Amidine Dications as Superelectrophiles

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Abstract: 2-Dimethylalkylammonium pyridinium and 2-dimethylalkylammonium pyrimidinium ditriflate salts are very powerful methylation agents toward phosphorus (triphenylphosphine) and nitrogen (triethylamine) nucleophiles. In competition experiments with triethylamine as nucleophile, these N-methyl disalts are more reactive methylation 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 methylation 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 and Hoogeveen studied the remarkable properties of such superelectrophilic dicaticonic species as 1–3 (Scheme 1). The reactivity of such superelectrophilic acids 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-BF₃), hydride transfer occurred from the 2-methylpropane group, represented by ν′. 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 made the revolutionary proposal that superelectrophilic activation might be present in the active site of the N₇N₁₀, methylenetetrahydromethanopterin dehydrogenase enzyme. This was proposed to explain the reactivity of the substrate, methylenetetrahydromethanopterin (11, toward H₂ 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 at a reactive site on the enzyme would rationalize the formal delivery of hydride from H₂. 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, 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.

In organic chemistry, some dications, e.g. pyrimidinium dication 15, have been isolated, but they are less reactive than the superelectrophilic amidine dications discussed above. Alkylation of 16 to form 15 requires no sacrifice of mesomeric stabilization.
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, but isolation of these species has not been reported, and characterization data are sparse. One tricationic salt, 18, has been isolated; 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 H2 to afford 20. The difference in reactivity toward hydrogen gas between dicationic pyridinium salt 19 and monocationic 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 H2 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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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 \(22 \rightarrow 24\) (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 electrode 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-diodopropane \(29\) (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-diodopropane 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 \(37\).\(^{29}\)

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 \(\pi\)-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.\(^{29}\) 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.\(^{30}\)

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

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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). Mono-cation 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 1H NMR analysis (Table 2). (It was recognized that slow reaction occurs between the disalt 19 and the CD3CN 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 sp3 nitrogen. Such transfers are very important in biology in the formation of methionine from homocysteine (Scheme 7). The methyl group is

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transferred from the tertiary amine N5-methyltetrahydrofibrate (N5-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 is that the N5-protonated ammonium salt 55 is the actual substrate for this transfer. Dicationic electrophiles have never been proposed as intermediates in that reaction, but would a dication be a reasonable intermediate? It is known that tetrahydrofibrates are easily oxidized structures, and recent cyclic voltammetry studies on the closely related tetrahydrobiopterins 58, 59 have shown a single two-electron wave in a reversible oxidation, implying that the second electron is converted to pyridone salt 49 upon the addition of d5-Me2SO4. 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-methylpyridine show very similar values for the relevant signals in the 1H NMR and 13C 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 δH 4.27 ppm used. Proton signal for Me group at δH 4.27 ppm used. Proton signal for Me group at δH 4.27 ppm used. Proton signal for ArH groups at δH 7.34 ppm used.

Hydrolysis of 21 also occurred very readily (in undried d6-DMSO) and led to hydroxyypyrimidinium salt 50 as shown 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 hydroxyypyrimidinium 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 CD3CN, or instantly upon the addition of d6-DMSO, hydroxyypyrimidinium 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-methylpyridine show very similar values for the relevant signals in the 1H NMR and 13C NMR spectra.

Table 2. Competitive Methylation Study of Triethylamine 42 with Disalts 19, 21 and 61 at 27 °C in CD3CN

| entry | disalt used | methylating reagent (MR) | amount remaining/% |
|-------|-------------|--------------------------|--------------------|
| 1     | 19          | MeI                      | 90                 |
| 2     | 19          | Me2SO4                   | 53                 |
| 3     | 19          | MeOTf                    | 94                 |
| 4     | 21          | Me2SO4                   | 23                 |
| 5     | 64          | Me2SO4                   | 53                 |

| 21 | X=N |
|---|---|
| 42 | X=N |
| 43 | X=N |
| 44 | X=N |
| 47 | X=N |
| 48 | X=N |
| 49 | X=N |

(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 N5-MeTHF) is involved. Within a protein, a disulfide might fit this role, but the published structure of the MetE enzyme, with both homocysteine and N5-MeTHF loaded, shows no disulfides. However, the preparation of the samples of the enzyme for X-ray crystallography involves treating the enzyme with Zn2+ but also with dicarboxamidophosphine or dithiothreitol (DTT), 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.

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(22) 1-Methyl-2-pyridone: 1H NMR (CDCl3) δ 3.54 (s, 3H, CH3), 6.17 (dd, J(H, H) = 8.1, 6.6, 1.4 Hz, 1H, H-5), 6.54 (dd, J(H, H) = 9.7, 6.6, 2.2 Hz, 1H, H-4), 7.34 (dd, J(H, H) = 8.1, 2.2 Hz, 1H, H-6); 13C NMR (CDCl3) δ 34.7 (CH3), 105.8 (CH), 128.2 (CH), 139.7 (CH), 162.9 (CO); Shiina, I.; Kawakita, Y. Tetrahedron Lett. 2003, 44, 1951–1955.

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The 1H NMR spectrum of 50 shows aromatic signals at δH (d6-DMSO) 6.91 and 8.83 ppm, further downfield than expected for that of a pyridine-type species.22 The 13C NMR spectrum shows the signal for the quaternary carbon in the ring at δC (d6-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 prepared23 from the known 2,6-diiodo-4-dimethylaminopyridine 59,24 and triflate 63 was prepared from pentane-1,3,5-triol 62 (Scheme 8). Reaction of pyridine 61 with 1,3,5-triflate 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 1H and 13C 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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