Superelectrophiles

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Superelectrophilic Amidine Dications: Dealkylation by Triflate Anion**

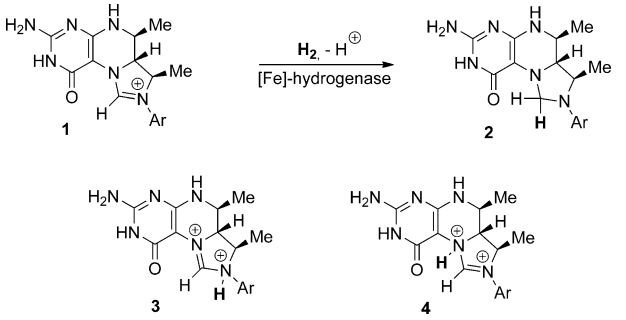
Luka S. Kovacevic, Christopher Idziak, Augustinas Markevicius, Callum Scullion, Michael J. Corr, Alan R. Kennedy, Tell Tuttle, and John A. Murphy**

Superelectrophilic behavior was first observed through activation of electrophiles in superacidic media,[1,2] but the existence of this type of behavior in other media is now of great interest.[2–5] Berkessel and Thauer suggested[3] that superelectrophilic activation could play a role in biology, specifically in the unusual enzymatic reduction of carbon dioxide to methane by certain methanogens.[6]

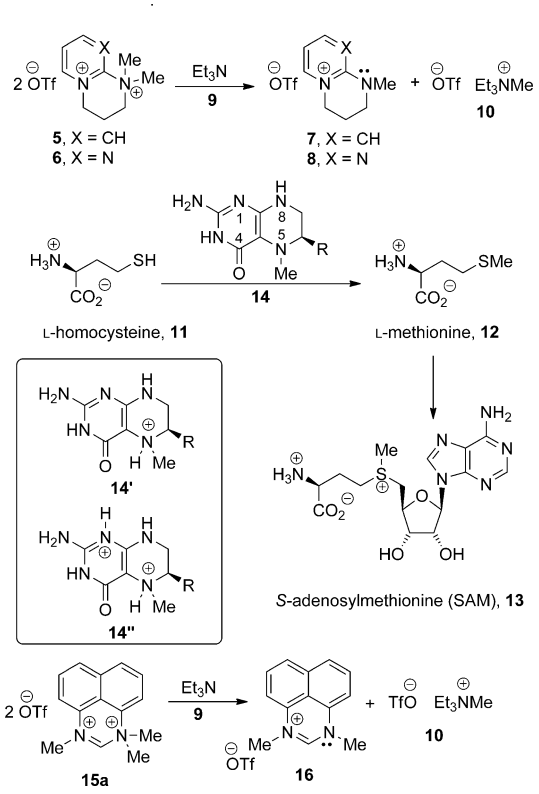
The key step in this enzymatic transformation involved the reduction of methenyltetrahydromethanopterin **1** to **2** by dihydrogen, mediated by an iron-containing hydrogenase. It was proposed that strong activation of **1** is needed within the enzyme for the hydrogenation to **2** to occur and that this would involve protonation of **1** to form a much more electrophilic species, that is, either the amidine dication **3** or **4**. It remained to be determined whether full protonation of **1** (as shown in Scheme 1) or a hydrogen-bonding interaction of **1** with an acidic group represents the necessary activation for the spontaneous hydrogenation to give **2**. Amidine dications have also been proposed as intermediates in synthetic transformations,[4,5] including the hydrolysis of amidines.[7] Salts **5** and **6**, the first fully characterized examples of amidine dications, were good methylating agents for the methylation of triethylamine **9** and had reactivity similar to dimethyl sulfate.[8] However, in a competition experiment involving a mixture of **5** and methyl triflate (MeOTf), and an amine as a nucleophile, MeOTf reacted completely and the salt **5** remained untouched, thus showing that MeOTf was the stronger methylating agent. This result is not surprising considering that the pK_a of triflic acid is -13[9] and that of $MeOSO_3H$, which is similar to that of sulfuric acid, is approximately -3,[9] thus suggesting that triflate anion is a better leaving group than the $MeOSO_3^-$ anion by a factor of approximately 10^{10}.

Herein, we report the design of amidine dications for the superelectrophilic cleavage of N–Me bonds and other N–R bonds. Methyl-transfer reactions involving MeN groups are central to life, an example being the conversion of homocysteine **11** into methionine **12**, which is a key amino acid and the precursor of *S*-adenosylmethionine **13**—the methyl-transfer agent routinely used by nature (Scheme 2).[10]

Two types of enzyme catalyze this transformation of homocysteine into methionine,[11] and the cobalamin-independent methionine synthase is the more remarkable. The



Scheme 1. Proposed amidine salts[3] in the reduction of **1** to **2**.



Scheme 2. Methyl-transfer reactions. Tf = trifluoromethanesulfonyl.

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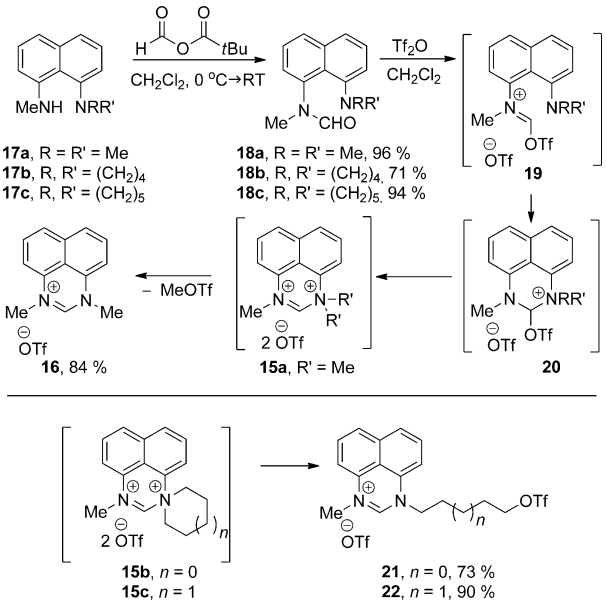
methyl-transfer agent is the tetrahydrofolate **14**. An important question concerns the level of activation that could be achieved for the Me–N bond in tertiary amine **14**,[12,13] a moiety that would normally be expected to be completely unreactive to methyl transfer. The current hypothesis is that cation **14′** (a conjugate acid of **14** with protonation at N^5) is attacked by a zinc-bound thiolate of homocysteine.[13] However, double protonation, as in **14″**, might lead to significantly enhanced reactivity, thus allowing attack by thiol **11** rather than by the corresponding thiolate. But how reactive could a Me–N_{sp^3} bond be?

We envisioned that amidine dications[8] could be used for exploring the limits of synthetic, as opposed to enzymatic, activation toward alkylation.[14,15] An important driving force for the methyl transfers from **5** and **6**, may be that the demethylation reveals a nitrogen lone pair, which can delocalize over the heteroaromatic ring, in the respective products **7** and **8**. Herein, we introduce a new type of amidine dication which was designed to be more reactive in demethylation reactions (Scheme 3). Salt **15a** should undergo demethylation to afford amidinium salt **16**. The lone pair of the demethylated



Scheme 3. Preparation and reactions of amidine dications **15**.

nitrogen atom is appropriately placed for extensive delocalization, which can be reflected in both the reaction kinetics and thermodynamics. The initial challenge was to explore the reactivity of **15**. In the preparation of target salt **15a**, formylation of **17a** afforded **18a** (Scheme 3). Treatment of the resulting formamide with triflic anhydride[15] did not give salt **15a**, but instead gave the expected product of demethylation of salt **15a**, that is, **16**, exclusively in 84% yield upon isolation. The completely selective formation of **16** and the absence of product arising from demethylation of the sp^2-hybridized nitrogen atom in **15a** supported our thinking that the electrons in the scissile C–N bond would be stabilized through their conjugation with the adjoining π system in the transition state of this reaction. To study the novel cleavage reactions further, two other substrates were prepared, the pyrrolidine **18b** and the piperidine **18c**.

If these substrates underwent analogous C–N bond cleavage reactions with triflate ion, then a product containing a triflate ester should be formed. The reaction of **18b** and **18c** with triflic anhydride in anhydrous dichloromethane again did not lead to the respective salts **15b** and **15c**, but instead gave the alkyl triflates **21** (73%) and **22** (90%) in very good yield, thus confirming the hypothesized substitution reaction involving triflate anion. These reactions must proceed by S_N2 mechanisms (see below) because the carbon atom at which substitution occurs in **15a–c** is a methylene or a methyl carbon atom and because the reactions afford a single product in high yield (no alkene resulting from elimination from **15b** and **15c** was observed). The increased reactivity of these systems, relative to **5**, is remarkable. The formation of an alkyl triflate in essentially quantitative yield, as described herein, means that the amidine cation **16** is approximately 100-fold better as a leaving group than triflate ion.[14b,c] To determine the mechanism of demethylation, we carried out a computational investigation on the reactive species outlined in Scheme 3.

The initial reaction of **18a** with triflic anhydride to form salt **19** (R = R′ = Me), which contains both a triflate substituent and a triflate counterion, was calculated as being exothermic ($\Delta G = -3.5$ kcal mol^{-1}). Calculations of the subsequent steps in the reaction show that they can occur either in the presence or in the absence of the triflate counterion (blue curve and red curve in Figure 1, respectively). The intermediate, **20**, which is formed in a facile reaction, is strongly favored thermodynamically relative to **19**. The counterion has little effect on the energetics of the step that forms intermediate **20**, which contains a tetrahedral triflate-bearing carbon atom. Calculations on a reaction involving direct abstraction of the methyl group by the sulfonyl oxygen atom of the triflate substituent *via* a 6-membered cyclic transition state derived from **20** suggest that it is not feasible. Instead, the triflate substituent spontaneously dissociates from the central carbon atom to be placed in the alignment necessary to cleave the C–N bond (see below).

However, in the subsequent step, the dissociation of the triflate moiety to form the planar dicationic species (**15a**), the counterion plays a stabilizing role; the presence of the counterion leads to a slight lowering of the barrier to dissociation as well as to a decrease in the endothermicity of the reaction to 5.8 kcal mol^{-1} (compared with 6.4 kcal mol^{-1}, which is the value calculated when no counterion is present, see Figure 1). Despite the presence of the counterion, the formation of **15a** is thermodynamically disfavored, and the reverse reaction (that is, **15a**→**20**) occurs with a very small barrier (0.5 kcal mol^{-1}). Therefore, the lifetime of **15a** is extremely short and, consistent with the experimental results, is unlikely to be observed. Conversely, the transformation of **20** into **16** is a strongly exothermic reaction (−21.9 kcal mol^{-1}) with an accessible barrier (20.9 kcal mol^{-1}; see Figure 1). For the transformation of **20** into **16**, the inclusion of the triflate counterion was found to play an important role in lowering the barrier to demethylation. However, the demethylation

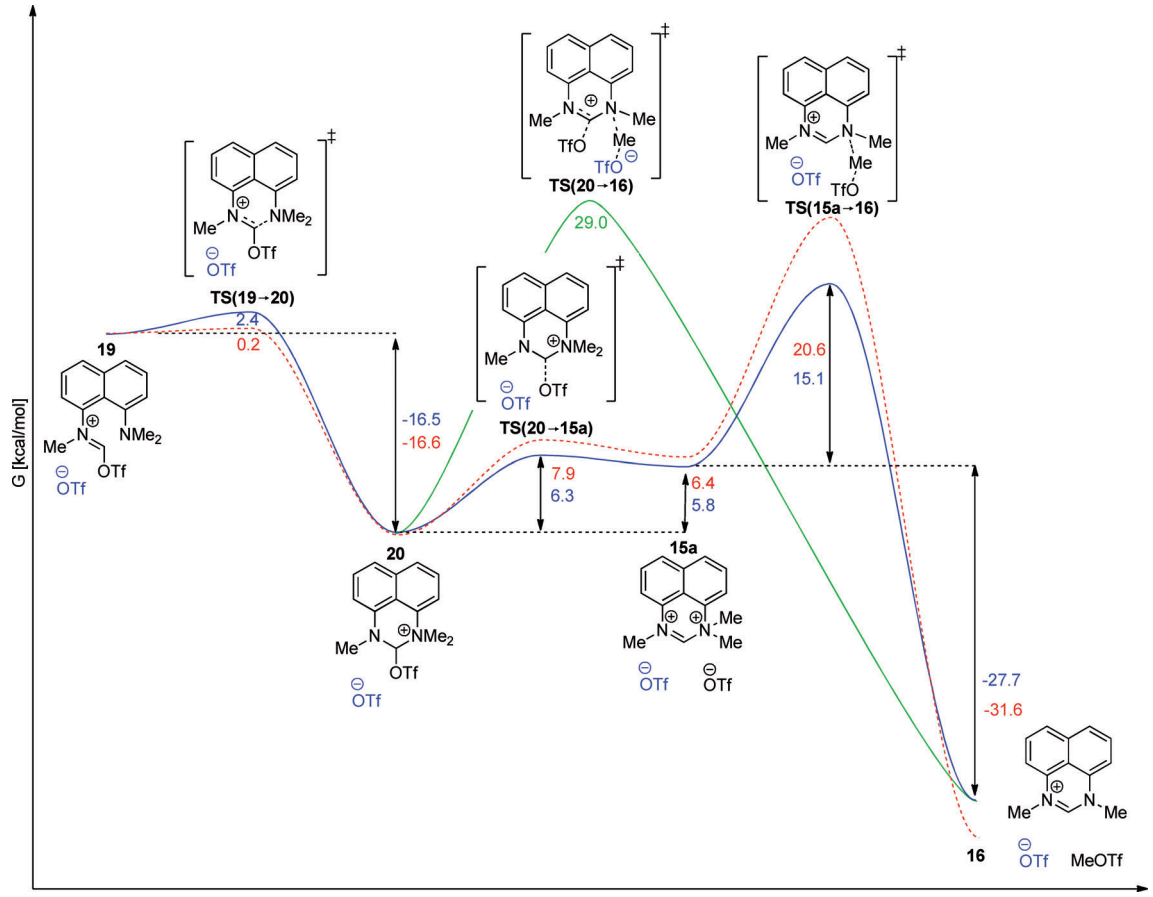


Figure 1. Free Energy (ΔG) profile for the formation of **16** from **19**, (R = Me) via the salt **15a**. Free energies are given in kcal mol^{-1}. Density functional theory (DFT) was used to characterize the respective minima (reactants, intermediates) and first order saddle points (transition states, TS's) on the potential energy surface. All structures were optimised in the solvent phase at the M06/6-311G level of theory.[16,17] The solvation model chosen for the study was the conductor-like polarizable continuum model (CPCM), using dichloromethane as the solvent. The red path corresponds to the calculated energy profile when the triflate counterion is not included in the computations, and the blue path is the energy profile with the counterion (also colored in blue) included; the green path represents a concerted E2 elimination pathway, which involves participation of both triflate moieties.

(formation of **16**) is only able to occur after the dissociation of the triflate substituent (this triflate moiety is colored in black in Figure 1) from the central tetrahedral carbon atom in **20** to form **15a** (see below). Whereas **15a** is unstable, relative to **20** or **16**, it represents a strongly bound reactant complex ($\Delta G =$ 18.2 kcal mol^{-1}) involving dissociated triflate anion for the subsequent demethylation reaction. The methyl group is then transferred to the triflate anion via a classical S_N2 transition state (Figure 2). The product **16** could also form through an alternative reaction pathway that occurs without the predissociation of the triflate substituent from **20** to form **15a**—the concerted attack of the triflate counterion (shown in blue in Figure 1) on the methyl group with a concomitant dissociation of the triflate substituent (**TS(20→16)**, green line, Figure 1], that is, an E2 reaction. The transition state for this pathway, which would lead directly to the product (**16**), was calculated and the associated activation free energy is $\Delta G^* = 29.0$ kcal mol^{-1}. This barrier is too high to make the associated mechanism plausible for the formation of **16** under the experimental conditions. Moreover, the competing process—dissociation to form **15a**, followed by a subsequent S_N2

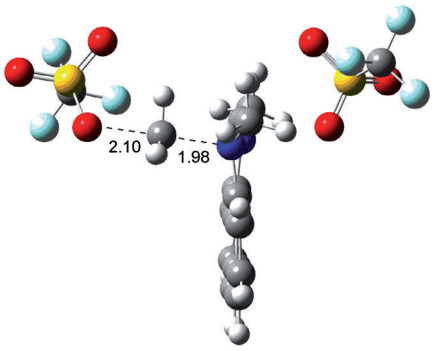
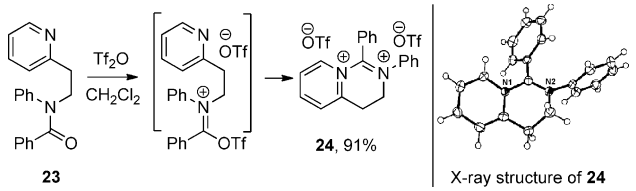


Figure 2. Geometry for **TS(15a→16)**. Distances are given in Å.

demethylation reaction to form **16**—has a significantly lower barrier and hence would be kinetically more favored (see the Supporting Information for similar results that were obtained from calculations on **18b**).

It is obvious that these amidine salts **15a–c** are extremely reactive. To demonstrate conclusively that this method, that is, reacting an amide with triflic anhydride[5] in the presence of

an amine, can lead to the isolation of a fully characterizable amidine salt and not involve dealkylative S_N2 reactions, we chose the precursor amide **23** (Scheme 4). When **23** was treated with triflic anhydride in CH_2Cl_2 it led to salt **24** being isolated in 91% yield and fully characterised by X-ray crystallography.[18]



Scheme 4. Preparation of amidine salt **24**. For the crystal structure, thermal ellipsoids are shown at 50% probability.

In conclusion, we have shown that when incorporated into novel dicationic amidine salts, $C–N_{sp^3}$ bonds can be strongly activated for cleavage, to an extent where even triflate anion can act as the dealkylating nucleophile. The demonstration of this synthetic form of activation suggests that tertiary amines in other settings could be similarly activated. Substrate **14** (Scheme 2) is an interesting example, whereupon formation of salt **14″** might lead to methyl transfer. Even if salt formation does not occur, substrate **14** has numerous heteroatoms that may interact with methionine synthase through hydrogen bonds that, cumulatively, could contribute to its activation for demethylation.

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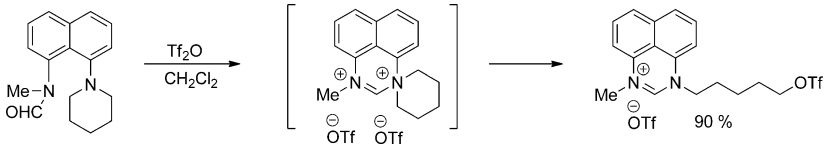
[18] CCDC 881667 (**24**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Communications

Superelectrophiles

L. S. Kovacevic, C. Idziak, A. Markevicius, C. Scullion, M. J. Corr, A. R. Kennedy, T. Tuttle,* J. A. Murphy* ____ ▮▮▮▮–▮▮▮▮

Superelectrophilic Amidine Dications: Dealkylation by Triflate Anion



Superelectrophiles: Formamides were designed that when treated with triflic anhydride would be transformed into superelectrophilic amidine dications. These dications were so electrophilic that they underwent in situ dealkylation by the triflate anion (see scheme; Tf = trifluoromethanesulfonyl). DFT calculations were used to determine the mechanistic details of the dealkylation reaction.