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Study on 1,3,5-Triazine Chemistry in Dehydrocondensation: *Gauche* Effect on the Generation of Active Triazinylammonium Species

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Abstract: The reaction of 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT) with various nitrogen-containing compounds, particularly tertiary amines (*tert*-amines), has been studied for the preparation of 2-(4,6-dimethoxy-1,3,5-triazinyl)trialkylammonium salts [DMT-Am(s)]. DMT-Ams derived from aliphatic *tert*-amines exhibited activity for the dehydrocondensation between a carboxylic acid and an amine to form an amide in a model reaction. Based on a conformational analysis of DMT-Ams and *tert*-amines by NMR and X-ray diffraction methods, we concluded that a β-alkyl group maintained in a *gauche* relationship with the nitrogen lone pair of *tert*-amines significantly hinders the approach of CDMT to the nitrogen. Thus, trimethylamine and quinuclidine without such alkyl groups readily react with CDMT whereas triethylamine, possessing two or three such *gauche* β-alkyl groups in the stable conformations, does not react at all. The theory of "*gauche* β-alkyl group effect" proposed here provides useful guidelines for the preparation of DMT-Ams possessing various tertiary amine moieties. An investigation of the dehydrocondensation activity of *tert*-amines in a CDMT/*tert*-amine system that involves in situ generation of DMT-Am, showed that the *gauche* effect of the β-alkyl group becomes quite pronounced; the yield of the amide decreases significantly with *tert*-amines possessing an unavoidable *gauche* β-alkyl group. Thus, the *tert*-amine/CDMT systems are useful for judging whether *tert*-amines can readily react with CDMT without isolation of DMT-Ams.

Keywords: amides · amines · conformation analysis · reaction mechanisms · structure–activity relationships

Introduction

Dehydrocondensation reactions that form amides and esters are essential tools for a wide range of organic chemistry because these functional groups occur in many drugs, natural products, polymers, and biomolecules. It has been more than ten years since we first correctly assigned the structure of 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMT-MM),[1,2] and proposed that DMT-MM would be a superior dehydrocondensation reagent for the formation of amides and esters (Scheme 1a).[3] The most outstanding property of DMT-MM is that it enables the formation of amide bonds from carboxylic acids and amines in aqueous or alcoholic solvents.[5] In fact, in the past decade, many applications of DMT-MM conducted in an aqueous or alcoholic solvent have been reported for the preparation or chemical modification of peptides,[6] nucleic acids,[7]

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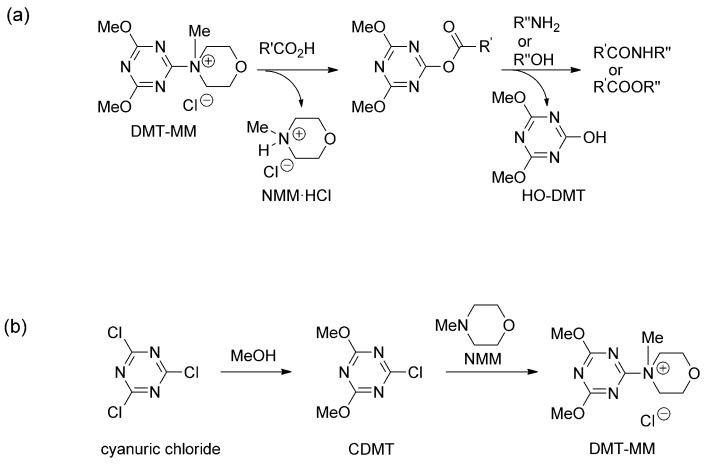


Scheme 1. a) Dehydrocondensation reaction using DMT-MM to produce amides or esters. b) Synthetic route to DMT-MM from cyanuric chloride.

sugars,[8,9] polysaccharides,[10] polymers or hydrogels,[11] various other materials,[12–14] and other common polar or less polar amides,[15] and for analytical chemistry.[16] As a result, the usefulness of this versatile reagent has now been well demonstrated.

DMT-MM is synthesized from cyanuric chloride via 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT),[1,17] and as can be readily seen from the synthetic process given in Scheme 1b, the compound has the remarkable advantage that the methoxy and *N*-methylmorpholinio groups and the counter anion (chloride ion) can be readily substituted with other similar types of functional groups to form various derivatives (Figure 1a). Substitution of the methoxy group with other alkoxy groups seems to mainly affect the physical properties, such as the solubility of the triazinyl compounds.[18,19]

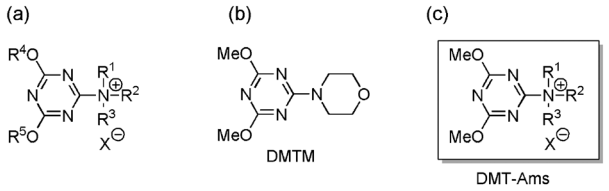


Figure 1. Structure of triazine-based dehydrocondensation reagents. a) General structure of triazine-based dehydrocondensation reagents. b) Structure of DMTM. c) General structure of dimethoxytriazine-based dehydrocondensation reagents [DMT-Am(X)].[21]

We have found that DMT-MM undergoes decomposition with liberation of chloromethane leading to the formation of DMTM (Figure 1b).[1,2,3a] This reaction occurs through attack of the chloride ion on the *N*-methyl group and is particularly promoted in less polar solvents. To avoid this decomposition, DMT-MM containing non-nucleophilic counter anions such as TfO^-, BF_4^-, and PF_6^-, instead of chloride, have been prepared.[18c,20]

On the other hand, the ammonium moiety may relate directly to the dehydrocondensation activity of DMT-MM, and thus seems to be more important. Recently, several derivatives of 2-(4,6-dimethoxy-1,3,5-triazinyl)trialkylammonium salts (DMT-Am(s): Figure 1c)[21] that include trimethylamine (TMA), *N*-methylpiperidine (NMP), quinuclidine (QD), and 1,4-diazabicyclo[2.2.2]octane (DABCO) have been prepared.[18c,20b,c,22] However, these compounds do not seem, to the best of our knowledge, to be remarkably superior to DMT-MM with respect to their reactivity, stability, and cost. We have achieved dehydrocondensations with a specific function, such as molecular recognition, by using *N*,*N*-dimethylglycine attached to a cyclodextrin, a crown ether, hydrophobic alkyl chains, or a protein ligand, through the ester group (Figure 2).[23] More recently, the asymmetric activation of racemic amino acids in moderate-to-good selectivity (20–90% *ee*) was reported by using DMT-Ams with strychnine or brucine as the tertiary amine moiety.[24]

Although it is empirically known that tertiary amines (*tert*-amine) do not all react equally with CDMT, the reactivity of *tert*-amines toward CDMT has not yet been investigated, which should be of great importance for developing new reagents for dehydrocondensation. The enigmatic propensity of *tert*-amines to react with CDMT may prevent the development of new dehydrocondensation reagents that are superior to DMT-MM. Herein, we describe the results of a systematic study focused on elucidating the reactivity of various nitrogen-containing compounds, particularly *tert*-amines, toward CDMT for the preparation of the corresponding DMT-Ams. The dehydrocondensation activity of the resulting DMT-Am is also discussed.

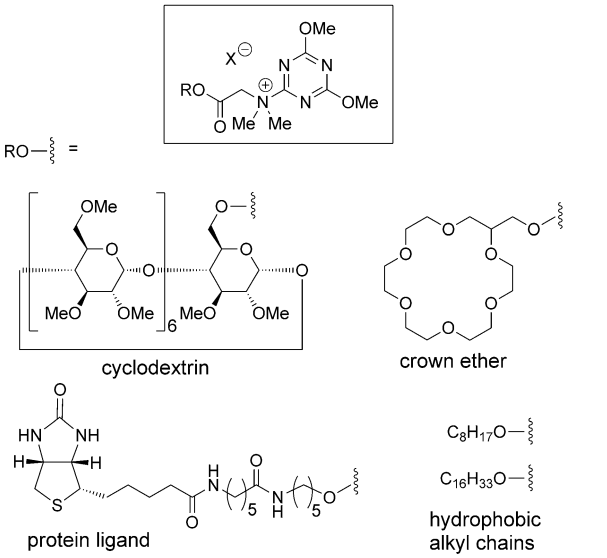
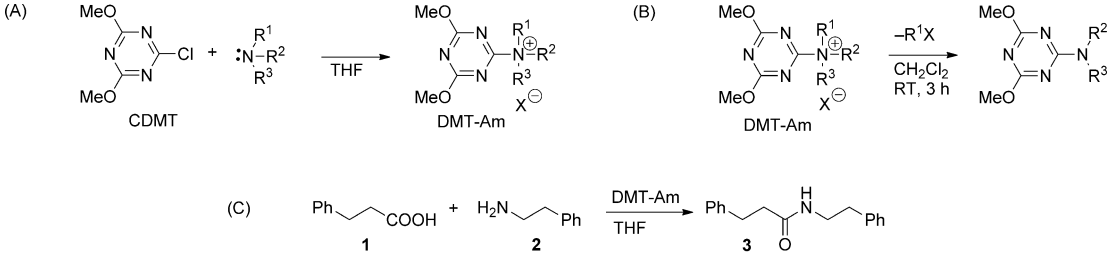


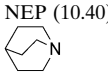
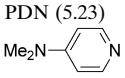
Figure 2. Dehydrocondensation reagents with a specific function based on DMT-Am.

Results and Discussion

Synthesis and condensation activity of DMT-Ams: The reaction between CDMT and various *tert*-amines or related nitrogen-containing compounds was examined, and the results are shown in Table 1, together with the results for the reaction of *N*-methylmorpholine (NMM), for comparison, which proceeds quantitatively within 30 min to yield DMT-MM.[1,3a] When NMP was treated with CDMT in tetrahydrofuran (THF) at room temperature, the reaction readily occurred to give a precipitate that appeared to be DMT-MP, but it was difficult to isolate in pure form, presumably because of partial demethylation.[2,25] To avoid the decomposition of DMT-MP caused by attack of the chloride ion on the *N*-methyl group, the reaction was conducted in the presence of lithium perchlorate ($LiClO_4$) dissolved in THF and, as a result, DMT-MP(ClO_4) was isolated as a precipitate in 96% yield. In contrast to NMM, the reactivity of *N*-ethylmorpholine (NEM) toward CDMT was considerably lower; the reaction resulted in production of DMT-EM in only 3% yield after 1 h. Furthermore, after 24 h, the yield increased to only 36%, and a complex mixture was formed; thus, a pro-

Table 1. Preparation, stability, and condensation activity of DMT-Ams. A) Preparation of DMT-Am; B) Stability of DMT-Am in CH_2Cl_2; C) Dehydrocondensation between 3-phenylpropionic acid **1** and phenethylamine **2** with DMT-Am.



Tertiary amines (pK_a)[b]	Abbreviation of DMT-Am	A: Preparation of DMT-Am			B: Stability of DMT-Am RT, 3 h, in CH_2Cl_2[c]	C: Condensation with DMT-Am to form **3**	
		X^-	Conditions	Yield [%]		Conditions	Yield [%]
	DMT-MM	Cl^-	RT, 30 min	100[a]	demethylation: 96%	RT, 4 h	84[a]
NMM (7.41)							
	DMT-MP	ClO_4^-	RT, 30 min	96	recovery: 100%	RT, 3 h	77
NMP (10.08)							
	DMT-EM	Cl^-	RT, 1 h	3	nc[d]	50°C, 48 h	35
NEM (7.70)		Cl^-	RT, 24 h	36[e]	nc		
		ClO_4^-	RT, 25 h	65	recovery: 74%		
	DMT-EP	Cl^-	RT, 1 h	30	deethylation: 62%	RT, 3 h	58
NEP (10.40)		ClO_4^-	RT, 1 h	31			
	DMT-QD	Cl^-	RT, 1 h	97	decomposition: 100%	RT, 3 h	90
QD (11.3)		ClO_4^-	RT, 1 h	96	nc		
	DMT-MPD	ClO_4^-	0°C, 20 min	97	recovery: 97%	RT, 3 h	91
MPD (10.46)							
Me_3N (TMA) (9.76)	DMT-TMA	Cl^-	RT, 45 min	85	demethylation: 100%	RT, 3 h	98
Me_2NEt (EDMA) (9.99)	DMT-EDMA	Cl^-	RT, 30 min	86	demethylation: 93% deethylation: 7%	RT, 4 h	90
$MeNEt_2$ (DEMA) (10.29)	DMT-DEMA	Cl^-	RT, 1 h	80	demethylation: 22% deethylation: 62%	RT, 6 h	86
Et_3N (TEA) (10.65)	(DMT-TEA)[f]	Cl^-	RT, 24 h	0	–	–	–
	(DMT-DMAN)[f]	Cl^-	RT, 1 h	0	–	–	–
DMAN (5.07)							
	DMT-PDN	Cl^-	RT, 1 h	32	recovery: 100%	nc	–
PDN (5.23)		ClO_4^-	RT, 1 h	30[e]	nc		
	DMT-DMAP	Cl^-	RT, 30 min	87	recovery: 91%	RT, 30 h	0
DMAP (9.7)		ClO_4^-	RT, 1 h	96[e]	nc		
	DMT-MIm	Cl^-	RT, 24 h	69	recovery: 97%	RT, 3 h	0
MIm (6.95)		ClO_4^-	RT, 1 h	56[e]	nc		

[a] The data was cited from literature (see ref. [1]). [b] The pK_a values were cited from literature (see ref. [27]). [c] Estimated by ^1H NMR analysis. [d] nc = reaction was not conducted. [e] Prepared for elemental analysis. [f] DMT-Am in parentheses could not be prepared.

longed reaction time leads to decomposition of the DMT-EM. The yield increased to 65% upon the addition of $LiClO_4$ to give DMT-EM(ClO_4). *N*-Ethylpiperidine (NEP) had a slightly higher reactivity than NEM, affording DMT-EP in 30% yield after 1 h. QD and *N*-methylpyrrolidine (MPD) reacted similarly to NMM, providing the corresponding DMT-Ams in high yields (97% in both cases).

With regard to acyclic *tert*-amines, TMA was found to react readily with CDMT to give DMT-TMA in 85% yield within 45 min, whereas triethylamine (TEA) did not react at all with CDMT, even after 24 h. Interestingly, the reactivity of TEA was dramatically improved by the substitution of only one ethyl group for a methyl group; *N*,*N*-diethyl-*N*-methylamine (DEMA) readily reacted with CDMT to give DMT-DEMA in 80% yield within 1 h. Thus, it seems that at least one methyl group is essential for the formation of DMT-Ams in acyclic *tert*-amines. However, in spite of possessing two methyl groups, *N*,*N*-dimethylaniline (DMAN),

an aromatic *tert*-amine, did not react with CDMT. Nitrogen-containing compounds with an sp^2-hybridized lone pair of electrons, such as pyridine (PDN), 4-(*N*,*N*-dimethylamino)-pyridine (DMAP), and *N*-methylimidazole (MIm), which are known to form active acylating reagents, react with CDMT to form precipitates. In particular, the yield using DMAP was good.

We examined the stability of DMT-Ams in CH_2Cl_2 at room temperature for 3 h; the conditions under which DMT-MM is decomposed through demethylation to give DMTM in 96% yield (Table 1B).[1] When DMT-TMA possessing a chloride ion was suspended and stirred in CH_2Cl_2, the solid disappeared within a few minutes and 4,6-dimethoxy-2-dimethylamino-1,3,5-triazine was formed. Similarly, DMT-Ams prepared from aliphatic *tert*-amines decomposed rapidly, whereas DMT-Ams(ClO_4) with the less nucleophilic perchlorate ion was recovered in high yields. DMT-PDN, -DMAP, and -MIm, possessing an sp^2-hybridized nitrogen moiety, were also found to be quite stable, even with chloride as the counter anion.

The activity of DMT-Ams in the dehydrocondensation was examined by the reaction of 3-phenylpropionic acid (**1**) and phenethylamine (**2**) in THF as a model system. The results are shown in Table 1C. The DMT-Ams that were obtained in good yields exhibited good condensation activity; the reactions occurred with the formation of amide **3** in high yields. However, DMT-EM and DMT-EP, which were obtained in low yields, exhibited poor activity; **3** was produced in 35 and 58% yield, respectively. Interestingly, DMT-DMAP and -MIm, containing an sp^2-hybridized nitrogen, did not form **3** at all.

Conformational analyses for DMT-Ams: In the ^{13}C NMR spectrum of 4-*tert*-butyl-1,1-dimethylpiperidinium iodide, the conformation of which should be fixed because of the sterically large *tert*-butyl group, an approximately 9 ppm upfield shift of the peak for the axial *N*-methyl group ($\delta =$ 47.8 ppm) compared with the equatorial *N*-methyl group ($\delta = 56.8$ ppm) due to the γ-*gauche* compression effect was observed (Figure 3).[26] The chemical shift for the *N*-methyl group of DMT-MP(ClO_4) in the ^{13}C NMR spectrum was observed at $\delta = 55.5$ ppm, and in the NOESY spectrum, no cross peak was observed between the *N*-methyl and the axial protons at the 3- and 5-positions. These results suggest that the *N*-methyl group occupies an equatorial position and that the triazinyl group occupies an axial position in the stable conformation of DMT-MP. In fact, this structure was confirmed by X-ray structural analysis, as shown in Figure 4a. This structural feature is similar to that of DMT-MM shown in Figure 3, which was also reported previously.[20b] On the other hand, a derivative of DMT-MP possessing a *tert*-butyl group at the 4-position of the piperidine moiety was prepared by reaction of CDMT and *N*-methyl-4-*tert*-butylpiperidine (MBP). Interestingly, the chemical shift of the *N*-methyl group of the resulting DMT-MBP(ClO_4) in the ^{13}C NMR spectrum exhibits an upfield shift of 9 ppm in comparison to DMT-MP. In addition, the NOESY spectrum

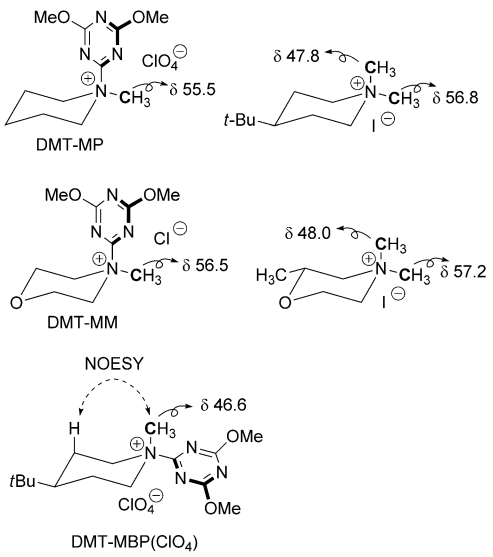


Figure 3. Conformational analyses of DMT-Ams with cyclic *N*-methylamines by ^1H and ^{13}C NMR spectroscopic analysis.

shows a correlation of the *N*-CH_3 ($\delta = 3.52$ ppm) with the axial H at the 3- and 5-positions (ca. $\delta = 1.95$ ppm), indicating that the *N*-methyl group occupies an axial position in this compound. In fact, the X-ray structure of DMT-MBP-(SbF_6) unequivocally shows the expected structure, with the triazinyl group in the equatorial position (Figure 4b). Thus, the structure with the axial triazinyl group is not always common in DMT-Ams composed of six-membered cyclic *tert*-amines.

Because the conformation of the piperidine ring possessing the 4-*tert*-butyl group in the equatorial position will be maintained during the reaction with CDMT to give DMT-MBP, the observed structure of DMT-MBP indicates that CDMT approaches the lone pair of electrons of the nitrogen exclusively from the equatorial side of *N*-methyl piperidine. Thus, it is reasonable to conclude that DMT-MM and DMT-MP were formed in a manner similar to DMT-MBP through equatorial attack of CDMT on NMM and NMP, and that the resulting DMT-Ams then underwent conformational inversion to the more stable alternative chair conformations with the flattened triazinyl group in the axial position (Figure 5).

To clarify the reaction path of the *N*-ethyl derivatives, the ^{13}C chemical shift for the methylene carbon of the *N*-ethyl group of DMT-EBP, which was prepared by the reaction of CDMT with *N*-ethyl-4-*tert*-butylpiperidine (EBP), was compared with those of DMT-EP and DMT-EM. As shown in Figure 6, the chemical shifts at approximately $\delta = 66$ ppm for the DMT-EP and DMT-EM indicate that the ethyl group occupies the equatorial position, whereas the upfield shift of 12 ppm for DMT-EBP corresponds to an axial ethyl group.[26] Thus, we conclude that the electrophilic reaction of CDMT toward the nitrogen of NEM and NEP also occurred from the equatorial side.

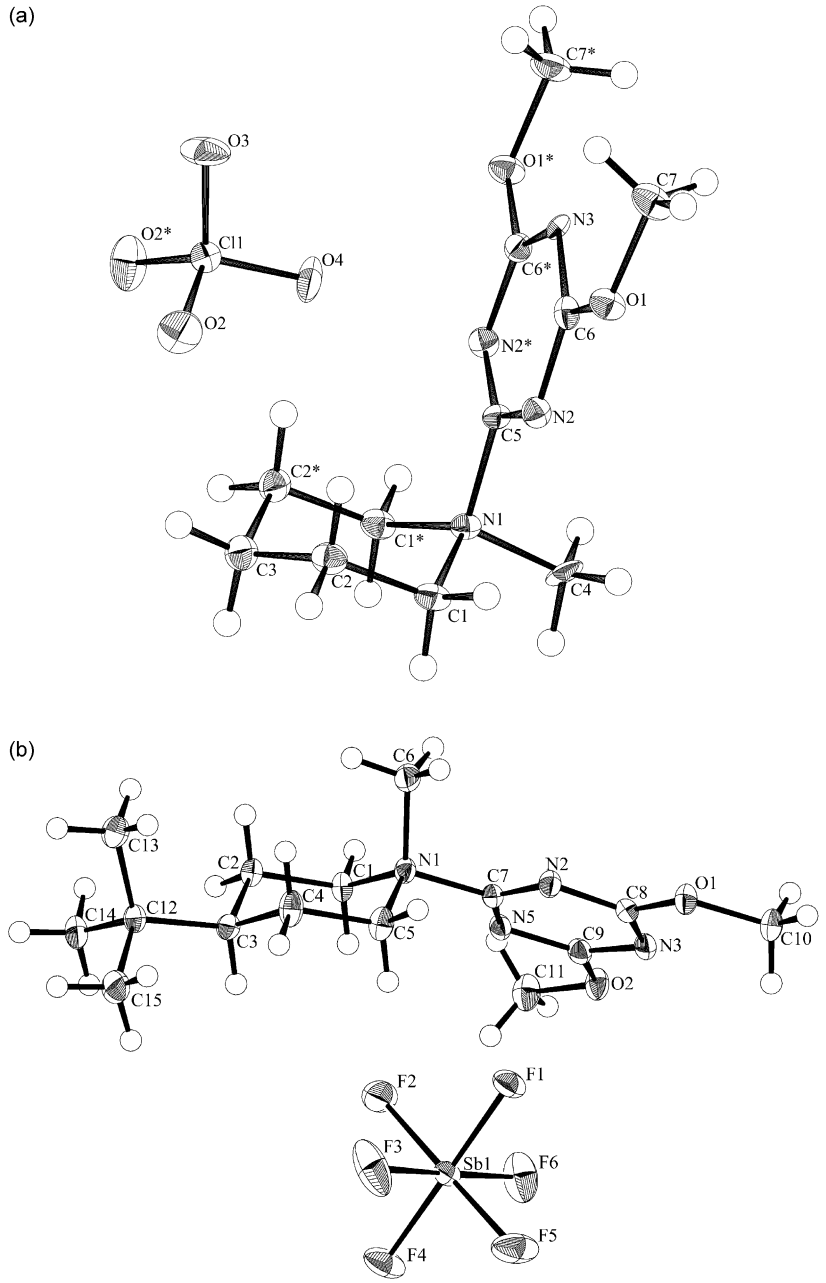


Figure 4. X-ray structure of DMT-Ams. a) DMT-MP(ClO_4) b) DMT-MBP(SbF_6).

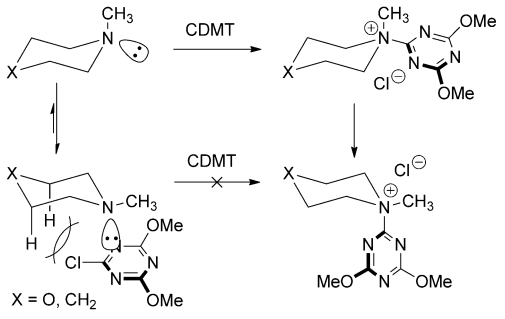


Figure 5. Reaction path for the generation of DMT-Ams with cyclic *N*-methylamines.

Mechanistic considerations for the synthesis of DMT-Ams: The β-*gauche* effect: There seems to be no correlation between the observed reactivity of amines toward CDMT (i.e., chemical yield of DMT-Ams) and the pK_a of their conjugate acids (see Table 1).[27] For example, in spite of similar pK_a values near 7.5, NMM readily reacts with CDMT to quantitatively give DMT-MM, whereas NEM reacts giving a low yield. The same tendency was observed in NMP and NEP, each having a pK_a of approximately 10. Although the pK_a values of the acyclic *tert*-amines (TMA, EDMA, DEMA, and TEA) fall within a relatively narrow range (9.7 to 10.7), only TEA does not react with CDMT at all. Thus, the type of substituent (for example, methyl or ethyl) on the nitrogen rather than the basicity may be correlated with the reactivity.

The N-methylation of 4-*tert*-butyl-*N*-methylpiperidine by trideuteriomethyl iodide was reported to proceed predominantly from the axial side in a ratio of 78:22.[28] By contrast, the above study indicates that the reaction of CDMT occurs exclusively from the equatorial side of the morpholine or piperidine ring. Because the nucleophilic attack of *tert*-amines to CDMT must occur in a direction perpendicular to the π-plane of the triazine ring, the approach of CDMT with a flattened structure from the axial side of six-membered *tert*-amines would be strongly hindered by the 1,3-diaxial interaction (Figure 5). Based on the free-energy difference between the two conformers (*N*-Me axial and equatorial) of NMM and NMP,[29] the proportion of the *N*-Me axial conformers that can undergo a reaction with CDMT will be a few percent or less. However, the proportion seems to be sufficiently large to enable a smooth reaction according to the Curtin–Hammett principle.[30]

On the other hand, the observed substantial decrease in the reaction rate of *N*-ethyl derivatives (NEM and NEP) with CDMT is attributable to a steric effect of the *N*-ethyl group, which is the only structural difference from NMM

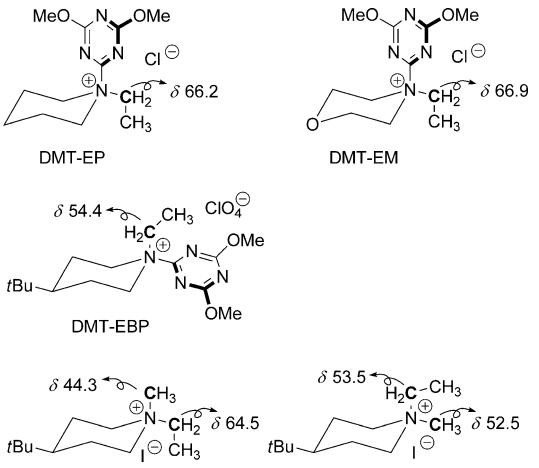


Figure 6. Conformational analyses of DMT-Ams with cyclic *N*-ethylamines by ^{13}C NMR spectroscopic analysis.

and NMP. Because CDMT reacts from the equatorial side of NEM and NEP, the conformation of the axial *N*-ethyl group based on the rotation about the N–C bond should be a critical factor. To minimize the 1,3-diaxial repulsion, the methyl group of the axial *N*-ethyl substituent should face outside the ring. As a result, the β-methyl group is in a *gauche* relationship with the nitrogen lone pair orbital that undergoes the reaction with CDMT (ax-G conformation) (Figure 7).[31]

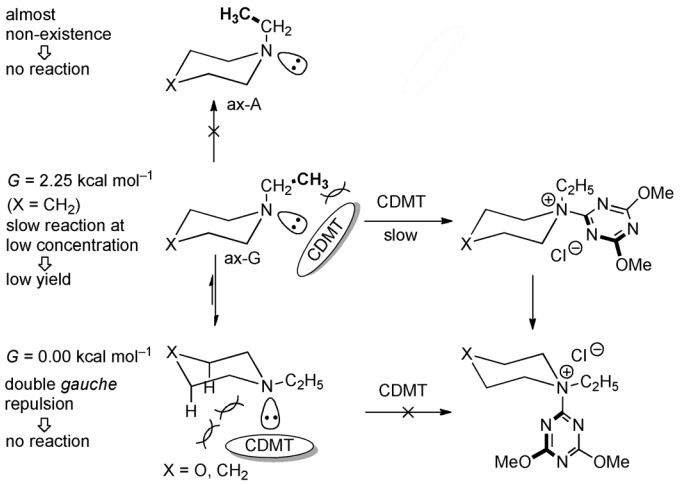


Figure 7. Reaction path for generation of DMT-Ams with cyclic *N*-ethylamines.

Such an inevitable *gauche* steric hindrance of a β-alkyl group can be considered to significantly prevent the approach of CDMT to the nitrogen. Although the ax-A conformation, in which the β-methyl group is directed toward the inside of the ring, is most suitable for the reaction, such a conformation would be too unstable to exist. The good reactivity of QD can be reasonably explained by its *anti* structure around the nitrogen lone pair, which is equal to the ax-A conformation of NEP. In addition, the fact that no reaction occurs from the axial side of piperidines (and hence of morpholines) can be explained by the 1,3-diaxial interaction, which has a double *gauche* relationship with the C2–C3 and C6–C5 bonds, which strongly sterically hinder the axial lone pair.

To evaluate the effect of the *gauche* β-methyl group, we examined the reaction of 1,2-dimethyl piperidine (DMP) with CDMT (Figure 8). In the chair conformation with the

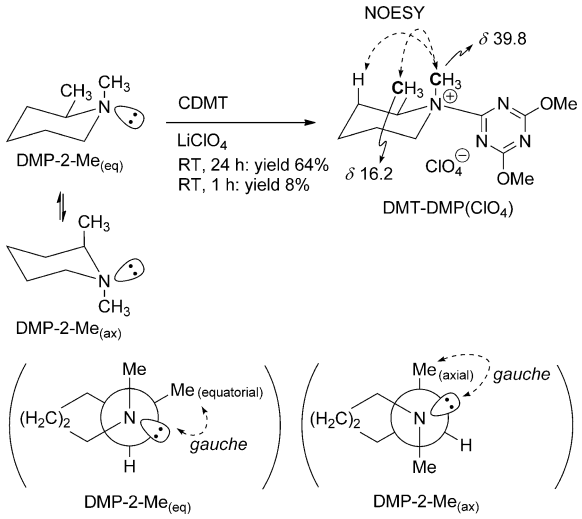


Figure 8. Reaction of 1,2-dimethylpiperidine (DMP) for the evaluation of the effect of the *gauche* β-methyl group. The 2-methyl group maintains a *gauche* relationship with the lone pair irrespective of the axial or equatorial position.

axial *N*-methyl and the equatorial lone pair orbital, the methyl group at the 2-position remains in a *gauche* relationship with the lone pair, irrespective of its position (axial or equatorial). Actually, the reaction of DMP is much slower than that of NMP, and gives the corresponding DMT-DMP-(ClO_4) in only 64% after 24 h. The ^{13}C NMR chemical shift for the *N*-methyl group of the resulting DMT-DMP is $\delta =$ 39.8 ppm, and the NOESY spectrum shows a correlation between the vicinal methyl groups and between the *N*-methyl and the 3- or 5-axial proton, indicating that the *N*-methyl group and the 2-methyl group occupy axial and equatorial positions, respectively. The upfield shifts of approximately 5 ppm for both the methyl groups can be attributed to a steric compression of the γ-*gauche* interaction between them. Thus, the reaction can be considered to occur in the 1,2-*cis* structure [DMP-2-$Me_{(eq)}$], as shown in Figure 8. Accordingly, we conclude that the introduction of one *gauche* β-methyl group to the nitrogen lone pair of electrons in NMP significantly retards the reaction with CDMT to give DMT-Am.

For acyclic *tert*-amines, the most suitable conformer of TEA for the reaction with CDMT is AAA, which has all methyl groups *anti* to the lone pair, as shown in Figure 9. The relative conformational energy of the AAA conformer

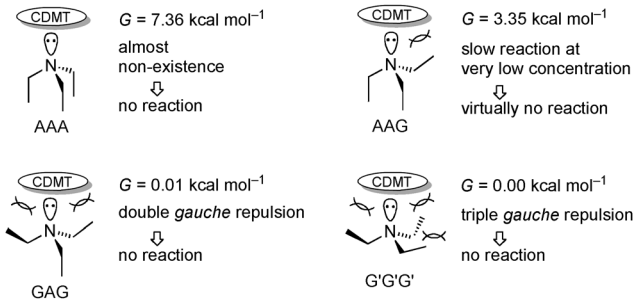


Figure 9. Conformational analysis of triethylamine (TEA) in the reaction with CDMT.

is reported to be 7.36 kcal mol^{-1} higher than that of the most stable G′G′G′ conformer, which has all β-methyl groups *gauche* to the lone pair with C_3 symmetry.[32] The fact that the reaction did not occur at all according to the Curtin–Hammett principle would indicate that TEA is virtually non-existent in the very unstable AAA conformation. As mentioned above, CDMT does not attack from the axial side of NMP or NMM at all because of the 1,3-diaxial interaction corresponding to the double *gauche* effect; therefore, we can exclude the reaction paths proceeding through the GAG and G′G′G′ conformers of TEA, both of which have two or three *gauche* β-methyl groups that will completely block the approach of CDMT to the nitrogen lone pair. Thus, to evaluate an alternative route to DMT-TEA via the AAG conformer, which has only one β-methyl group *gauche* to the lone pair, we examined the reaction of CDMT with *N*-isopropyl-*N*,*N*-dimethylamine (IPDMA), the major conformer of which (ca. 69% in proportion based on the free-energy difference) has one isopropyl methyl group *anti* and the other *gauche* to the lone pair and corresponds to the AAG conformer of TEA (Figure 10).[33] The expected DMT-IPDMA was obtained in only 48% yield after 1 h despite the reaction proceeding via the major conformer, indicating that the reaction is significantly retarded, but not

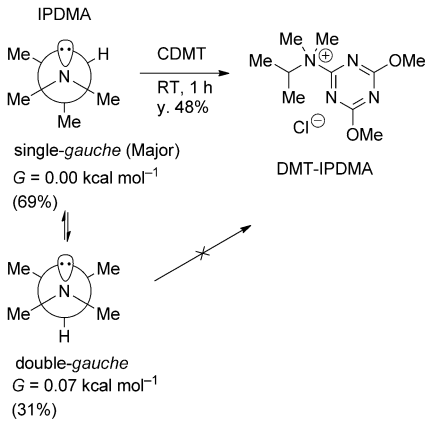


Figure 10. Reaction of *N*,*N*-dimethyl-*N*-isopropylamine (IPDMA) with CDMT. The proportions of each conformer at 25°C calculated based on the ΔG values are given in parentheses.

completely repressed, by the addition of one *gauche* β-methyl group. In the case of TEA, the least stable conformation is AAA (7.36 kcal mol^{-1}) followed by AAG (second unstable conformer; 3.35 kcal mol^{-1}). On the other hand, other conformers (GAG and G′G′G′) are much more stable (ca. 0 kcal mol^{-1}). Thus, the concentration of the AAG conformer should be very low.[32,34,35] As a result, because of the synergistic effect of the low concentration of the AAG conformer and the slow reaction via AAG involving the β-*gauche* effect, no detectable amount of DMT-TEA was produced with TEA under ambient conditions.

In the case of DEMA, which reacted with CDMT giving a good yield, it has been reported that the AG′ and AA conformers are approximately 0.47 and 3.82 kcal mol^{-1} higher in energy, respectively, than the most stable GG′ conformer, and that the AG′ conformers are present in concentrations that are sufficiently high to be detected by NMR spectroscopic analysis (Figure 11).[32] However, based on the ob-

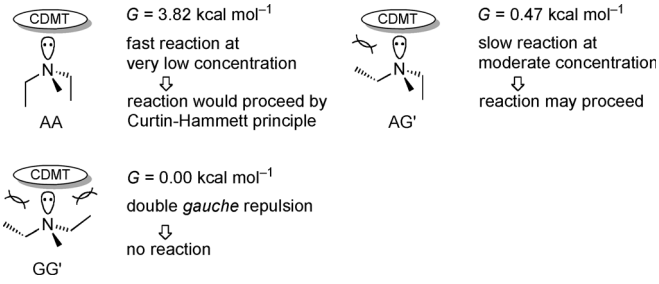


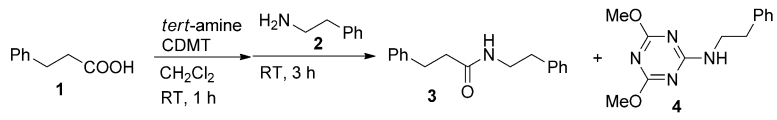
Figure 11. Conformational analysis of *N*,*N*-diethyl-*N*-methylamine (DEMA) in the reaction with CDMT.

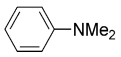
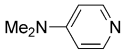
served slow reaction of CDMT with IPDMA, despite a high proportion of the conformer (69%), the reaction proceeding through the similarly hindered AG′ conformer of DEMA is unlikely to explain the fact that 80% yield of DMT-DEMA was obtained within 1 h. Thus, it is reasonable to conclude that the reaction mainly proceeded via the AA conformer following the Curtin–Hammett principle, rather than through the AG′ conformer, indicating that the reaction rate without β-*gauche* repulsion should be large.

Evidence for the reaction mechanism: In situ generation of DMT-Am: The dehydrocondensation of carboxylic acids and amines using CDMT in the presence of NMM had been believed to proceed through the direct reaction between carboxylates and CDMT.[17b,36] However, in 2001, we showed that the reaction using CDMT without NMM became much slower, and only a trace amount of amide was produced, but that the reaction was promoted by the addition of *N*,*N*-dimethylglycine esters.[23a] This fact indicates that the formation of DMT-Ams from CDMT and *tert*-amines is essential for dehydrocondensation. Because *tert*-amine is regenerated in the reaction of DMT-Ams and carboxylates, it can act as a catalyst. Thus, the combination of CDMT and a catalytic amount of *tert*-amine constitutes a novel, aqueous, catalytic amide-forming reaction. By introducing various functional

groups such as a cyclodextrin, a crown ether, hydrophobic alkyl chains, and protein ligands, novel useful catalytic systems can be developed for dehydrocondensation (Figure 2).[23] In this context, the dehydrocondensation activity of the *tert*-amines employed in the present study was investigated in the reaction of **1** and **2** in a CDMT/*tert*-amine system, in which DMT-Ams would be formed in situ during the reaction, and not isolated. A mixture of **1** and a stoichiometric amount of the *tert*-amine dissolved in CH_2Cl_2 was treated with CDMT for 1 h, and then **2** was added; the results are shown in Table 2.[37] Using the *tert*-amines (NMM, NMP) that readily undergo coupling with CDMT to form DMT-Ams, we obtained amide **3** in good yields. In contrast, when *tert*-amines NEM and TEA, which either reacted slowly or not at all with CDMT, were used, amide **3** was not obtained, and instead, compound **4**, resulting from direct coupling between CDMT and phenethylamine **2**, was obtained in significant yields.

Table 2. Dehydrocondensation of **1** and **2** in the CDMT/*tert*-amine system.



Tertiary amines		Yield of **3** [%]	Tertiary amines		Yield [%][a] **3**	**4**
(NMM)		96	(NEM)		0	82
(NMP)		97	(NEP)		24	55
(QD)		71	(DMAN)		0	75
(MPD)		86	(DMAP)		8	34
Me_2NEt		96	(MIm)		0	72
$MeNEt_2$		84	Et_3N		0	90

[a] CDMT-phenethylamine coupling product **4** was formed as a byproduct.

We monitored the reaction of CDMT and butyric acid in the presence of either NMM or TEA by ^1H NMR spectroscopic analysis. A solution of the acid and the *tert*-amine in [D_3]acetonitrile was mixed with CDMT under anhydrous conditions, and the resulting solution was analyzed. As shown in Figure 12a, in the presence of NMM, the intermediate triazinyl butyrate was formed in a significant amount after 5 min, and the yield of the ester was estimated to be more than 50% based on a comparison of the amounts of the product and the remaining starting acid, which disappeared within 45 min. A small amount of DMT-MM was detected after 5 min, and it did not increase significantly until 1 h. In addition, no DMT-MM precipitate was observed during the analysis, indicating that the rate of disappearance of DMT-MM by attack of the butyrate is almost same as or faster than that of its generation from CDMT and NMM. The signal for butyryl chloride appeared after 15 min and increased with time. Because there are no nucleophiles such as amines or alcohols present to produce amides or esters, the chloride ion, which is the only nucleophile generated from CDMT in the system, attacked the activated triazinyl ester to form the acid chloride. On the other hand, when the reaction was conducted in the presence of TEA instead of NMM, most of the reactants (CDMT and the acid) remained unchanged, even after 1 h (Figure 12b). At this time, small amounts of the activated triazinyl butyrate and butyric anhydride were observed, suggesting that the carboxylate anion can react directly with CDMT at a very slow rate. In this case, because the chloride ion concentration is very low, the activated ester undergoes reaction with the unreacted starting acid to form the anhydride.

Thus, as expected from our proposed reaction mechanism for the CDMT/*tert*-amine system, a clear relationship was observed between the reactivity of *tert*-amines toward CDMT and their reaction activity for the CDMT/*tert*-amine system. Using the *tert*-amines that exhibit a good reactivity toward CDMT, amides can be obtained in good yields in the CDMT/*tert*-amine system. The advantage of the CDMT/*tert*-amine system is that, even if reactions involve the generation of a DMT-Am chloride that is difficult to isolate because of dealkylation, the amide can be obtained in a good yield, as observed in the case of NMP in Table 2. In contrast, when the reactivity of *tert*-amines toward CDMT is low because of the *gauche* repulsion, an alternative reaction of the primary amine **2** with CDMT to produce **4** predominates. This side reaction should be particularly critical in the CDMT/*tert*-amine catalytic system, because a catalytic amount of the *tert*-amine coexists with a stoichiometric amount of the reactant primary or secondary amine in the same reaction medium.[38] Thus, the CDMT/*tert*-amine system should be useful for determining whether a *tert*-amine can readily generate the corresponding DMT-Am without isolating it.

Recently, Kaminski reported that quinine and quinidine readily react with CDMT at 0°C for 30 min; however, the resulting DMT-Ams could be neither isolated nor identified because of their instability.[24] If these results are confirmed, they are the only counterexamples to our theory of the *gauche* β-alkyl effect, because these amines have a branched alkyl group [hydroxy-(6-methoxyquinolin-4-yl)methyl group] at the α-position of the nitrogen of the QD moiety. Thus, to evaluate whether the DMT-Am is quantitatively generated, we attempted the condensation of **1** and **2** in the CDMT/quinine system. As a result, amide **3** was produced in only 22% yield along with 31% yield of **4**. Because this result is similar to that obtained for NEP, we can conclude that quinine (and similarly quinidine) cannot quantitatively react with CDMT within 30 min at 0°C. For further confirmation, we attempted the preparation of the relevant DMT-Am by reaction of quinine and CDMT in THF at 0°C in the

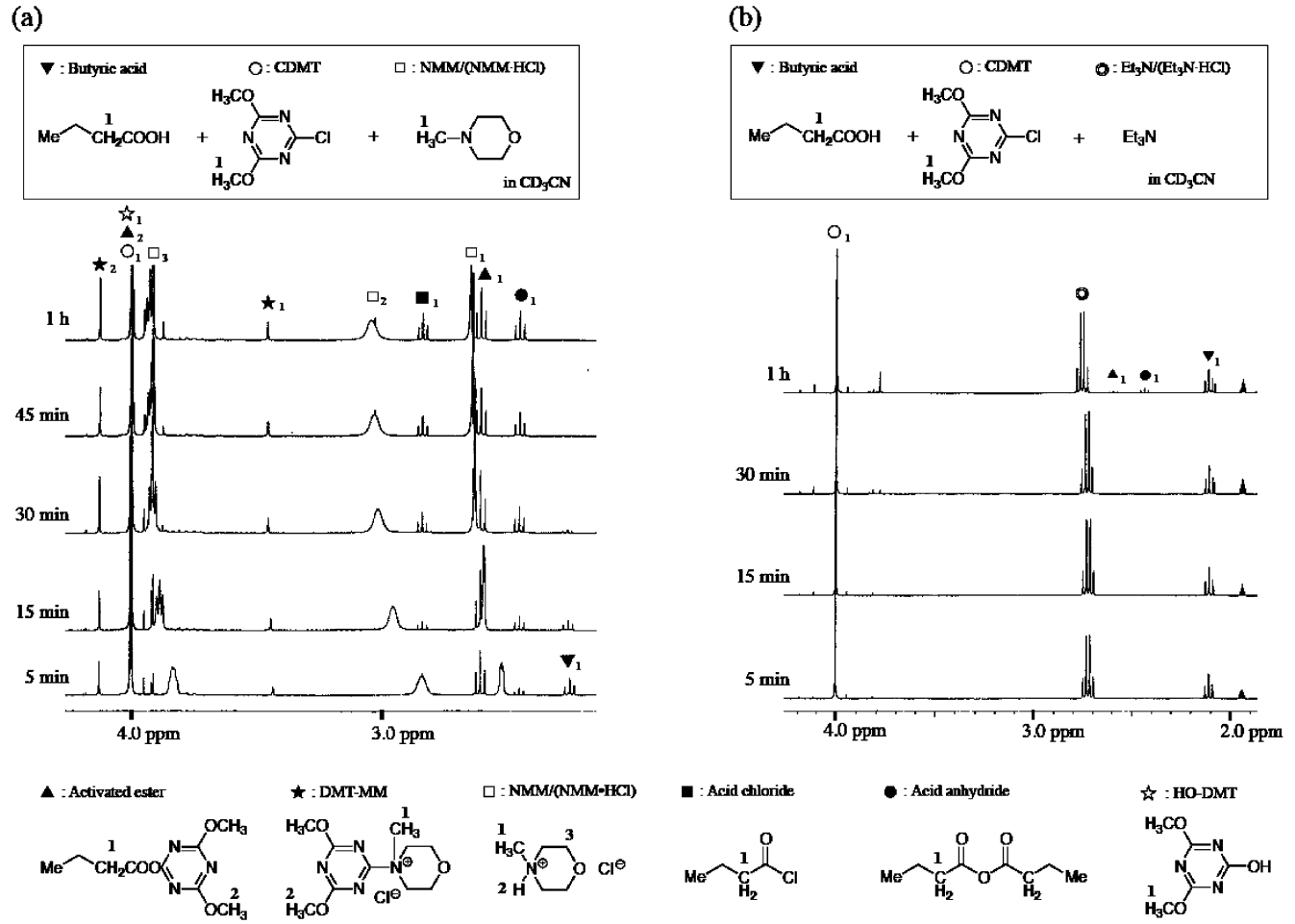


Figure 12. NMR spectroscopic analysis of a mixture of butyric acid and CDMT in the presence of a *tert*-amine. a) NMM b) TEA. Conditions: 0.1 mM of each compound in [D_3]acetonitrile.

presence or absence of $LiClO_4$. No precipitate was observed after 1 h, and both the starting compounds remained, as determined by TLC analysis. Consequently, these amines are not an exception to our postulate.

Conclusion

We have shown that the direct reaction of CDMT with carboxylates is very slow, whereas DMT-Ams, represented by DMT-MM, resulting from the substitution of the chloride of CDMT with *tert*-amines, react rapidly with carboxylates to give the activated triazinyl carboxylates, which undergo coupling with amines or alcohols to give amides or esters. Nitrogen-containing compounds that successfully react with CDMT to form DMT-Ams are limited to aliphatic *tert*-amines, and aromatic *N,N*-dimethylaniline does not react with CDMT. Although compounds containing an sp^2-hybridized nitrogen, such as pyridines and 1-methylimidazole, were found to react with CDMT, the resulting DMT-Ams did not exhibit dehydrocondensation activity. When DMT-Am is susceptible to auto-decomposition through dealkylation by the chloride ion, the more stable perchlorate DMT-Am(ClO_4) can be obtained in high yields by simply conducting the reaction in the presence of $LiClO_4$. A methyl or larger substituent maintained in a *gauche* relationship with the nitrogen lone pair sterically hinders the approach of CDMT to the lone pair. In the case of *tert*-amines possessing a single *gauche* β-alkyl group, such as the ax-G-conformers of NEM and NEP, and α-branched amines such as DMP or IPDMA, the reaction with CDMT proceeds considerably more slowly, but can still occur. However, the resulting DMT-Ams exhibited only moderate dehydrocondensation activity. In the case of *tert*-amines possessing two *gauche* β-alkyl groups, such as NMM, NMP, NEM, and NEP, having an N-alkyl group in the equatorial position, and TEA, the approach of CDMT to the lone pair is completely inhibited. For the CDMT/*tert*-amine system involving the in situ formation of DMT-Ams, *tert*-amines without *gauche* β-alkyl groups need to be employed to prevent the formation of by-products such as **4** that result from the direct reaction of a primary or secondary amine reactant with CDMT. The pres-

ent study provides a foundation for developing a range of triazine-based dehydrocondensation reagents with new functionality that can be applied in various fields of chemistry.

Experimental Section

General methods: Anhydrous dichloromethane was prepared by distillation from CaH_2 prior to use. *N*-Methyl and *N*-ethyl-4-*tert*-butylpiperidine were prepared by methylation[39] or ethylation[40,41] of 4-*tert*-butylpiperidine, prepared from 4-*tert*-butylpyridine according to the reported method.[42] Other solvents and chemicals were obtained from commercial sources and used as received unless otherwise noted. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker DPX 400 spectrometer. Chemical shifts are reported as δ values relative to tetramethylsilane as internal standard. Infrared spectra were recorded with a Thermo Nicolet FTIR AVATAR 360 spectrometer. ESI-MS and EI-MS spectra were recorded with a Waters Micromass ZQ 2000 spectrometer and JEOL JMS-700 spectrometer, respectively. HRMS were measured with a Bruker Daltonics micrOTOF-Q II spectrometer. Preparative thin-layer chromatography (TLC) was performed with Merck precoated silica gel plates. Melting points are uncorrected. Unless otherwise noted, the chloride salts of DMT-Ams were synthesized from CDMT with the corresponding tertiary amine according to the preparation of DMT-MM reported previously.[3a]

General procedure for the preparation of DMT-Am perchlorate—1-(4,6-dimethoxy-1,3,5-triazin-2-yl)-1-methylpiperidinium perchlorate [DMT-MP(ClO_4)]: 1-Methylpiperidine (621 mg, 6.27 mmol) was added to a solution of CDMT (1.0 g, 5.7 mmol) and lithium perchlorate (667 mg, 6.27 mmol) in THF (19 mL) at RT. After stirring for 30 min, the precipitate was collected by suction, washed with THF, and dried under reduced pressure to give DMT-MP(ClO_4) (1.85 g, 96%). M.p. 144–147°C; IR (KBr): $\tilde{\nu}$=1606, 1523, 1461, 1367, 1103, 1054, 956, 823 cm^{-1}; ^{1}H NMR (CD_3OD): δ=1.59–2.00 (m, 6H), 3.42 (s, 3H), 3.61–3.70 (m, 2H), 4.01 (s, 6H), 4.46–4.55 ppm (m, 2H); ^{13}C NMR (D_2O): δ=20.3 (CH_2), 21.0 (CH_2), 55.5 (N^+CH_3), 56.9 (OCH_3), 62.0 (N^+CH_2), 170.8 (NCN^+), 173.9 ppm ($COCH_3$); MS: *m*/*z*: 239 [$M-ClO_4$]$^+$; elemental analysis calcd (%) for $C_{11}H_{19}ClN_4O_6$: C 39.00, H 5.65, N 16.54; found: C 38.98, H 5.52, N 16.34.

4-(4,6-Dimethoxy-1,3,5-triazin-2-yl)-4-ethylmorpholinium chloride (DMT-EM): Yield: 36%; colorless crystals; m.p. 132–135°C; IR (KBr): $\tilde{\nu}$=1633, 1544, 1490, 1390, 1133, 950, 908, 815 cm^{-1}; ^{1}H NMR (CD_3OD): δ=1.21 (t, *J*=7.3 Hz, 3H), 3.78–3.91 (m, 4H), 3.97 (q, *J*=7.3 Hz, 2H), 4.02–4.10 (m, 2H), 4.19 (s, 6H), 4.52–4.60 ppm (m, 2H); ^{13}C NMR (CD_3OD): δ=8.0 (CH_2CH_3), 57.6 (OCH_3), 59.9 (CH_2), 63.3 (CH_2), 66.9 (CH_2CH_3), 170.1 (NCN^+), 175.3 ppm ($COCH_3$).

4-(4,6-Dimethoxy-1,3,5-triazin-2-yl)-4-ethylmorpholinium perchlorate [DMT-EM(ClO_4)]: Yield: 65%; colorless crystals; m.p. 214–216°C; IR (KBr): $\tilde{\nu}$=1612, 1525, 1483, 1378, 1085, 1041, 910, 817 cm^{-1}; ^{1}H NMR (CD_3OD): δ=1.22 (t, *J*=7.3 Hz, 3H), 3.78–3.89 (m, 4H), 3.95 (q, *J*=7.3 Hz, 2H), 4.07–4.16 (m, 2H), 4.20 (s, 6H), 4.53–4.62 ppm (m, 2H); elemental analysis calcd (%) for $C_{11}H_{19}ClN_4O_7$: C 37.24, H 5.40; found: C 36.99, H 5.31.

1-(4,6-Dimethoxy-1,3,5-triazin-2-yl)-1-ethylpiperidinium chloride (DMT-EP). Yield: 30%; colorless crystals; m.p. 74–80°C; IR (KBr): $\tilde{\nu}$=1614, 1544, 1484, 1378, 1110, 1041, 900, 817 cm^{-1}; ^{1}H NMR (CD_3OD): δ=1.18 (t, *J*=7.3 Hz, 3H), 1.59–1.88 (m, 4H), 1.88–1.98 (m, 2H), 3.55–3.65 (m, 2H), 3.83 (q, *J*=7.3 Hz, 2H), 4.17 (s, 6H), 4.46–4.55 ppm (m, 2H); ^{13}C NMR (CD_3OD): δ=8.3 (CH_2CH_3), 22.3 (CH_2), 22.4 (CH_2), 57.5 (OCH_3), 61.0 (N^+CH_2), 66.2 ($N^+CH_2CH_3$), 170.7 (NCN^+), 175.4 ppm ($COCH_3$); elemental analysis calcd (%) for $C_{12}H_{21}ClN_4O_2\cdot1/2H_2O$: C 39.84, H 6.13; found: C 39.63, H 5.82.

1-(4,6-Dimethoxy-1,3,5-triazin-2-yl)-1-ethylpiperidinium perchlorate [DMT-EP(ClO_4)]: Yield: 31%; colorless crystals; ^{1}H NMR (CD_3OD): δ=1.18 (t, *J*=7.2 Hz, 3H), 1.59–1.88 (m, 4H), 1.88–1.98 (m, 2H), 3.55–3.65 (m, 2H), 3.83 (q, *J*=7.2 Hz, 2H), 4.17 (s, 6H), 4.46–4.55 ppm (m, 2H); elemental analysis calcd (%) for $C_{12}H_{21}ClN_4O_6$: C 40.86, H 6.00; found: C 40.62, H 5.72.

1-(4,6-Dimethoxy-1,3,5-triazin-2-yl)quinuclidinium chloride (DMT-QD): Yield: 97%; pale-yellow crystals; m.p. 97–99°C; IR (KBr): $\tilde{\nu}$=1606, 1548, 1475, 1363, 1110, 1008, 838, 815 cm^{-1}; ^{1}H NMR (CD_3OD): δ=2.13–2.22 (m, 6H), 2.33 (sept, *J*=3.3 Hz, 1H), 4.00–4.08 (m, 6H), 4.16 ppm (s, 6H); ^{13}C NMR (CD_3OD): δ=20.1 (CH), 23.5 (CH_2), 56.0 (OCH_3), 56.3 (N^+CH_2), 172.6 (NCN^+), 173.6 ppm ($COCH_3$); Because of the instability of the chloride, elemental analysis was carried out with its perchlorate; elemental analysis calcd (%) for $C_{12}H_{19}ClN_4O_6\cdot1/2H_2O$: C 40.06, H 5.60; found: C 40.09, H 5.30.

1-(4,6-Dimethoxy-1,3,5-triazin-2-yl)-1-methylpyrrolidinium perchlorate [DMT-MPD(ClO_4)]: Yield: 97%; colorless crystals; m.p. 122–125°C; IR (KBr): $\tilde{\nu}$=1618, 1477, 1373, 1328, 1251, 1083, 935, 823 cm^{-1}; ^{1}H NMR (D_2O): δ=2.19–2.42 (m, 4H), 3.55 (s, 3H), 3.82–3.92 (m, 2H), 4.16 (s, 6H), 4.42–4.52 ppm (m, 2H); ^{13}C NMR (D_2O): δ=22.0 (CH_2), 51.6 (N^+CH_3), 57.0 (OCH_3), 65.8 (N^+CH_2), 170.1 (NCN^+), 173.6 ppm ($COCH_3$); MS: *m*/*z*: 225 [$M-ClO_4$]$^+$; elemental analysis calcd (%) for $C_{10}H_{17}ClN_4O_6$: C 36.99, H 5.28; found: C 37.07, H 5.24.

***N*-(4,6-Dimethoxy-1,3,5-triazin-2-yl)-*N*,*N*,*N*-trimethylammonium chloride (DMT-TMA)**: To a solution of CDMT (1.0 g, 5.70 mmol) in THF (20 mL) was bubbled excess trimethylamine gas, generated by neutralization of its hydrochloride, through a drying tube filled with sodium hydroxide for 30 min. The resultant crystals were filtered and washed with THF. Yield: 1.14 g (85%); colorless crystals; m.p. 96–101°C; IR (KBr): $\tilde{\nu}$=1604, 1523, 1481, 1376, 1054, 821 cm^{-1}; ^{1}H NMR (CD_3OD): δ=3.60 (s, 9H), 4.17 ppm (s, 6H); ^{13}C NMR (CD_3OD): δ=55.0 (N^+CH_3), 57.6 (OCH_3), 174.0 (NCN^+), 175.2 ppm ($COCH_3$); MS: *m*/*z*: 199 [$M-Cl$]$^+$. Because of the hygroscopicity of the chloride, elemental analysis was carried out after counteranion exchange to perchlorate; elemental analysis calcd (%) for $C_8H_{15}ClN_4O_6$: C 32.17, H 5.06; found: C 32.21, H 4.99.

***N*-(4,6-Dimethoxy-1,3,5-triazin-2-yl)-*N*-ethyl-*N*,*N*-dimethylammonium chloride (DMT-EDMA)**: Yield: 86%; colorless crystals; m.p. 80–84°C; IR (KBr): $\tilde{\nu}$=1616, 1540, 1484, 1375, 1045, 821 cm^{-1}; ^{1}H NMR (CD_3OD): δ=1.27 (t, *J*=7.2 Hz, 3H), 3.53 (s, 6H), 3.98 (q, *J*=7.2 Hz, 2H), 4.17 ppm (s, 6H); ^{13}C NMR (D_2O): δ=8.3 (CH_2CH_3), 51.1 (N^+CH_3), 57.1 (OCH_3), 63.7 (CH_2CH_3), 171.1 (NCN^+), 173.6 ppm ($COCH_3$); MS: *m*/*z*: 213 [$M-Cl$]$^+$. Elemental analysis was carried out with its perchlorate; elemental analysis calcd (%) for $C_9H_{17}ClN_4O_6$: C 34.57, H 5.48; found: C 34.51, H 5.36.

***N*-(4,6-Dimethoxy-1,3,5-triazin-2-yl)-*N*,*N*-diethyl-*N*-methylammonium chloride (DMT-DEMA)**: Yield: 80%; colorless crystals; m.p. 90–92°C; IR (KBr): $\tilde{\nu}$=1606, 1477, 1365, 1249, 1047, 815 cm^{-1}; ^{1}H NMR (CD_3OD): δ=1.26 (t, *J*=7.2 Hz, 6H), 3.44 (s, 3H), 3.81–3.92 (m, 2H), 4.08 (q, *J*=7.2 Hz, 1H), 4.11 (q, *J*=7.2 Hz, 1H), 4.17 ppm (s, 6H); ^{13}C NMR (D_2O): δ=8.0 (CH_2CH_3), 44.4 (N^+CH_3), 57.1 (OCH_3), 62.4 (CH_2CH_3), 170.1 (NCN^+), 173.6 ppm ($COCH_3$); MS: *m*/*z*: 227 [$M-Cl$]$^+$. Elemental analysis was carried out with its perchlorate; elemental analysis calcd (%) for $C_{10}H_{19}ClN_4O_6$: C 36.76, H 5.86; found: C 36.75, H 5.77.

1-(4,6-Dimethoxy-1,3,5-triazin-2-yl)pyridinium chloride (DMT-PDN); Yield: 32%; colorless crystals; m.p. 138–142°C; IR (KBr): $\tilde{\nu}$=1621, 1560, 1467, 1363, 1145, 1097, 1027, 939, 798 cm^{-1}; ^{1}H NMR (CD_3OD): δ=3.14 (s, 6H), 8.34–8.40 (m, 2H), 8.96–9.03 (m, 1H), 10.10–10.14 ppm (m, 2H); ^{13}C NMR (CD_3OD): δ=57.7 (OCH_3), 129.4 (*m*-pyr), 142.4 (*o*-pyr), 153.4 (*p*-pyr), 166.4 (NCN^+), 175.2 ppm ($COCH_3$); MS: *m*/*z*: 219 [$M-Cl$]$^+$. Elemental analysis was carried out with its perchlorate; elemental analysis calcd (%) for $C_{10}H_{11}ClN_4O_6$: C 37.69, H 3.48; found: C 37.76, H 3.47.

1-(4,6-Dimethoxy-1,3,5-triazin-2-yl)-4-(dimethylamino)pyridinium chloride (DMT-DMAP): Yield: 87%; colorless crystals; m.p. 290°C (dec.); IR (KBr): $\tilde{\nu}$=1662, 1558, 1456, 1363, 1184, 1143, 1099, 1010, 931, 840, 813, 754 cm^{-1}; ^{1}H NMR (D_2O): δ=3.39 (s, 6H), 4.10 (s, 6H), 7.06 (d, *J*=7.9 Hz, 2H), 9.02 ppm (d, *J*=7.9 Hz, 2H); ^{13}C NMR (CD_3OD): δ=40.7 [$N(CH_3)_2$], 56.7 (OCH_3), 107.8 (*m*-pyr), 136.0 (*o*-pyr), 158.6 (*p*-pyr), 163.9 (NCN^+), 173.0 ppm ($COCH_3$); MS: *m*/*z*: 262 [$M-Cl$]$^+$. Elemental analysis was carried out with its perchlorate. elemental analysis calcd (%) for $C_{12}H_{16}ClN_5O_6$: C 39.84, H 4.46; found: C 39.78, H 4.44.

1-(4,6-Dimethoxy-1,3,5-triazin-2-yl)-3-methyl-1*H*-imidazolium chloride (DMT-MIm): Yield: 69%; colorless crystals; m.p. 166–170°C; IR (KBr): $\tilde{\nu}$=1614, 1554, 1515, 1483, 1367, 1259, 1187, 1143, 1103, 1083, 981, 923, 817, 781 cm^{-1}; ^1H NMR (CD_3OD): δ=4.08 (s, 3H), 4.17 (s, 6H), 7.80 (d, J=2.2 Hz, 1H), 8.41 (d, J=2.2 Hz, 1H), 10.04 ppm (s, 1H); ^{13}C NMR (CD_3OD): δ=37.6 (N^+CH_3), 57.2 (OCH_3), 120.4 (5-imid.), 126.4 (4-imid.), 138.5 (2-imid.), 163.2 (NCN^+), 175.0 ppm ($COCH_3$); MS: m/z: 222 $[M-Cl]^+$. Elemental analysis was carried out with its perchlorate; elemental analysis calcd (%) for $C_9H_{12}ClN_5O_6\cdot 1/2H_2O$: C 32.69, H 3.96; found: C 32.72, H 3.62.

4-*tert*-Butyl-1-(4,6-dimethoxy-1,3,5-triazin-2-yl)-1-methylpiperidinium perchlorate [DMT-MBP(ClO_4)]: Yield: 95%; colorless crystals; m.p. 98–104°C; IR (KBr): $\tilde{\nu}$=1618, 1546, 1479, 1378, 1101, 933, 815 cm^{-1}; ^1H NMR (CD_3OD): δ=0.99 (s, 9H), 1.50–1.61 (m, 1H), 1.90–2.12 (m, 4H), 3.52 (s, 3H), 3.93–4.08 (m, 4H), 4.16 ppm (s, 6H); ^{13}C NMR (CD_3OD): δ=22.7 (CH_2), 27.4 ($C(CH_3)_3$), 32.9 ($C(CH_3)_3$), 44.7 (*C*H-*t*Bu), 46.6 (N^+CH_3), 57.4 (OCH_3), 63.2 (N^+CH_2), 175.0 (NCN^+), 175.2 ppm ($COCH_3$). Structural details were determined by X-ray crystallographic analysis.

4-*tert*-Butyl-1-(4,6-dimethoxy-1,3,5-triazin-2-yl)-1-ethylpiperidinium perchlorate [DMT-EBP(ClO_4)]: Yield: 89%; colorless crystals; m.p. 141.5–142.5°C; IR (KBr): $\tilde{\nu}$=1608, 1567, 1519, 1471, 1376, 1103, 1070, 815 cm^{-1}; ^1H NMR (CD_3OD): δ=0.98 (s, 9H), 1.14 (t, J=7.2 Hz, 3H), 1.45–1.56 (m, 1H), 1.84–1.98 (m, 2H), 2.00–2.10 (m, 2H), 3.78 (dt, J=3.3, 13.3 Hz, 2H), 4.02 (q, J=7.2 Hz, 2H), 4.13–4.20 ppm (m, 8H); ^{13}C NMR (CD_3OD): δ=8.3 (CH_2CH_3), 22.7 (CH_2), 27.5 ($C(CH_3)_3$), 33.0 ($C(CH_3)_3$), 44.8 (*C*H-*t*Bu), 54.4 (CH_2CH_3), 57.5 (OCH_3), 60.6 (N^+CH_2), 173.8 (NCN^+), 175.2 ppm ($COCH_3$); MS: m/z: 309 $[M-ClO_4]^+$; elemental analysis calcd (%) for $C_{16}H_{29}ClN_4O_6$: C 47.00, H 7.15; found: C 47.04, H 6.89.

1-(4,6-Dimethoxy-1,3,5-triazin-2-yl)-1,2-dimethylpiperidinium perchlorate [DMT-DMP(ClO_4)]: Yield: 64%; colorless crystals; m.p. 173–174°C; IR (KBr): $\tilde{\nu}$=1611, 1558, 1524, 1470, 1369, 1096, 1051, 822 cm^{-1}; ^1H NMR (CD_3OD): δ=1.19 (d, J=6.6 Hz, 3H), 1.70–1.84 (m, 1H), 1.90–2.18 (m, 5H), 3.40 (s, 3H), 3.63–3.71 (m, 1H), 4.01–4.11 (m, 1H), 4.17 (s, 6H), 4.58–4.68 ppm (m, 1H); ^{13}C NMR (CD_3OD): δ=16.2 ($CHCH_3$), 21.1 (5-piper.), 22.3 (4-piper.), 28.6 (3-piper.), 39.8 (N^+CH_3), 57.5 (OCH_3), 67.0 (6-piper.), 69.4 (2-piper.), 174.2 (NCN^+), 175.3 ppm ($COCH_3$); MS: m/z: 253 $[M-ClO_4]^+$; elemental analysis calcd (%) for $C_{12}H_{21}ClN_4O_6$: C 40.86, H 6.00; found: C 40.74, H 5.84.

***N*-(4,6-Dimethoxy-1,3,5-triazin-2-yl)-*N*-isopropyl-*N*,*N*-dimethylammonium chloride (DMT-IPDMA)**: Yield: 58%; colorless crystals; m.p. 110–111°C; IR (ATR): $\tilde{\nu}$=1613, 1544, 1488, 1380, 1337, 1105, 1034, 821 cm^{-1}; ^1H NMR (D_2O): δ=1.37 (d, J=6.6 Hz, 6H), 3.43 (s, 6H), 4.15 (s, 6H), 4.54 ppm (sept, J=6.6 Hz, 1H); ^{13}C NMR (CD_3OD): δ=15.9 ($CHCH_3$), 47.2 (N^+CH_3), 56.5 (OCH_3), 70.9 (CH_3CHCH_3), 172.6 (NCN^+), 174.0 ppm ($COCH_3$); elemental analysis calcd (%) for $C_{10}H_{19}ClN_4O_2$: C 45.71, H 7.29; found: C 45.44, H 7.24.

Demethylation of DMT-Ams: A suspension of DMT-Am (0.22 mmol) in CH_2Cl_2 (2 mL) was stirred for 3 h at RT. The reaction mixture was filtered and the filtrate was concentrated to give a residue that was analyzed by NMR spectroscopy.

General procedure for the dehydrocondensation with CDMT/*tert*-amine system: CDMT (35.1 mg, 0.20 mmol) was added to a solution of phenylpropionic acid (30.0 mg, 0.20 mmol) and *N*-methylmorpholine (18.4 mg, 0.18 mmol) in anhydrous dichloromethane (3 mL) at RT. After stirring for 1 h at RT, phenethylamine (22.0 mg, 0.18 mmol) was added at RT. The mixture was stirred for 3 h and extracted with ether. The organic phase was washed successively with water, sat. Na_2CO_3, 5% HCl, and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by preparative TLC (AcOEt) to give *N*-phenethyl-3-phenylpropanamide.[3a]

***N*-(4,6-Dimethoxy-1,3,5-triazin-2-yl)-*N*-phenethylamine (4)**: Colorless crystals; m.p. 113.5–114°C; IR (ATR): $\tilde{\nu}$=1621, 1581, 1476, 1461, 1363, 1106, 815 cm^{-1}; ^1H NMR (CD_3OD): δ=2.90 (t, J=7.0 Hz, 2H), 3.71 (td, J=7.0, 6.2 Hz, 2H), 3.91 (s, 3H), 3.98 (s 3H), 5.54–5.63 (m, 1H), 7.19–7.34 ppm (m, 5H); ^{13}C NMR (CD_3OD): δ=36.1 (CH_2CH_2Ph), 42.6 (CH_2CH_2Ph), 54.9 (OCH_3), 55.0 (OCH_3), 126.9 (Ph), 129.0 (Ph), 129.2 (Ph), 139.2 (Ph), 168.5 (2-triazine), 172.4 ($COCH_3$), 173.0 ppm ($COCH_3$); HRMS: m/z calcd for $C_{13}H_{17}N_4O_2$: 261.1346 $[M+H]^+$; found: 261.1346.

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