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Amidine Dications as Superelectrophiles

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Abstract: 2-Dimethylalkylammonium pyridinium and 2-dimethylalkylammonium pyrimidinium ditriflate salts are very powerful methylating agents toward phosphorus (triphenylphosphine) and nitrogen (triethylamine) nucleophiles. In competition experiments with triethylamine as nucleophile, these *N*-methyl disalts are more reactive methylating agents than dimethyl sulfate. Reaction of the pyridinium dications with water as an oxygen nucleophile leads to attack at the 2-position of the heteroaromatic ring and displacement of an ammonium group; 2-hydroxypyridinium compounds are formed in the first instance, which are easily converted to 2-pyridones. Extending the scope of the reactions, a tricationic 2,6-bis(dimethylalkylammonium)pyridinium salt has also been prepared and characterized and its reactivity as a methylating agent assessed in comparison with that of the dications.

Introduction

The development of superacids as non-nucleophilic solvents allowed detailed studies of highly reactive acidic and electrophilic organic dications and polycations. For example, the teams of Olah[1] and Hogeveen[2] studied the remarkable properties of such superelectrophilic[3] dicationic species as **1**−**3** (Scheme 1). The reactivity of such superelectrophiles also led to novel intermolecular chemistry as exemplified by the reaction of acetyl cation **5** with 2-methylpropane **7**.[4,5] In the absence of superacid, no reaction was observed, whereas in superacid ($HF\text{-}BF_3$), hydride transfer occurred from the 2-methylpropane **7** to afford *tert*-butyl cation **9** and protonated acetaldehyde **10**. The enhanced reactivity was ascribed to added activation of the acetyl cation **5** by the superacid. At one extreme, this could feature protonation to afford the dication **6**, whereas a less extreme activation could arise through hydrogen bonding (protosolvation) enhancing the polarization of the carbonyl group, represented by **6′**. The unstable species **6** and/or **6′** were neither isolated nor detected spectroscopically, but were inferred from the unusual chemistry that was observed.

Whatever their stability in superacids, the possibility of formation or detection of such reactive species in more routine solvents seemed remote. However, in 1995, Berkessel and Thauer[6] made the revolutionary proposal that superelectrophilic activation might be present in the active site of the N^5,N^{10}-methylenetetrahydromethanopterin dehydrogenase enzyme.[7,8] This was proposed to explain the reactivity of the substrate, methenyltetrahydromethanopterin **11**, toward H_2 in the hydrogenase enzyme, affording methylenetetrahydromethanopterin **14** as product (Scheme 2). At the time of the proposal, it was thought that the enzyme contained no functional metal, and hence that activation of substrate **11** to form a stronger electrophile, the unprecedented amidine dication **12** or **13**, by protonation[6] at a reactive site on the enzyme would rationalize the formal delivery of hydride from H_2. Such a protonation would remove the very strong resonance stabilization present in amidinium salt **11**, leading to exceptionally high reactivity for **12** and **13**. (As with the activation of the acetyl cation **6**, hydrogen-bonding of the additional proton to **11** would represent a less extreme activation than full protonation.) Whereas it is now recognized that an iron atom is situated in the active site,[8] the role of the metal ion has not yet been fully elucidated, and the original activation proposed by Berkessel and Thauer still stands. This reaction is currently the subject of energetic investigation.[9]

In organic chemistry, some dications, e.g. pyrimidinium dication **15**, have been isolated,[10] but they are less reactive than the superelectrophilic amidine dications discussed above. Alkylation of **16** to form **15** requires no sacrifice of mesomeric

(1) (a) Olah, G. A.; Grant, J. L.; Spear, R. J.; Bollinger, M.; Serianz, A.; Sipos, G. *J. Am. Chem. Soc.* **1976**, *98*, 2501–2507. (b) Prakash, G. K.; Krishnamurthy, V. V.; Herges, R.; Bau, R.; Yuan, H.; Olah, G. A.; Fessner, W. D.; Prinzbach, H. *J. Am. Chem. Soc.* **1986**, *108*, 836–838. (c) Olah, G. A.; White, A. M. *J. Am. Chem. Soc.* **1968**, *90*, 6087–6091.

(2) Hogeveen, H.; Kwant, P. W. *Tetrahedron Lett.* **1973**, *14*, 1665–1670.

(3) Superelectrophiles bear more than a single positive charge and are considerably more reactive than their monocationic precursors: (a) Olah, G. A.; Klumpp, D. A. *Superelectrophiles and Their Chemistry*; Wiley-Interscience: NJ, 2008. (b) Olah, G. A.; Klumpp, D. A. *Acc. Chem. Res.* **2004**, *37*, 211–220. (c) Olah, G. A. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 767–788.

(4) Brouwer, D. M.; Kiffen, A. A. *Recl. Trav. Chim. Pays-Bas* **1973**, *92*, 689–697.

(5) Olah, G. A.; Germain, A.; Lin, H. C.; Forsyth, D. A. *J. Am. Chem. Soc.* **1975**, *97*, 2928–2929.

(6) Berkessel, A.; Thauer, R. K. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2247–2250.

(7) Also known as iron−sulfur cluster-free [Fe]-hydrogenase or H_2-forming methylenetetrahydromethanopterin dehydrogenase (Hmd): Zirngibl, C.; Hedderich, R.; Thauer, R. K. *FEBS Lett.* **1990**, *261*, 112−116.

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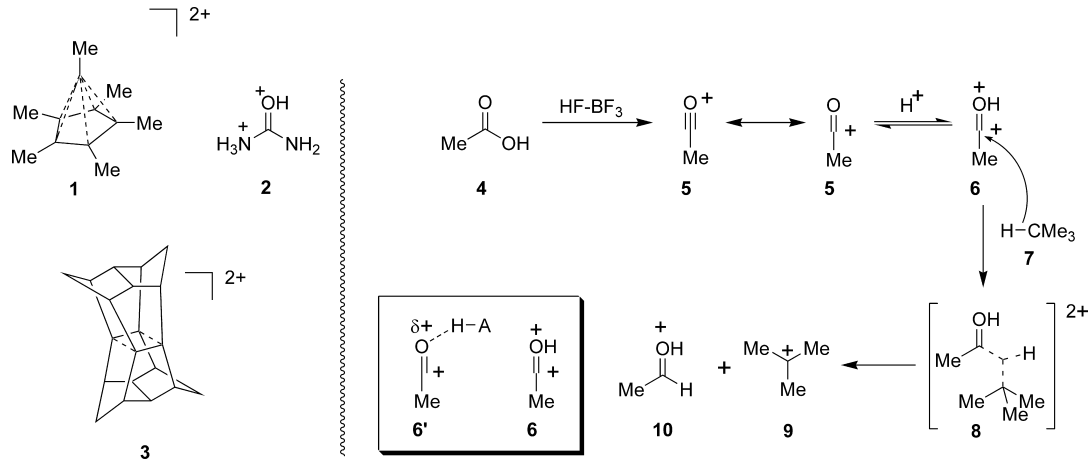
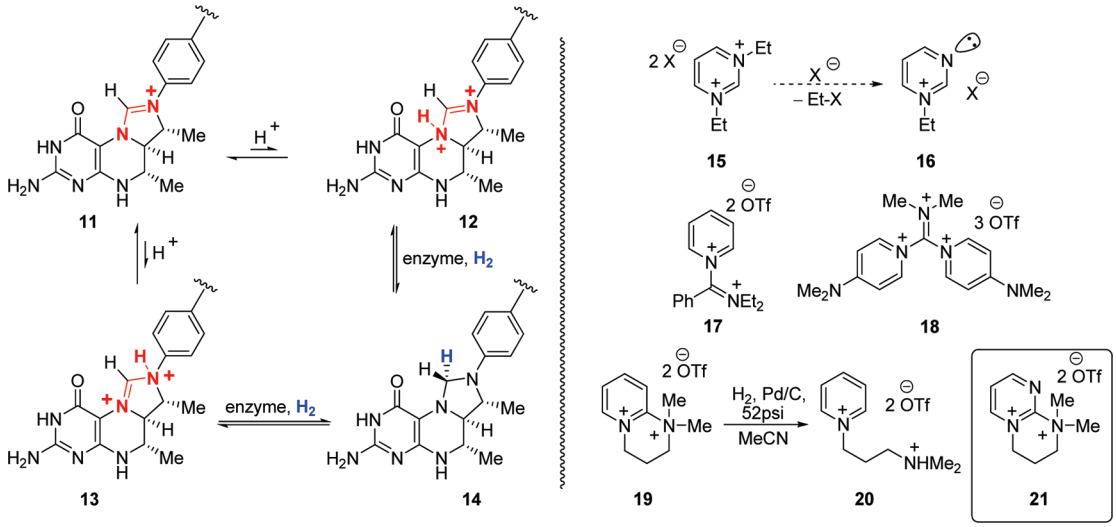
10.1021/ja908191k CCC: $40.75

Scheme 1. Superelectrophiles in superacid



Scheme 2. Dication superelectrophiles



stabilization, and hence, de-ethylation of **15** does not have the added driving force seen for the amidine dications.

Recently, dications such as **17** have been suggested as intermediates in a number of organic synthetic reactions,[11] but isolation of these species has not been reported, and characterization data are sparse.[12] One tricationic salt, **18,** has been isolated;[13] but its reactivity has not been described. However, it is clear that the chemistry of organic dications is now of significant interest.

We recently announced the isolation and characterization of the first amidine dications **19** and **21** and the highly reactive reduction of **19** with H_2 to afford **20**.[9f] The difference in reactivity toward hydrogen gas between dicationic pyridinium salt **19** and moncationic pyridinium salt **20** was very marked, with product **20** being completely unreactive under the hydrogenation conditions. The reactivity of disalt **19** supports the high reactivity proposed by Berkessel and Thauer for their putative disalt intermediates **12** and **13**. (Dications **12** and **13** should be even more reactive toward H_2 than **19** since addition of hydrogen to **19** very likely causes temporary loss of aromaticity in forming a dihydropyridinium intermediate that then collapses to **20**, whereas addition of hydrogen to **12** and **13** would cause no loss of aromaticity.)

This article now describes the clues that set us on the path to the preparation and isolation of these dications, the reactivity of such dications toward phosphorus-, nitrogen- and oxygen-

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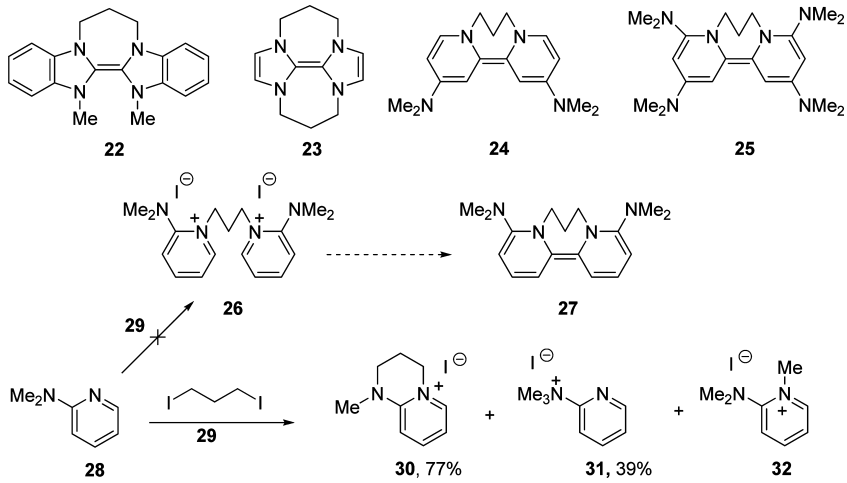
Scheme 3. Electron Donors: Approaches to **27** Produce a Curious Result



nucleophiles, and the preparation and reactivity of a salt containing a related trication.

Results and discussion

Recent studies[14] had allowed us to prepare very strong neutral organic electron donors **22**−**24** (Scheme 3). These compounds, in their ground-state, reduce aryl halides to the corresponding aryl radicals or aryl anions by transfer of one or two electrons, respectively. In doing so, radical cations and dications that show extensive stabilization by the nitrogen atoms are formed from these donors. Among these donors, the most conveniently prepared was the 4-dimethylaminopyridine-derived compound **24** and we were keen to investigate the effect of yet more powerful analogues that featured additional substitution on this bipyridine scaffold. Such donors might be prepared by adding to the electron density of **24** with additional appropriately placed electron-releasing substituents, e.g. **25**.

As a prelude to preparing **25**, we sought to prepare **26** as a precursor to **27** to estimate the effect of the dimethylamino substituents in these positions. This compound was to be prepared by reaction of 2-dimethylaminopyridine (2-DMAP) **28** with 1,3-diiodopropane **29** (Scheme 3). Instead of the expected **26**, three products were formed, **30**−**32**. (Compounds **30** and **31** were isolated from this mixture (in 77% and 39% yield, respectively, based on **29** as limiting reagent—see Supporting Information), while **32** was inferred by comparison of the NMR of the mixture with the analogous triflate salt **39**, shown in Scheme 5.) Salts **31** and **32** arose by methylation of 2-DMAP **28**, and **30** featured incorporation of the 1,3-diiodopropane and loss of a methyl group. In principle **30** could have arisen by demethylation of intermediate monocations **33** or **35** by the pathways shown (Scheme 4). (We envisage that the demethylation step is promoted by DMAP **28**. Alternatively, demethylation could be triggered by iodide ion; this would result in formation of iodomethane, which on reaction with DMAP **28** would afford salts **31** and **32**.)

Experience of pyridinium salt reactivity[15] suggests that such an easy demethylation would be surprising under these conditions, and thus, we proposed that a much more electrophilic species might be in play, i.e. the unprecedented disalt **37**.[9f]

Barbieri and co-workers showed that in 2-DMAP **28**, unlike in 4-DMAP, the dimethylamino group is out of the plane of the ring.[16] In turn, this suggests imperfect overlap between the exocyclic N lone pair and the ring π-system; as a result it is not surprising that 2-DMAP undergoes preferential alkylation on the exocyclic nitrogen.[16] Hence, the favored sequence of events leading to **30** goes through ammonium salt **35** and amidine dication salt **37**. To see whether salt **37** could be prepared, isolated, and characterized, the above experiment was repeated, but the diiodide **29** was replaced by propane-1,3-ditriflate, and the conditions were changed to avoid an excess of **28** being in the reaction at any time. This afforded the ditriflate salt **19** as reported earlier.[9f] Similarly, the disalt **21** was prepared from reaction of 2-dimethylaminopyrimidine with propane-1,3-ditriflate, and both dication salts **19** and **21** were characterized by single-crystal X-ray structure determinations and spectroscopic means.[9f]

The reactivity of ditriflate salt **19** was now investigated (Scheme 5). In particular we were keen to compare its reactivity

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(12) A ^{1}H NMR spectrum and a ^{19}F NMR spectrum were consistent with a two-component mixture containing **17**.[11g]

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(14) (a) Murphy, J. A.; Khan, T. A.; Zhou, S.-Z.; Thomson, D. W.; Mahesh, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1356–1360. (b) Murphy, J. A.; Zhou, S.-Z.; Thomson, D. W.; Schoenebeck, F.; Mahesh, M.; Park, S. R.; Tuttle, T.; Berlouis, L. E. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 5178–5183. (c) Schoenebeck, F.; Murphy, J. A.; Zhou, S.-Z.; Uenoyama, Y.; Miclo, Y.; Tuttle, T. *J. Am. Chem. Soc.* **2007**, *129*, 13368–13369. (d) Murphy, J. A.; Garnier, J.; Park, S. R.; Schoenebeck, F.; Zhou, S.-Z.; Turner, A. T. *Org. Lett.* **2008**, *10*, 1227–1230. (e) Garnier, J.; Murphy, J. A.; Zhou, S.-Z.; Turner, A. T. *Synlett* **2008**, *14*, 2127–2131. (f) Cutulic, S. P. Y.; Murphy, J. A.; Farwaha, H.; Zhou, S.-Z.; Chrystal, E. *Synlett* **2008**, 2132–2136. (g) Murphy, J. A.; Schoenebeck, F.; Findlay, N. J.; Thomson, D. W.; Zhou, S.-Z.; Garnier, J. *J. Am. Chem. Soc.* **2009**, *131*, 6475–6479.

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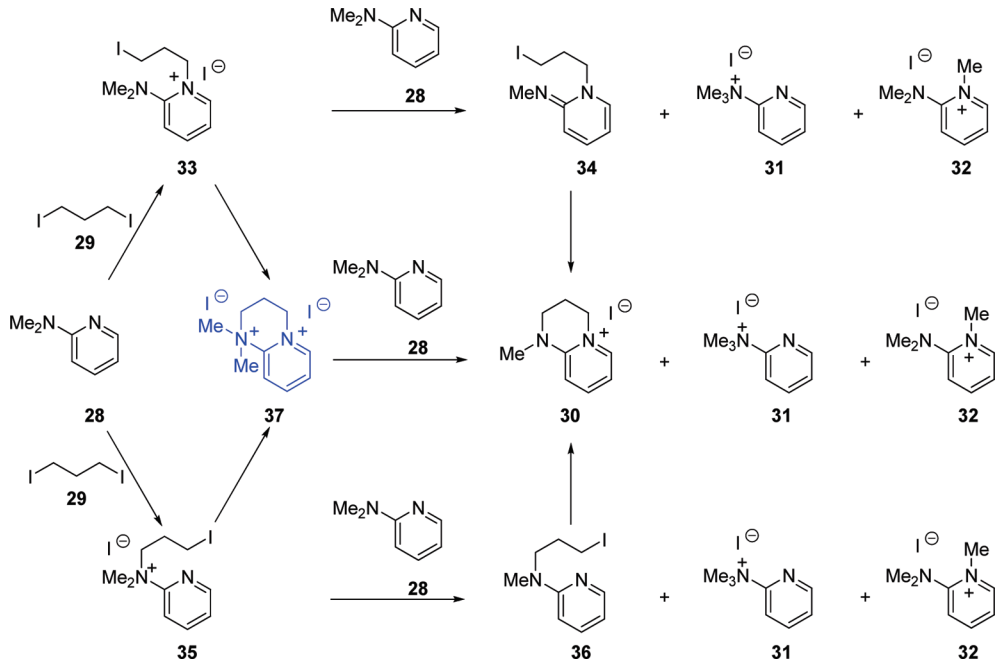
Scheme 4



Scheme 5

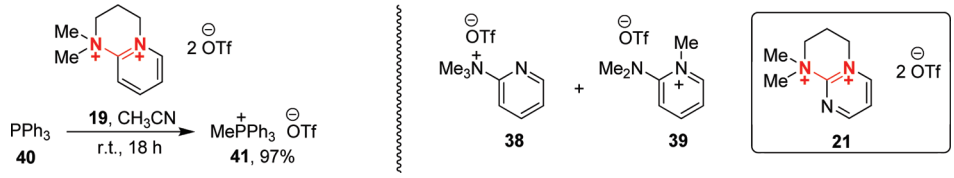


Table 1. Results of Methylation of Triphenylphosphine **40**

entry	salt	solvent	*T*/°C	**40** recovered/%	salt recovered (**38** or **39**)/%	yield **41**/%
1	**19**	PhCl	reflux	–	N.A.	95
2	**19**	CH_3CN	r.t.	–	N.A.	97
3	**38**	PhCl	reflux	29	29	52
4	**38**	CH_3CN	r.t.	96	98	–
5	**39**	PhCl	reflux	100	67	–
6	**39**	CH_3CN	r.t.	90	84	–

with monocationic counterparts, **38** and **39**. All three salts were separately reacted with triphenylphosphine **40** as a nucleophile in both chlorobenzene at reflux and acetonitrile at r.t. In chlorobenzene the salts were reacted at reflux temperature to ensure solubility. The results (Table 1) show that disalt **19** shows the highest reactivity, methylating triphenylphosphine **40** in almost quantitative yield in both solvents (entries 1−2). Monocation salt **38** exhibited some reactivity, showing 52% methylation of **40** after 18 h in chlorobenzene (Table 1, entry 3) but showing no reaction with **40** when acetonitrile was the solvent (entry 4). In contrast, monocation **39** showed no reaction with **40** in either solvent (entries 5−6).

To determine the power of disalt **19** as a methylating reagent toward nitrogen nucleophiles, in comparison to the commercially available methylating reagents iodomethane, dimethyl sulfate, and methyl trifluoromethanesulfonate, each individual methylating reagent and disalt **19** were reacted in a 1:1 competition reaction. Equimolar solutions of **19** (1 equiv) and each separate commercial methylating reagent (1 equiv) were treated with triethylamine **42** (1 equiv), which was found to undergo very fast methylation at r.t. upon treatment with disalt **19** (Scheme 6). Using cyclooctatetraene **46** as an internal nonreacting NMR standard, the quantities of each methylating reagent before and after the addition of triethylamine **42** in each competition experiment were determined by ^{1}H NMR analysis (Table 2). (It was recognized that slow reaction occurs between the disalt **19** and the CD_3CN solvent—hence, the need for an inert standard, cyclooctatetraene **46**.)

As can be seen from the results, disalt **19** is a far more powerful methylating reagent than iodomethane (Table 2, entry 1), with 100% of the iodomethane being present 5 min after the addition of **42**. Disalt **19** even shows slightly higher reactivity than dimethyl sulfate (Table 2, entry 2), with 47% and 41% of **19** and dimethyl sulfate being consumed respectively (i.e., 53% and 59% remaining at the end of the experiment). In the case of methyl trifluoromethanesulfonate (entry 3), the high reactivity of this potent methylating reagent is shown, with virtually no demethylation of disalt **19** observed.

To test the methylating ability of disalt **21**, the competitive methylation of triethylamine **42** with dimethyl sulfate was examined. The results (entry 4) show that pyrimidine disalt **21** is indeed a stronger methylating reagent than dimethyl sulfate with 23% and 70% of the methylating reagents remaining, respectively, after treatment with one equivalent of triethylamine **42**.

These compounds are the most reactive substrates known for transfer of a methyl group from an sp^3 nitrogen. Such transfers are very important in biology[17] in the formation of methionine **52** from homocysteine **51** (Scheme 7). The methyl group is

(17) Matthews, R. G. *Acc. Chem. Res.* **2001**, *34*, 681–689.

Scheme 6. Reaction of Disalts with Triethylamine **42**, with Water, and with NaOH

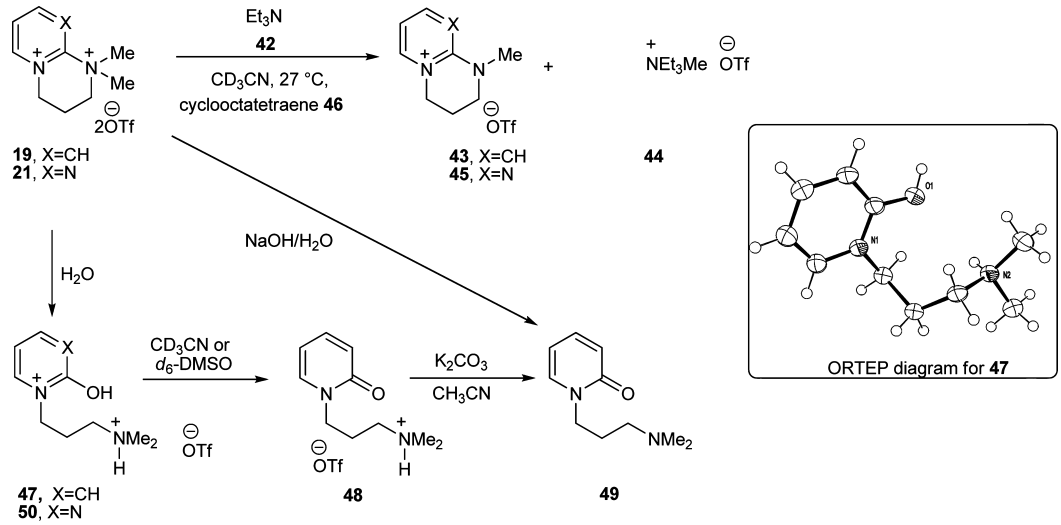


Table 2. Competitive Methylation Study of Triethylamine **42** with Disalts **19**, **21** and **61** at 27 °C in CD_3CN

entry	disalt used	methylating reagent (MR)	amount remaining[a]/%	
			disalt	MR
1	**19**	MeI	0[b]	100[c]
2	**19**	Me_2SO_4	53[b]	59[d]
3	**19**	MeOTf	94[b]	0[e]
4	**21**	Me_2SO_4	23[f]	70[d]
5	**64**	Me_2SO_4	53[g]	–

[a] All proton signal integrations were taken relative to 1,3,5,7-cyclooctatetraene at δ_H 5.77 ppm. All experiments were carried out in CD_3CN. [b] Proton signal for Me groups at δ_H 3.84 ppm used. [c] Proton signal for Me group at δ_H 2.09 ppm used. [d] Proton signal for Me groups at δ_H 3.94 ppm used. [e] Proton signal for Me group at δ_H 4.27 ppm used. [f] Proton signal for Me groups at δ_H 3.85 ppm used. [g] Proton signal for ArH groups at δ_H 7.30 ppm used.

transferred from the tertiary amine N^5-methyltetrahydroflate (N^5-MeTHF, **53**) and extensive discussion has taken place on the possible mechanism of the reaction. In the MetE enzyme, where the transfer takes place directly to homocysteine, the currently accepted proposal[17] is that the N^5-protonated ammonium salt **55** is the actual substrate for this transfer. Dicationic electrophiles have never been proposed as intermediates in that reaction,[18] but would a dication be a reasonable intermediate? It is known that tetrahydrofolates are easily oxidized structures,[19] and recent cyclic voltammetry studies on the closely related tetrahydrobiopterin **58**,[19] have shown a single two-electron wave in a reversible oxidation, implying that the second electron is transferred as easily or more easily than the first. If N^5-MeTHF, **53**, transfers two electrons, then it forms a dication **56**. Such a highly reactive electrophile could be an excellent substrate for methyl transfer, and since the transfer of a methyl group from N^5-MeTHF is widely viewed as a reaction with a problematic mechanism[17] (in terms of the likely degree of reactivity of **55**), then (along with the hydrogenase proposal of Berkessel and Thauer), this could be another example where superelectrophiles have a key role to play in enzyme reactions.[20] We are now scrutinizing the relative ease of transfer of the methyl group from dicationic and monocationic derivatives of **53** and will report on this in due course.

Returning to the reactivity of disalt **19**, its reactions with water and also with sodium hydroxide were next examined. With water, conversion into hydroxypyridinium disalt **47** occurred cleanly (Scheme 6), and this disalt was fully characterized, including a single crystal X-ray structure determination. The compound is quite reactive, and over a period of several days in CD_3CN, or instantly upon the addition of d_6-DMSO, hydroxypyridinium salt **47** was converted to pyridone salt **48**. This was shown by an upfield shift in the ring protons and corresponding ring carbon signals. Comparison of the NMR spectra of pyridone salt **48** and 1-methylpyridone[22] show very similar values for the relevant signals in the ^1H NMR and ^{13}C NMR spectra.

Reaction of 2-DMAP disalt **19** with saturated sodium hydroxide solution led to the formation of pyridone **49**. The absence of the protonated nitrogen of **48** is shown by the upfield shift in the methyl and methylene protons of **49** compared to **48**. Pyridone **49** shows methylene protons at δ_H (d_6-DMSO) 1.79, 2.34, and 3.88 ppm compared to 2.04, 3.05, and 3.93 ppm for pyridone **48**. The methyl protons in **49** appear as a singlet at δ_H (d_6-DMSO) 2.24 ppm and as a doublet at δ_H (d_6-DMSO) 2.78 ppm $J(H,H) = 5.0$ Hz for pyridone salt **48**. Conversion of pyridone salt **48** to pyridone **49** was simply achieved by treating the former with base (Scheme 6).

Hydrolysis of **21** also occurred very readily (in undried d_6-DMSO) and led to hydroxypyrimidinium salt **50** as shown

(18) For earlier chemical modelling, and discussion of mechanistic possibilities, including oxidation, see: Hilhorst, E.; Chen, T. B. R. A.; Iskander, A. S.; Pandit, U. K. *Tetrahedron* **1994**, *50*, 7837–7848.

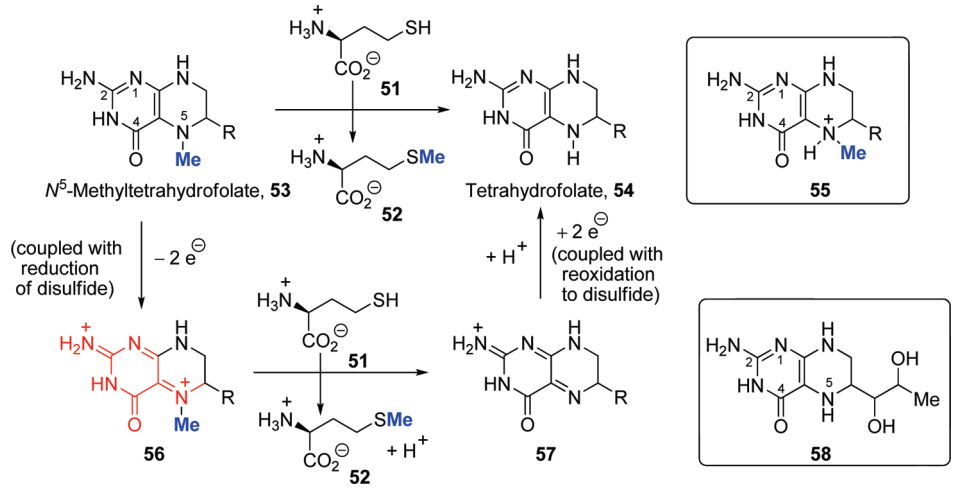
(19) Hoke, K. R.; Crane, B. R. *Nitric Oxide* **2009**, *20*, 79–87.

(20) This begs the question of how the proposed oxidation would occur. It is known that no external co-factor (that could be reduced, to balance the oxidation of the N^5-MeTHF) is involved. Within a protein, a disulfide might fit this role, but the published structure of the MetE enzyme, with both homocysteine and N^5-MeTHF loaded, shows no disulfides. However, the preparation of the samples of the enzyme for X-ray crystallography involves treating the enzyme with Zn^{2+} but also with *tris*(2-carboxyethyl)phosphine or dithiothreitol (DTT),[21] reagents that are specifically designed to break disulfide bonds. When prepared in the absence of such reductants, a disulfide is seen in the protein structure.[21a]

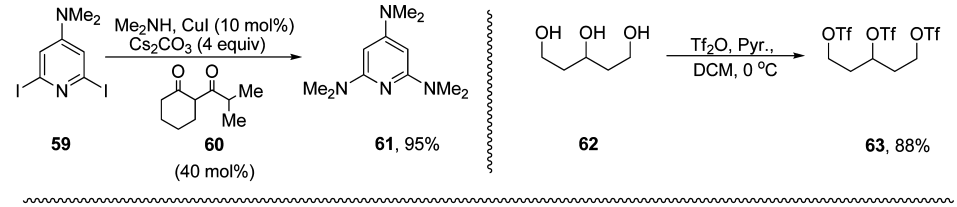
(21) (a) Pejchal, R.; Ludwig, M. L. *PLoS Biology* **2005**, *3*, 254–265. (b) Ferrer, J.-L.; Ravanel, S.; Robert, M.; Dumas, R. *J. Biol. Chem.* **2004**, *279*, 44235–44238.

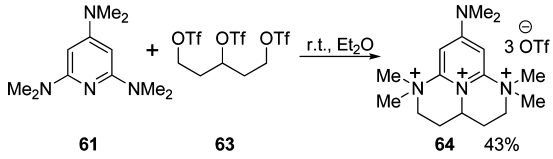
(22) 1-Methyl-2-pyridone: ^1H NMR ($CDCl_3$) δ 3.54 (s, 3H; CH_3), 6.17 (ddd, $J(H,H) = 8.1, 6.6, 1.4$ Hz, 1H, H-5), 6.54 (dd, $J(H,H) = 9.7, 1.4$ Hz, 1H, H-3), 7.34 (ddd, $J(H,H) = 9.7, 6.6, 2.2$ Hz, 1H, H-4), 7.35 (dd, $J(H,H) = 8.1, 2.2$ Hz, 1H, H-6); ^{13}C NMR ($CDCl_3$) δ 34.7 (CH_3), 105.8 (CH), 120.2 (CH), 138.8 (CH), 139.7 (CH), 162.9 (CO); Shiina, I.; Kawakita, Y. *Tetrahedron Lett.* **2003**, *44*, 1951–1955.

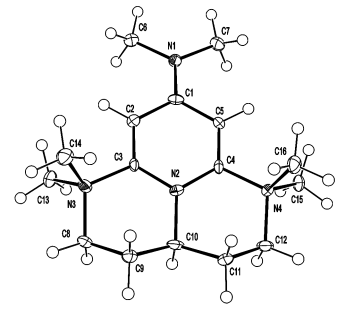
Scheme 7



Scheme 8. Synthesis of Trication Salt **64**







ORTEP diagram of the trication of **64**

(Scheme 6). The ^{1}H NMR spectrum of **50** shows aromatic signals at δ_H (d_6-DMSO) 6.91 and 8.83 ppm, further downfield than expected for that of a pyridone-type species.[22] The ^{13}C NMR spectrum shows the signal for the quaternary carbon in the ring at δ_C (d_6-DMSO) 149.6 ppm, further upfield than expected if a pyrimidone had formed.

The amidine disalts **19** and **21** are the first amidine dication salts to be isolated, characterized and studied, which on dealkylation, afford resonance-stabilized amidinium salts. To develop this chemistry, we sought to prepare a salt that incorporates a trication. For this, 2,4,6-tris(dimethylamino)pyridine **61** was prepared[23] from the known 2,6-diiodo-4-dimethylaminopyridine **59**,[24] and tritriflate **63** was prepared from pentane-1,3,5-triol **62** (Scheme 8). Reaction of pyridine **61** with 1,3,5-tritriflate **63** in the presence of diethyl ether led to formation of trisalt **64** (43%). Full characterization of trisalt **64**, including X-ray crystal structure determination, confirmed that the structure was indeed as shown.

Salt **64** was subjected to the methylation competition reaction with dimethyl sulfate as carried out previously. The results showed that trication **64** had approximately the same reactivity as dimethyl sulfate (Table 2, entry 5). The enhanced electrophilicity expected from a tricationic electrophile is balanced in this case by the electron-releasing effect of the *p*-dimethylamino group.

In summary, we have reported the methylating ability of dication salts **19** and **21**. Both salts show methylating power stronger than that of dimethyl sulfate. Trication salt **64** has also been synthesized and shows decreased methylating ability compared to dication salts **19** and **21**, influenced by the *p*-dimethylamino group.

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Supporting Information Available: Experimental procedures as well as ^{1}H and ^{13}C NMR spectra of compounds and CIF files for **47** and **64**. This material is available free of charge via the Internet at http://pubs.acs.org.

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