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Amidine Dications: Isolation and [Fe]-Hydrogenase-Related Hydrogenation

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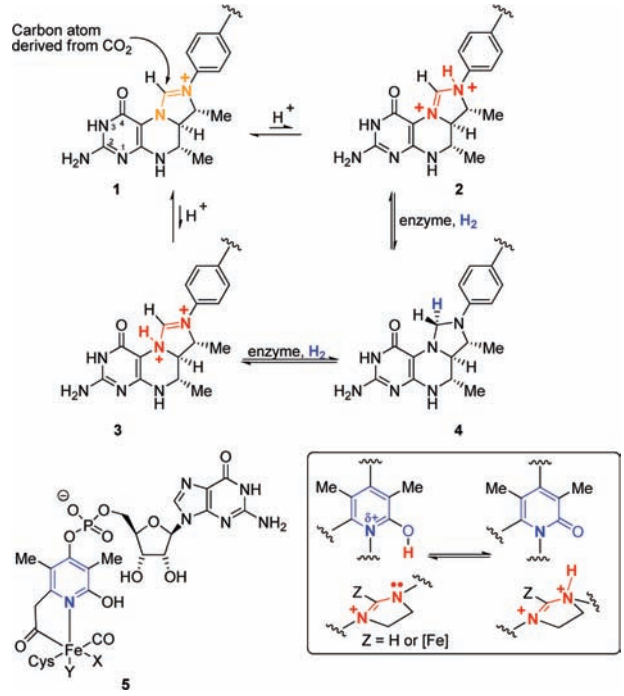
Recycling excess carbon dioxide into useful chemicals is a topical and important challenge. Methanogenic bacteria reduce carbon dioxide to methane. In a key step, an [Fe]-hydrogenase[1] containing a single atom of iron in the active site effects[2] the conversion of N^5,N^{10}-methenyltetrahydromethanopterin [methenyl-H_4MPT$^+$] (**1**) to the reduced product, methylene-H_4MPT (**4**) (Scheme 1). In this step, the incorporated carbon atom derived from CO_2 is thus reduced from the formic acid oxidation state in **1** to the formaldehyde oxidation state in **4**. A greater understanding of this process could be very useful in planning a role for CO_2 as a chemical feedstock.

Berkessel and Thauer proposed[3] a mechanism for this intriguing transformation that involves superelectrophilic activation of the amidinium salt **1** as dication **2** and/or **3**. Such dications should significantly enhance the reactivity of the N−C−N carbon of the amidine. Their proposal is important not only in providing a possible rationale for the chemistry but also in extending the idea of superelectrophiles[4,5] to the world of biology, far away from the superacid media where they have been generated to date. Recently, the structure of the iron complex **5** at the active site of this hydrogenase was reported on the basis of X-ray studies.[1b,6] From this, complexation of a 2-hydroxypyridine to Fe through a nitrogen atom was proposed. Such a hydroxy group should be very acidic and might provide the proton used in the activation of **1** (Scheme 1 inset). Recent revision of the structure of the iron complex in the enzyme to **5**, based on an EXAFS study,[6b] adds to the challenge of modeling the iron complex.[7]

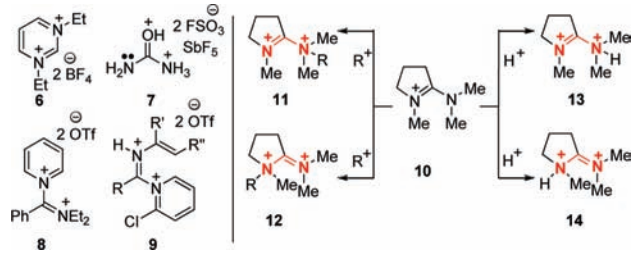
In relation to the organic substrate **1**, the dication proposal of Berkessel and Thauer has not been modeled in the laboratory.[8,9] The amidine dications **2** and **3** are likely to be very reactive, so questions arise about their very existence, particularly in the environment of an enzyme, which is so much less polar than the superacid medium where superelectrophiles have usually been made to date. [Pyrimidine dications (e.g., **6**[10a]) are known, as is **7**,[10b] the diprotonated form of urea formed in superacid solution. Recent elegant synthetic investigations have afforded spectroscopic evidence in favor of intermediates **8**[10c] and **9**,[10d] but these compounds have not been isolated or fully characterized.[10e,f]] This article demonstrates the preparation, isolation, and full characterization of salts based on superelectrophilic amidine dications[10g] in organic solvent as well as the regiospecific reaction of one such salt with H_2 gas in the presence of a metal catalyst (Pd/C), mimicking the behavior in the hydrogenase.

The preparation of amidine dications such as **2** and **3** sets a major challenge. We chose to avoid protonation of amidinium salts such as **10** as the route to our target dication structures, instead choosing alkylation (Scheme 2). If alkylation of salt **10** could be achieved, it should lead to dications **11** and/or **12**. For these compounds, spectroscopic characterization and even isolation might be possible, in contrast to ephemeral protonated counterparts such as **2**, **3**, **13**, and **14**. The alkylated amidine dications (e.g., **11** and **12**) would

Scheme 1. Enzymatic Reduction of Substrate **1**



Scheme 2. Amidinium Dications



be useful probes of reactivity in comparison with monocation **10**, paralleling the comparison of dications **2** and **3** with monocation **1**.

Our choice of a suitable starting amidine stemmed from the known[11] but surprising methylation product of 2-dimethylaminopyridine (2-DMAP) (**15**) (Scheme 3). Reaction with MeI preferentially afforded product **16** (X = I) rather than methylation on the ring nitrogen, consistent with imperfect overlap of the exocyclic N lone pair in **15** with the π system of the pyridine ring. We reasoned that since alkylation occurs on the exocyclic nitrogen of **15**, the ring nitrogen in the resulting monocation might be capable of reaction as a nucleophile and thereby lead to the desired dications. In the event, reaction of 2-DMAP **15** with ditriflate **17** led to reactive 2-DMAP disalt **18** in 98% yield (Scheme 3). The structure of

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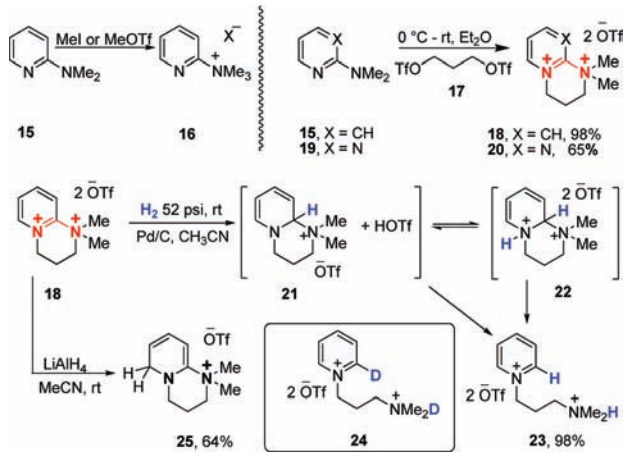
Scheme 3. Alkylation of **15** and **19** and Hydrogenation of **18**



sensitive disalt **18** was confirmed by ^{1}H and ^{13}C NMR spectroscopy, an X-ray crystal structure, and mass spectrometry (MS) analysis, which showed a signal at *m*/*z* 82 with a ^{13}C satellite peak separation of 0.5 u, denoting the dication portion of disalt **18**.

To see whether a more reactive dication could be formed, 2-dimethylaminopyrimidine (**19**) was prepared and reacted with ditriflate **17**. Recrystallization gave pure disalt **20** (65%).

The key enzymatic reaction to be modeled with these dications is the conversion of **2** or **3** to **4**. As **20** has a very short lifetime in acetonitrile, the more stable of our two characterized dications, **18**, was chosen for further study. If hydrogenation were effected, and if the substrate were to behave analogously to proposed intermediates **2** and **3** from the hydrogenase reaction by formally receiving "hydride" on the central carbon of the amidine dication, the reaction would afford intermediate **21** and/or **22**. It was recognized that hydrogenation of substrate **18** should be more difficult than that of **2** or **3**, since the aromaticity of the pyridinium salt would be disrupted in such intermediates. However, these intermediates would likely undergo isomerization to the pyridinium salt **23**. As a monocationic pyridinium ring rather than a dicationic superelectrophile, this compound would be expected to undergo hydrogenation far less readily than **18**, facilitating its isolation.

Reaction of **18** with hydrogen gas (52 psi) led to clean formation of pyridinium salt **23**, which was isolated in 98% yield (Scheme 3). No evidence of further reduction of **23** or of intermediates en route to **23** could be seen. [When salt **16** (X = OTf) was exposed to H_2/Pd/C under the same conditions, no reaction was seen, underlining the enhanced reactivity of dication **18** relative to monocationic pyridinium salts]. Repeating the reaction of **18** with deuterium gas (54 psi) led to the corresponding specifically labeled product **24**. No evidence was seen of labeling in other positions on the pyridinium ring, such as might arise from regiodiverse, reversible H_2/D_2 additions.

The observed hydrogenation *formally* results from abstraction of hydride from H_2 by the highly electrophilic substrate **18**. However, to probe whether hydride-delivery reagents would give the same result, disalt **18** was reacted with a more normal hydride source, $LiAlH_4$. This cleanly afforded dihydropyridine **25** (64%), a regiochemical outcome quite different from that seen in the hydrogenation reaction.

It is clear that significant activation of an amidinium salt toward reaction with H_2 arises in dication **18**, as predicted by Berkessel and Thauer for **2** or **3**. The details of the mechanism of hydrogen transfer in the enzyme as well as details of the reactive complex remain to be elucidated. In particular, the interaction between iron complex **5** and substrate **1** could involve substrate **1** acting as a ligand on the Fe atom of **5**, either by coordination through the carbonyl oxygen at C4 (see **1** in Scheme 1) or possibly as an N-heterocyclic carbene (see the Scheme 1 inset, Z = [Fe]) arising from deprotonation of the amidinium salt region of **1**. Binding the substrate in such a way could station it appropriately for delivery of hydrogen and formation of **4**.

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Supporting Information Available: Experimental procedures, NMR spectra for the compounds discussed, and CIF files for compounds **18** and **20**. This material is available free of charge via the Internet at http://pubs.acs.org.

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