,6-disubstituted-1,3,5-triazines leads to discussion of the mechanism of activation of a carboxylic group by means of triazine condensing reagents. Without a doubt, the crucial stage comprises the two subsequent substitution reactions in the triazine ring. The first one, which involves substitution of the chlorine atom by amine leading to quarternal ammonium salt, has been found to be extremely sensitive to steric hindrance of amine substituents. The second reaction, which is exceptionally tolerant to the steric hindrance of activated carboxylic acid, involves substitution of the amine leaving group by the carboxylate ion, affording triazine "superactive esters".

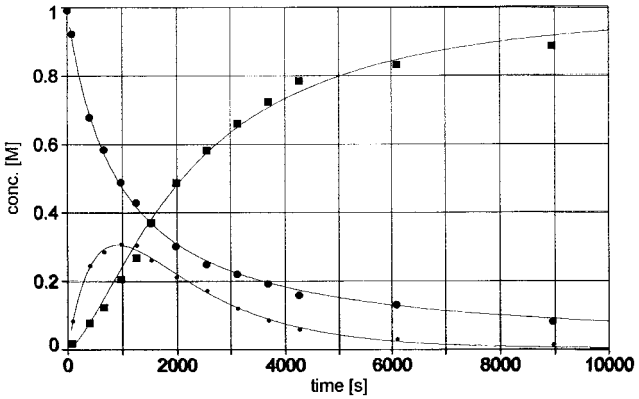


Figure 2. Reaction of NMM with **1** in acetonitrile-d_6 solution at −5 °C (●−●−●, substrate **1**; ■−■−■, final product **3**; ●−●−●, intermediate **9**).

Even taking into account the increase of steric repulsion accompanying the quaternization of the nitrogen atom and increased repulsion caused by the hybridization change from sp^2 to sp^3 on the carbon atom of the triazine ring and the decrease of hindrance in the reverse hybridization change, the strong dependence during the first stage on steric hindrance suggests a sterically crowded transition state. Thus, we excluded the participation of the triazine carbonium ion as highly improbable. Instead we considered two possibilities; the synchronous, S_N2-like mechanism, postulated by Williams for the triazine (a) and the classic stepwise S_NAr mechanism involving two separate stages of addition−elimination (b).

Examination of the mixture of compounds yielded by the reaction of CDMT with NMM in a chloroform solution revealed the presence of the intermediate product excluding synchronous mechanism of substitution a and strongly suggests the participation of classic addition−elimination mechanism b. The characteristic pattern of the plot of the intermediate concentration vs time (Figure 2) further confirms the presence of an intermediate in the two subsequent reaction steps.

At low temperature, it was possible to cumulate the intermediate product **9** in the reacting mixture to reach over 50% of the concentration of the starting reactant, but all attempts to isolate it were unsuccessful because

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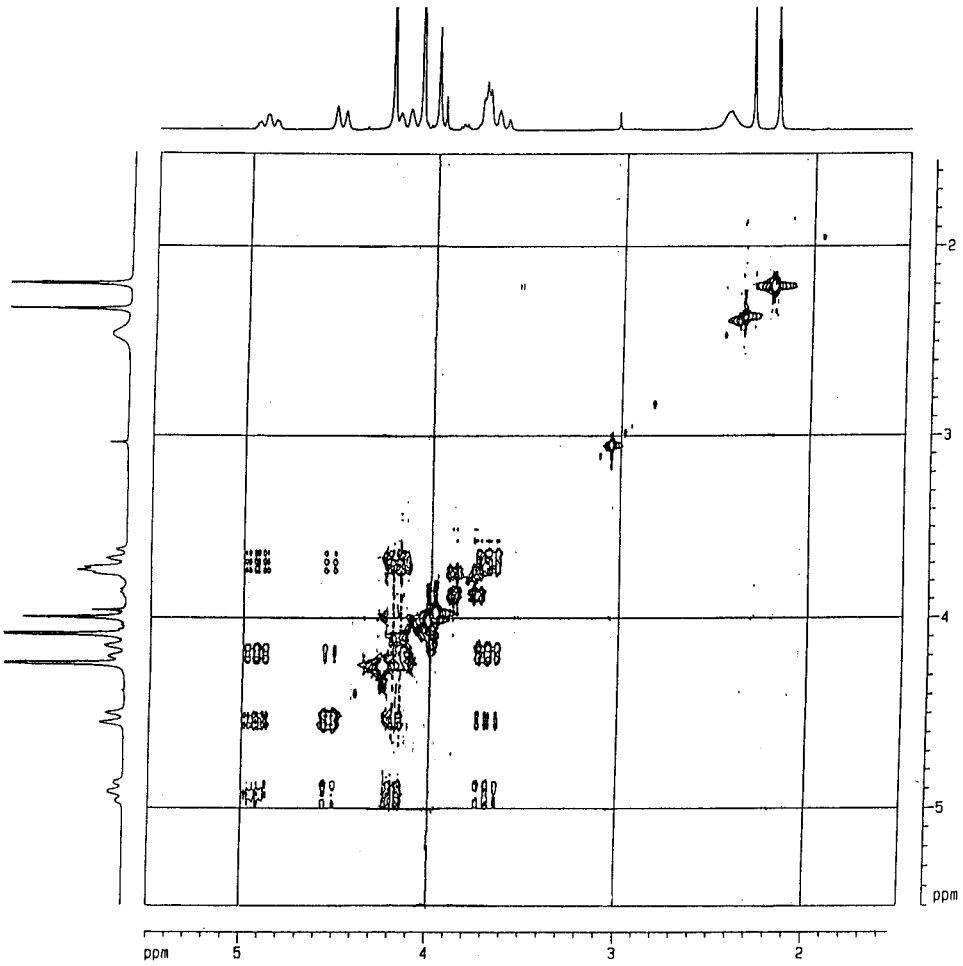


Figure 3. COSY spectrum of the reaction mixture of **1** with NMM. The intermediate **9** cumulated to about 50%. Temperature −45 °C.

of its rapid decomposition to **3** at temperatures exceeding 5 °C. Besides COSY experiments (Figure 3), unequivocal interpretation of the spectrum has been confirmed by low-temperature experiments (Figure 4). These show a multiplet of methylene group at temperatures −30 to −50 °C that at room temperature is covered by signals of substrates and **3**. The resultant spectrum of intermediate **9** was characteristic for the symmetrically substituted morpholine ring; two proton doublet of triplets at 4.90 ppm, J = 12, 2 Hz; doublet at 4.54 ppm, J = 12 Hz; doublet of doublets at 4.20 ppm, J = 12, 2 Hz, and broad triplet at 3.72 ppm, J = 12 Hz; singlet at 4.25 ppm (OCH_3); and singlet at 4.03 ppm NCH_3 (see Table 5).

We were able to demonstrate in an experiment involving exchange of 4,6-dimethoxy-1,3,5-triazine ring in **9** with CDMT-d_6 deuterated in both methyl groups that the addition of *N*-methylmorpholine to CDMT is partially reversible. When a mixture containing 21% of unreacted CDMT and 51% of intermediate **9** was treated with a 5-fold excess of CDMT-d_6 and allowed to completely transform to **3**, about 29% of CDMT remained unreacted (if the addition step was irreversible 19% of unreacted CDMT should be expected). Moreover, the signal ratio of CH_3O/CH_3N protons in the final product changed from 2:1 observed for unlabeled compound to 1.7:1. Since the difference in the ratios is beyond the error in the NMR measurements, this proves the exchange of triazine ring in **3** and the reversibility of the addition stage. The extent of the exchange, however, was significantly lower than that calculated for the fast exchanging system ($k_1 \gg k_2$).

We excluded reversibility of the second step (Scheme 2b) because no exchange of the triazine ring between **3** and CDMT-d_6 was observed (the ratio of CH_3N/CH_3O remains unchanged).

The proposed two-stage, addition−elimination mechanism has been further confirmed by studies of the kinetic isotope effects of chlorine and nitrogen.

Isotope Effects. The chlorine kinetic isotope effect was determined from the differences in isotopic composition of the product at low and full conversion levels using dead-end kinetic conditions. An appropriate excess of triazine was used so that after full consumption of *N*-methylmorpholine the required fraction of triazine conversion was achieved. Morpholinium salt **2** was filtered and then dissolved in THF−water and treated with an excess of silver nitrate to quantitatively precipitate chloride ions as silver chloride, which was then subjected to isotope analysis by a hybrid FAB-isotope ratio mass spectrometer MI 1201E (PO Electron, Ukraine). Samples of about 5 mg of silver chloride were deposited on the silver tip of the direct insertion probe. Xenon atoms of 6 keV hitting the surface of the probe at an incidence angle of 45° were used for ionization. The negative ions formed in this way were accelerated by the potential of 5 kV and detected in a Faraday cup collector system. The spectra contained almost exclusively chlorine peaks at 35 and 37 m/z. The mean value of the (M

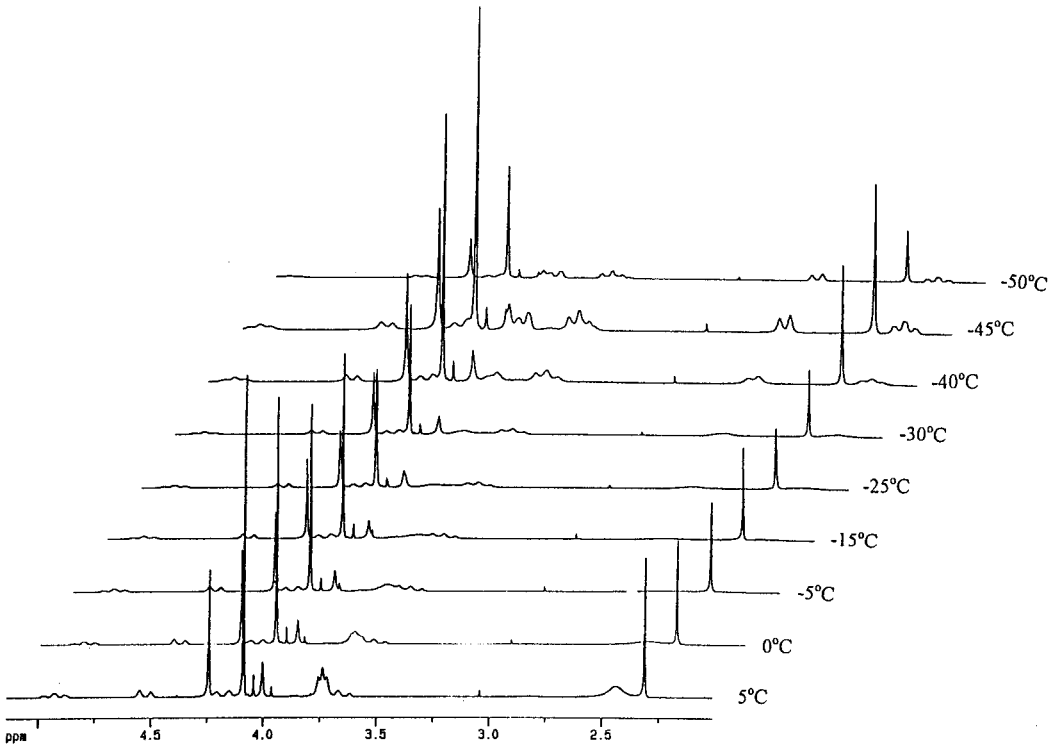
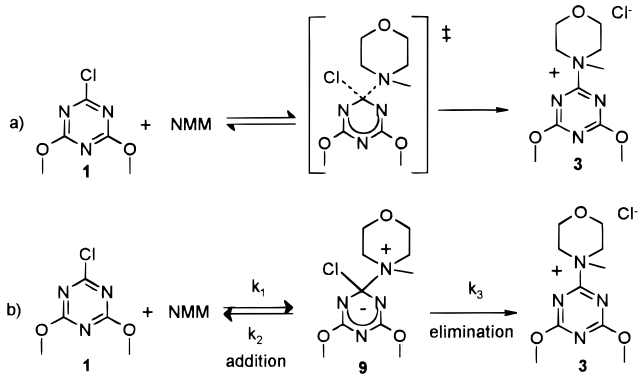


Figure 4. ^{1}H NMR spectrum of the reaction mixture of **1** with NMM. The intermediate **9** cumulated to reach 50% concentration. Temperature range 5 to −50 °C.

Table 5. ^{1}H and ^{13}C NMR (δ) Data of 9

solvent	NCH_3	NCH_2-	OCH_2-	OCH_3	triazine
^{1}H NMR ($CDCl_3$)	4.03 ppm	4.90 (double triplet, J = 12, 2 Hz), 4.54 (doublet, J = 12 Hz)	4.20 (double doublet, J = 12, 2 Hz), 3.72 (triplet, J = 12 Hz)	4.25	
^{13}C NMR ($CDCl_3$)	57.43	59.20	62.45	56.99	170.74, 173.84

Scheme 2



+ 2)/(M) isotopic ratio was obtained from up to 50 separate determinations, each being an average of 10 individual measurements. The total ion current under the above-mentioned conditions is stable for 0.5−1 h, yielding a precision of ±0.03−0.07%.

In the case of the morpholine nitrogen isotope effect, the low conversion samples were processed using an excess of NMM (0.05 M) over triazine at 5 °C, so that only a fraction of morpholine was reacted while the entire amount of triazine was exhausted. The excess of NMM was precipitated after treatment with dry HCl. The precipitate was filtered, washed with dry THF, and dried. The morpholinium salt was redissolved in chloroform and separated by passing through a silica gel column. The NMM samples obtained in the above way were combusted, and the isotopic composition of nitrogen was measured. About 10 mg of sample was required per measurement. Isotope ratio measurements were done using a Finnigan Delta S isotope-ratio mass spectrometer combined on-line with a Hereaus elemental analyzer. The natural isotopic composition of nitrogen was obtained from the original NMM sample.

The chlorine kinetic isotope effect was calculated from eq 1[24]

$$k_{35}/k_{37} = \frac{\ln(1-f)}{\ln(1-fR_{Pf}/R_{P\infty})} \quad (1)$$

where f is the fraction of reaction, and R is isotopic ratio of the product after full conversion, R_∞, and after small conversion, R_{Pf}, respectively.

For the calculations of the nitrogen isotope effect, an equation analogous to eq 1, but derived for the analysis of the isotopic ratios of reactant, was used:

$$k_{14}/k_{15} = \frac{\ln(1-f)}{\ln[(1-f)(R_{Sf}/R_{S0})]} \quad (2)$$

It was further modified to include the δ values rather than isotope ratios R according to

$$R_{Sf}/R_{S0} = (1000 + \delta_f)/(1000 + \delta_0) \quad (3)$$

(21) Paneth, P. *J. Am. Chem. Soc.* **1985**, *107*, 7070−7071.

where δ values are relative isotopic ratios, defined as $\delta_i = (R_i/R_{st} - 1)1000$ and δ_0 and δ_f are relative isotopic compositions of the remaining reactant at the beginning of the reaction ($i = 0$) and at a fraction of reaction f ($i = f$), respectively, compared to the isotopic ratio of a standard R_{st}. The value depends on the isotopic composition of the standard used in the mass spectrometric measurements, but this value drops out at the final calculation of the isotope effect.

The equation can be rearranged to yield a linear function of logarithm of isotopic composition on logarithm of reaction progress:

$$\ln(1000 + \delta_f) = \frac{1}{k_{14}/k_{15}} \ln(1 - f) + \ln(1000 + \delta_0) \quad (4)$$

The slope of this function gives the value of the isotope effect. Both methods yield practically the same value of the nitrogen kinetic isotope effect.

Kinetic Isotope Effects. Kinetic isotope effects are used as a tool for distinguishing alternative mechanisms of organic reactions. In a typical approach, the experimental values are compared with the theoretical predictions for alternative pathways. A more sophisticated method has been postulated but never tested experimentally.[21,22] It was shown theoretically that the reaction complexity can be traced by the dependence of the observed isotope effect on the reaction progress even when chemical detection of an intermediate fails due to its low concentration. The same is true for those reactions that are so fast that the determination of the intermediates is not possible. This is the case of the reaction under investigation here. We observed a significant chlorine kinetic isotope effect, $k_{35}/k_{37} = 1.0058 \pm 0.0005$, and no morpholine nitrogen kinetic isotope effect, $k_{14}/k_{15} = 1.0001 \pm 0.0006$. These results could be easily explained on the basis of the S_N1-type mechanism, in which the C−Cl bond breakage occurs in the transition from the reactant to the transition state, and there is no involvement of morpholine in the rate-determining process. This mechanistic possibility has been, however, excluded on the basis of kinetic observations of selectivity toward different amines and first order in *N*-methylmorpholine.

Intuitively, if the alternative synchronous S_N2 like mechanism was correct then a smaller chlorine isotope effect should be expected. In accordance with this expectation, model calculations at the semiempirical level, using AM1 Hamiltonian, yielded nitrogen and chlorine isotope effects of 0.9939 and 1.0023, respectively. The nitrogen kinetic isotope effect is an incoming group isotope effect, in which case the two main factors determining the magnitude of an isotope effect partially cancel each other. We have shown for similar quarternization of para-substituted *N*,*N*-dimethylaniline that in fact this isotope effect is small, being in the range 0.9985−1.0036, depending on the substituent.[23] Thus, the nitrogen isotope effect can be explained within this mechanism. The chlorine kinetic isotope effect, on the other hand, is substantially larger than expected. Furthermore, a closer inspection of individual results reveals that there

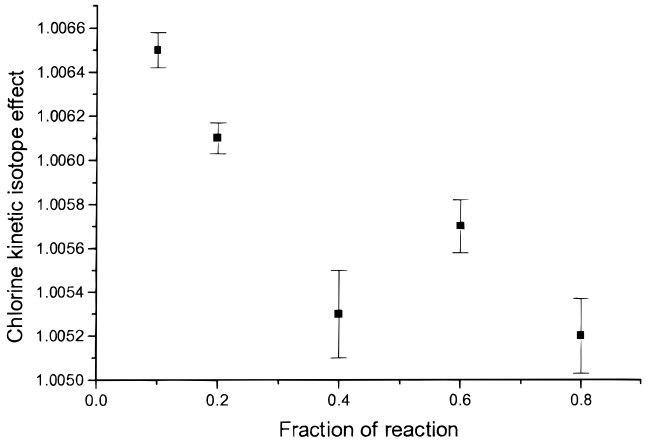


Figure 5. Experimental chlorine isotope effect (changes with reaction progress).

is a trend in measured values of this isotope effect with the reaction progress. This cannot be explained on the basis of the synchronous S_NAr mechanism.

The remaining alternative is a stepwise mechanism with an adduct intermediate. If the reaction of this type can be described by the scheme

$$S \underset{k_2}{\overset{k_1}{\rightleftharpoons}} I \xrightarrow{k_3} P \quad (5)$$

and the steady-state approximation is valid, then the observed isotope effect ${}^{obs}(k_L/k_H)$ is related to the isotope effects on the individual rate constants $(k_L/k_H)_i$ ($i = 1-3$) by the equation

$${}^{obs}(k_L/k_H) = (k_L/k_H)_1\left[\frac{(k_L/k_H)_3/(k_L/k_H)_2 + k_3/k_2}{1 + k_3/k_2}\right] \quad (6)$$

The observed isotope effect lies between the values for the two extreme cases of k_3/k_2 being equal to zero (k_2 much smaller than k_3) or infinity (opposite relation of rate constants). These limiting values of the isotope effect are given by

$${}^{obs}(k_L/k_H) = (k_L/k_H)_1(k_L/k_H)_3/(k_L/k_H)_2 \quad (7)$$

for $k_3/k_2 = 0$,

$${}^{obs}(k_L/k_H) = (k_L/k_H)_1$$

and for $k_3/k_2 \rightarrow \infty$.

We estimated the range for the kinetic isotope effects to be 0.9780−1.0012 for nitrogen and 1.0082−0.9996 for chlorine, respectively. As can be seen, both experimental values are within the predicted ranges. However, while the nitrogen isotope effect is close to the upper limit, suggesting that $k_3 \ll k_2$, the chlorine isotope effect is much closer to the limit, indicating the oposite relation of the rate constants. Thus, these two values cannot be simultaneously explained on the basis of the model.

Reconciliation of both results is only possible when it is recognized that the experimental chlorine isotope effect changes with the reaction progress as shown in Figure 5. Such a dependence means that the reaction is complex but the steady-state approximation is not valid.[21] The

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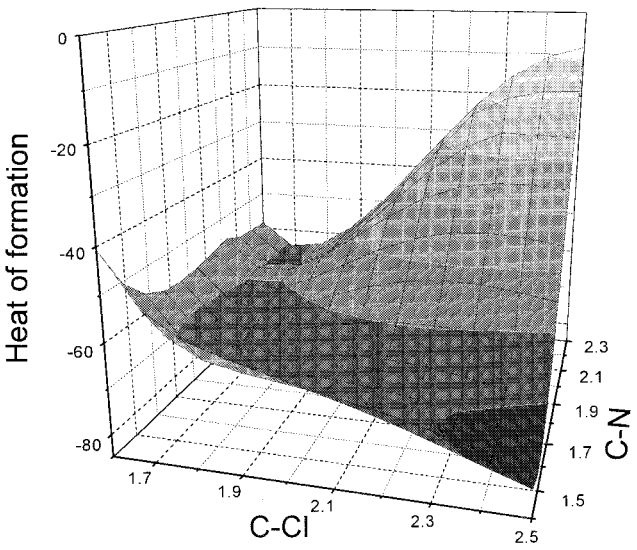

Figure 6. Potential energy surface for reaction of **1** with NMM calculated for polar solvent using COSMO model.

value of the isotope effect extrapolated to the *Y* axis equals

$$^{obs}(k_L/k_H)_0 = (k_L/k_H)_1(k_L/k_H)_3 \qquad (8)$$

From the curve, it can be estimated that this value should be close to 1.008−1.009. This is in excellent agreement with the value 1.0082 predicted theoretically.

Further support of the proposed mechanism comes from the differences in the behavior of nitrogen and the chlorine isotope effects. The nitrogen kinetic isotope effect does not exhibit the dependence on the reaction progress that is seen for the chlorine isotope effect. This is in accordance with the proposed explanation. Measurements of the nitrogen isotope effect were performed using the isotopic composition of the remaining reactant, while the chlorine isotope effect was calculated from the isotopic ratios of the product. If the sequential reaction described in the Scheme 3 is irreversible ($k_2 = 0$) or the reversibility is negligible ($k_2 \ll k_3$) then one should expect such a different behavior of isotope effects. The changes in the chlorine kinetic isotope effect reflect the complexity of the mechanism and changes of the concentrations of all reagents throughout the reaction progress. At the same time, if the formation of the reactant from the intermediate is negligible, the changes in the isotopic composition of the reactant reflect only the first reaction (with the rate constant k_1) and thus behave normally.

Calculations. Theoretical calculations of the reaction (Scheme 3) were performed at the semiempirical level. The simple gas-phase calculations are not suitable for this reaction since the product is ionic and presumably highly stabilized in a solvent of considerable polarity. The grid calculations revealed that the two Hamiltonians used, AM1 and PM3, predict different mechanisms for the reaction in question. Using the continuous solvent model COSMO and the AM1 Hamiltonian, we were able to optimize a structure of the transition state corresponding to the S_N2-like mechanisms. This was possible if the dielectric constant was larger than 6.

The PM3 Hamiltonian potential energy surface (PES) for the dielectric constant equal to 20 is illustrated in Figure 6. A similar PES was obtained in the gas-phase calculations, although the stability is reversed; i.e., reactants are more stable than products. Analysis of this PES indicates an intermediate formation with apparent activation energy, followed by decomposition to the product proceeding over a very shallow barrier.

All stationary points (reactants, products, intermediate, and transition states) were optimized, and force field calculations confirmed them to be either stable molecules (no imaginary frequencies) or transition states (exactly one imaginary frequency). We were also successful in optimizing the structure of the intermediate using gas-phase calculations and PM3 Hamiltonian. Analogous calculations with the AM1 Hamiltonian proved unsuccessful. We found three conformations, **3a**, **3e** (Scheme 2), and a twisted one, to be stable with heats of formation being closely similar for all three.

Conclusions

The activation of carboxylic acids by means of CDMT is a multistep process proceeding via triazinylammonium salts **3**−**6** formed in situ in the presence of the appropriate amine. The rate of formation of **3**−**6** strongly depends on the steric hindrance of N-substitutents. For more hindered amines, the rapid loss of reactivity is observed. The efficiency of **3** in the condensation reaction was confirmed by its successful use in the synthesis of triazine esters **7a**,**b** and amides **8a**−**f**.

On the basis of NMR studies, we postulate for compound **3** the presence of one dominant conformer with a triazine located as an axial substituent of morpholine ring.

Identification of the intermediate **9** excludes synchronous mechanism and strongly suggests the classic S_NAr addition−elimination mechanism.

Semiempirical modeling of the reaction, as well as measured nitrogen and chlorine kinetic isotope effects, also support this mechanism.

Experimental Section

General Methods. Melting points were determined in open tubes and were uncorrected. Proton magnetic resonance spectra (^{1}H NMR) were measured with a Bruker DPX 250 MHz spectrometer, using TMS as internal reference.

4-(4,6-Dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (3). The solution of 2-chloro-4,6-dimethoxy-1,3,5-triazine (**1**) (8.80 g, 50 mM) in benzene (30 mL) was cooled to 0−5 °C, and *N*-methylmorpholine (5.5 mL, 50 mM) was added dropwise. After 1 h, the white precipitate was diluted with petroleum ether (70 mL), filtered, washed with ether (3 × 30 mL), and dried in a vacuum desiccator under KOH, P_2O_5, and paraffin turnings, affording **3** as a white amorphous powder: yield 10.9 g, 79%; mp 120−122 °C dec (lit.[25] mp 90−98 °C); ^{1}H NMR (DMSO-d_6) δ 3.04 (s, 3H, NCH_3), 3.60 (t, 4H, J = 4.2 Hz, CCH_2O), 3.71 (t, 4H, J = 4.2 Hz, CCH_2N), 3.82 (s, 6H, OCH_3); ^{13}C NMR (DMSO-d_6) δ 27.028 (NCH_3), 44.424 (NCH_2C), 54.975 (OCH_3), 66.632 (OCH_2C), 167.095 (N*C*N), 172.950 (N*C*O).

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4-(4,6-Diphenoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium Chloride (4). The solution of 2-chloro-4,6-diphenoxy-1,3,5-triazine (**2**) (14.96 g, 50 mM) in benzene (40 mL) was cooled to 0−5 °C, and *N*-methylmorpholine (5.5 mL, 50 mM) was added dropwise. After 1 h, the white precipitate was diluted with petroleum ether (70 mL), filtered, washed with ether (3 × 30 mL), and dried in a vacuum desiccator under KOH, P_2O_5, and paraffin turnings, affording **4** as a white amorphous powder: yield 12.43 g, 62%; mp 140−153 °C dec; ^{1}H NMR ($CDCl_3$) δ 3.00 (s, 3H), 3.64 (m, 8H), 7.18 (m, 6H), 7.31 (m, 4H).

4-(4,6-Dimethoxy-1,3,5-triazin-2-yl)tetramethylguanidinium Chloride (5). The solution of 2-chloro-4,6-dimethoxy-1,3,5-triazine (**1**) (8.80 g, 50 mM) in benzene (30 mL) was cooled to 0−5 °C, and TMG (6.25 mL, 50 mM) was added dropwise. After 1 h, the white precipitate was diluted with petroleum ether (70 mL), filtered, washed with ether (3 × 30 mL), and dried in a vacuum desiccator under KOH, P_2O_5, and paraffin turnings, affording **5** as a white amorphous powder: yield 7.26 g, 35%; mp 171−179 °C; ^{1}H NMR ($CDCl_3$) δ 2.91 (s, 3H), 3.06 (s, 9H), 3.96 (s, 6H), 7.36 (s, 1H).

4-(4,6-Diphenoxy-1,3,5-triazin-2-yl)tetramethylguanidinium Chloride (6). The solution of 2-chloro-4,6-diphenoxy-1,3,5-triazine (**2**) (14.96 g, 50 mM) in benzene (40 mL) was cooled to 0−5 °C, and TMG (6.25 mL, 50 mM) was added dropwise. After 1 h, the white precipitate was diluted with petroleum ether (70 mL), filtered, washed with ether (3 × 30 mL), and dried in a vacuum desiccator under KOH, P_2O_5, and paraffin turnings, affording **6** as a white amorphous powder: yield 7.26 g, 35%; mp 199−212 °C; ^{1}H NMR ($CDCl_3$) δ 2.83 (s, 3H), 3.04 (s, 9H), 7.18 (m, 6H), 7.31 (m, 4H, *o*-C_6H_5), 8.82 (s, 1H).

Acylation of 4-(4,6-Dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium Chloride. General Procedure. The suspension of 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (**3**) (1.38 g, 5 mM) in dichloromethane (10 mL) was vigorously stirred, cooled to 0 °C, and treated with carboxylic acid (5 mM). The stirring was continued at 0 °C overnight and then at room temperature for an additional 10 h. The resulting mixture was diluted with dichloromethane (10 mL) and washed successively with water, 10% citric acid solution, water, 0.5 M sodium bicarbonate solution, and then water again, dried with anhydrous magnesium sulfate, filtered, and evaporated to dryness. The solid residue was recrystallized from cyclohexane, affording **7a**,**b**, which were found chromatographically and spectroscopically to be identical to authentic samples prepared by the standard procedure.

Synthesis of Amides 8a−f Involving the Use of 4-(4,6-Dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium Chloride (2) as Coupling Reagent. General Procedure. The suspension of 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (**3**) (1.38 g, 5 mM) in dichloromethane (10 mL) was vigorously stirred, cooled to 0 °C, and treated with carboxylic acid (5 mM). The stirring was continued at 0 °C overnight, an appropriate amine (5 mM) was added dropwise, and stirring was continued for 3 h and then at room temperature for an additional 10 h. The resulting mixture was diluted with dichloromethane (10 mL) and washed successively with water, 10% citric acid solution, water, 0.5 M sodium bicarbonate solution, and then water again, dried with anhydrous magnesium sulfate, filtered, and evaporated to dryness. The solid residue was recrystallized from ethyl acetate/petroleum, yielding **8a**−**f**, which were found chromatographically and spectroscopically to be identical to authentic samples prepared by the typical procedure.[16]

Kinetic Methods. The rate of reaction of trimethylacetic acid with CDMT was measured in CD_3CN solution. Stock solutions containing (a) a mixture of 1 M CDMT and 1 M trimethylacetic acid, (b) 1 M *N*,*N*-dimethylaniline, (c) 1 M triethylamine, (d) 1 M NMM, and (e) 1 M TMEDA in acetonitrile-d_3 were prepared. The reagents were conditioned at the reaction temperature for 30 min before use, and then a−c were injected into an NMR tube by microsyringe and diluted with acetonitrile-d_3 to obtain the required concentrations after the addition of amine (solutions d and e). The samples were conditioned for an additional 5 min, and then the reactions were initiated by adding the appropriate solution of NMM or TMEDA.

Acknowledgment. Financial support from the State Committee for Sciencific Research (KBN) through Grant No. 3.T09A.067.08 and Technical University of Lodz Funds is gratefully acknowledged.

JO972020Y