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consistent with the conclusions summarized in **4**.

Other NOEs (Table II) give information about possible conformational states of the peptide. Proton **3b** gives NOEs to both α_3 and ω_3 with the former being more intense. Protons α_3 and ω_3 are on opposite sides of the molecule—see **2**); thus there is probably some conformational flexibility of the aromatic ring **3**, with **3b** on average being somewhat nearer to α_3 than to ω_3. Also noteworthy is the NOE $\alpha_2 \leftrightarrow \delta_2$ (Table II). This NOE establishes that the side chain of residue **2** spends some of its time coiled up such that the terminal carbon atom of the sidechain is proximate to its α-CH proton. The structure of WS-43708A is reproduced with stereochemical detail in **5**; and, as a CPK model, in a conformation which is in accord with the above findings, in Figure 1. In this latter representation, we have rotated the covalent structure **1** through 180° about a vertical axis bisecting the C–C bond connecting the aromatic residues **1** and **3**. This has been done because what transpires to be a concave face of the molecule is now presented upwards.

The site to which WS-43708A binds in exerting its antibacterial activity is unknown. However, addition of the cell wall analogue N-Ac-D-Ala-D-Ala[7] to a DMSO-d_6 solution of the antibiotic free base affected neither the chemical shifts nor the line shapes of the proton resonances. This situation still pertained as trifluoroacetic acid was then added stepwise to the solution to reduce the "pH". Additionally, the addition of N-Ac-D-Ala-D-Ala, or di-N-Ac-Lys-D-Ala-D-Ala[7] to a solution containing WS-43708A (0.1–0.2 mg/mL in 0.02 M sodium citrate buffer, pH 5.1) did not affect its original UV spectrum. We conclude that WS-43708A exerts its physiological action on cell wall biosynthesis other than by binding to mucopeptide precursors terminating in D-Ala-D-Ala.

Experimental Section

^{1}H NMR spectra were obtained on a Brucker AM-400 spectrometer using approximately 20 mg/mL solutions in DMSO-d_6. One-dimensional spectra were usually recorded with a spectral width of 3500–4500 Hz and 16K data points. Two-dimensional double quantum filtered COSY (DQFCOSY), NOESY, and CAMELSPIN experiments were all run in the phase-sensitive mode. NOESY spectra were measured with various mixing times (0.3–0.5 s) to obtain the optimum NOES without spin diffusion. Two CAMELSPIN experiments were recorded with different transmitter offsets to check for false enhancements;[4] the same spin-locking durations of 200 ms was used in both cases. All the 2D data matrices consisted of 512 2K spectra, which yielded, after zero-filling in F1 and Fourier transformation, a 1-MW square matrix. A maximum of 32 scans were accumulated in each t_1 fid with proper phase cycling. The data were subjected to Lorentizian–Gaussian multiplications in t_2 and sine bell multiplication (SSB1 valve of 3) in t_1 prior to transformation. UV studies were carried out with a Pye Unicam PU 8800 UV/Vis spectrometer and followed a previously published procedure.[7]

Acknowledgment. We thank SERC for financial support and Dr. M. Hashimoto (Fujisawa Pharmaceutical Co. Ltd.) for a sample of WS-43708A.

Registry No. Antibiotic WS-43708A, 100296-21-7.

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Formal Transfers of Hydride from Carbon–Hydrogen Bonds. Attempted Generation of Molecular Hydrogen by Intramolecular Reduction of Protons Bound by 2,3-Dihydro-1,3-dimethyl-2-(2-pyridinyl)-1*H*-benzimidazole

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Received May 4, 1987

2,3-Dihydro-1,3-dimethyl-2-(2-pyridinyl)-1*H*-benzimidazole (**5**) is designed to bind electrophilic substrates and reduce them by an internal transfer of hydride. The intended binding site is the nitrogen atom of the pyridine ring, and the source of hydride is the carbon–hydrogen bond at C_2 of the dihydrobenzimidazole ring. In the preferred conformation of compound **5**, the carbon–hydrogen bond is activated as a donor of hydride by two antiperiplanar lone pairs, and the intended binding site is nearby. Protons bind primarily to the nitrogen atom of the pyridine ring as expected, but they are not reduced to molecular hydrogen. Instead, two other reactions are triggered by protonation. One is heterolysis of the carbon–carbon bond between the dihydrobenzimidazole and pyridinium rings, and the other is a 1,2-shift of hydride from the activated carbon–hydrogen bond to the pyridinium ring. The failure of compound **5** to reduce protons to molecular hydrogen can be attributed primarily to unfavorable thermodynamics; the hydridic carbon–hydrogen and acidic nitrogen–hydrogen bonds of salt **5**-H$^+$ are inadequately activated, so alternative reactions are more rapid. Formation of hydrogen may also be disfavored because salt **5**-H$^+$ adopts an unsuitable conformation or because an appropriate trajectory for intramolecular protonation of the activated carbon–hydrogen bond is unattainable.

We are interested in the design and synthesis of reducing agents that have some of the features of redox enzymes, including a receptor site that recognizes and binds reducible substrates, and an adjacent site that acts as a donor of hydride. In enzymatic reductions involving the coenzyme NADH, Cannizzaro reactions, Meerwein–Ponndorf–Verley reductions, and other important redox reactions, carbon–hydrogen bonds serve as the donors of hydride. The subdued reactivity of these bonds makes them particularly suitable when the substrate must be recognized, oriented, and activated by a receptor before the transfer of hydride takes place. We have therefore begun to study compounds in which a reducible substrate is held close to a suitably activated carbon–hydrogen bond.[1]

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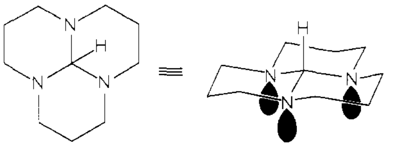
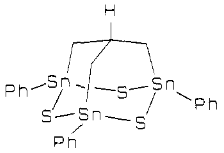
Carbon–hydrogen bonds activated by antiperiplanar lone pairs or carbon–metal bonds are especially good formal donors of hydride.[2] For example, orthoformamide **1** reduces mineral acids to molecular hydrogen,[2c] and stannaadamantane **2** reduces activated halides to the corresponding hydrocarbons.[2a] Related compounds like the fanciful aminal **3**, which contains a receptor site and an adjacent carbon–hydrogen bond activated by two antiperiplanar lone pairs, may therefore be able to bind suitable substrates S^+ and reduce them by an internal transfer of hydride (eq 1). Realization of this hypothetical reduction would presumably require that the lone pairs remain antiperiplanar to the carbon–hydrogen bond in complex **4** and that the bound substrate assume a position near the activated carbon–hydrogen bond. We accepted the challenge of designing a molecule complex enough to satisfy these conformational requirements, yet simple enough to be easy to make.



1



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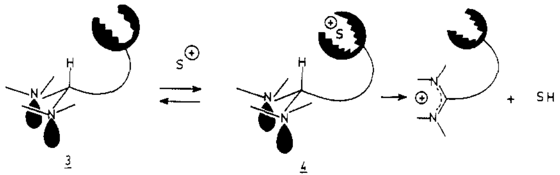
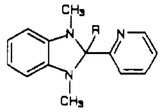


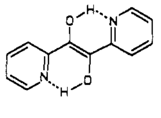
(1)

3 4

A potential solution to this problem is provided by 2,3-dihydro-1,3-dimethyl-2-(2-pyridinyl)-1*H*-benzimidazole (**5**). This simple molecule contains a carbon–hydrogen bond adjacent to two lone pairs in a dihydroaromatic ring, and the pyridyl nitrogen can serve as a point of attachment for reducible substrates. Compound **5** was easily synthesized in 64% yield by the condensation[3] of 2-pyridinecarboxaldehyde with *N*,*N*′-dimethyl-1,2-benzenediamine.[4] This condensation was best effected in benzene at 25 °C in the presence of 4-Å molecular sieves, since the more vigorous conditions of azeotropic distillation led to the formation of large amounts of enediol **6**, the product of a benzoin condensation of 2-pyridinecarboxaldehyde.[5] Oxidation of dihydrobenzimidazole **5** occurred readily, providing evidence for the high reactivity of the activated carbon–hydrogen bond.[3,6] For example, oxidation with iodine in the presence of potassium carbonate produced 1,3-dimethyl-2-(2-pyridinyl)benzimidazolium iodide (**7**) in 54% yield.[7]



5 (R = H)
5-d (R = D)



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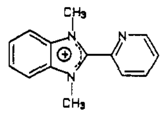
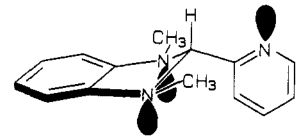
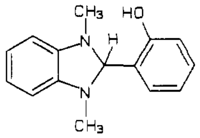


7

We believe that a delicate balance of steric and electronic factors[8] makes structure **5a** the major conformer of compound **5**. In this structure, the five-membered ring has the expected envelope shape,[9] the hybridization of its two nitrogen atoms is shallowly pyramidal,[8a,d] and the two lone pairs are axial and antiperiplanar to the activated carbon–hydrogen bond. In addition, the pyridine ring is nearly perpendicular to the average plane of the five-membered ring, and the lone pair of the pyridyl nitrogen avoids the other two lone pairs. This preferred conformation is very similar to structure **8a**, which is adopted by the closely related dihydrobenzimidazole **8** in the solid state.[10] Both nitrogen atoms of the dihydrobenzimidazole ring of compound **8** are distinctly pyramidal, the *N*-methyl groups are equatorial, and the dihedral angle defined by the average planes of the hydroxyphenyl and dihydrobenzimidazole rings is 77°. Although the pyramidalization of one nitrogen in dihydrobenzimidazole **8** and the large dihedral angle result in part from the need to incorporate an internal hydrogen bond, we believe that structure **8a**



5a



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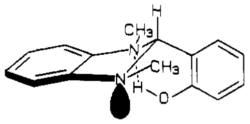

8 8a

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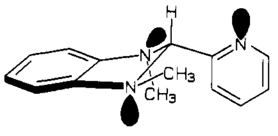
serves as a reliable model for the conformations of other dihydrobenzimidazoles. Additional indirect support for hypothetical conformation **5a** comes from studies of nicotine[11] and other relatives of dihydrobenzimidazole **5**.[6c] In contrast, molecular mechanics calculations[12] predict that the five-membered ring should be nearly planar and that the nitrogen atoms should be sp^2 hybridized. This discrepancy presumably arises because current versions of the molecular mechanics programs may systematically underestimate the pyramidalization of nitrogen in derivatives of aniline.

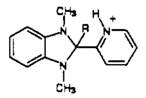
Direct evidence that compound **5** prefers conformation **5a** came from spectroscopic studies in solution and in the solid state. The ^1H NMR spectrum of compound **5** ($CDCl_3$) revealed that H_3 of the pyridine ring, which is directed toward the axial lone pairs of the dihydrobenzimidazole ring in hypothetical conformer **5a** and should therefore be deshielded,[13] is in fact δ 0.70 ppm farther downfield than the corresponding hydrogen in 2-methylpyridine.[14] Under these conditions, the other pairs of corresponding hydrogens have chemical shifts that differ by no more than δ 0.25. In addition, the proposed antiperiplanar orientation of the carbon–hydrogen bond at C_2 of the dihydrobenzimidazole ring and the two adjacent lone pairs should allow mixing of σ^*_{CH} with the lone-pair orbitals and lead to spectroscopically detectable weakening of the carbon–hydrogen bond.[15] Aliphatic carbon–hydrogen stretching produces two strong bands at 2860 and 2800 cm^{-1} in the infrared spectrum of dihydrobenzimidazole **5** (KBr) as well as a series of weaker Bohlmann bands ranging from 2740 to 2550 cm^{-1}. This region of the infrared spectrum of deuterium-labeled compound **5**–*d*, which was prepared by reducing benzimidazolium iodide **7** with $NaBD_4$,[16] contains only the strong bands at 2860 and 2800 cm^{-1} and a broad carbon–deuterium stretching band centered at 1990 cm^{-1}. We conclude that the *N*-methyl groups of compound **5** are responsible for the two strong bands at 2860 and 2800 cm^{-1} and that stretching of the carbon–hydrogen bond at C_2 of the dihydrobenzimidazole ring occurs at a lower frequency. This carbon–hydrogen bond is therefore distinctly weakened, but not as dramatically as the central carbon–hydrogen bond of orthoformamide **1**.[2b] Weakening of the activated carbon–hydrogen bond in dihydrobenzimidazole **5** is presumably less striking because fewer antiperiplanar lone pairs are present, and because the delocalized nature of the HOMO of a benzenediamine and the shallow pyramidalization of its nitrogen atoms prohibit strong mixing with σ^*_{CH}.[8e,f]

The only other conformation of dihydrobenzimidazole **5** that is consistent with these observations is structure **5b**, in which one lone pair is equatorial and one is axial. We doubt that conformer **5b** is preferred, however, since it is destabilized by the interaction of an axial methyl group with the pyridine ring. Furthermore, the ^1H NMR spectrum of compound **5** showed only one kind of *N*-methyl group even at very low temperatures (CHF_2Cl, −153 °C), indicating the predominance of symmetrical conformer **5a** or the presence of a mixture of conformers rapidly interconverted by inversion at nitrogen.[8f]



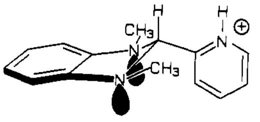
5b

The lone pair of the pyridyl nitrogen in dihydrobenzimidazole **5** is therefore well positioned to bind reducible substrates near an activated carbon–hydrogen bond. We hoped that this favorable juxtaposition would allow compound **5** to bind protons and reduce them to molecular hydrogen.[2c,17] The conjugate acid of 2-methylpyridine (pK_a 5.9)[18] is weaker than the conjugate acid of 1,2-benzenediamine (pK_a 4.5),[18] so protonation of compound **5** might be expected to produce pyridinium salt **5**-H^+.

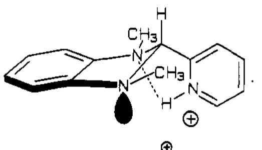


5-$H^{\oplus}$ (R = H)

5-d-$H^{\oplus}$ (R = D)

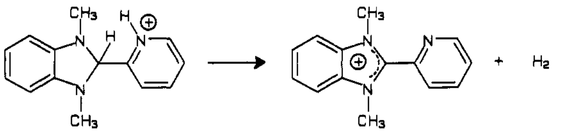


5a-$H^{\oplus}$



5c-$H^{\oplus}$

This expectation was supported by NMR spectroscopy, since the hydriodide formed in 83% yield by treating dihydrobenzimidazole **5** with 1 equiv of hydrogen iodide showed strongly deshielded pyridyl hydrogens and only moderately deshielded *N*-methyl hydrogens. If salt **5**-H^+ were able to adopt conformation **5a**-H^+, the potentially hydridic hydrogen of the activated carbon–hydrogen bond and the acidic hydrogen of the nitrogen–hydrogen bond would be juxtaposed, perhaps facilitating the formation of molecular hydrogen (eq 2). Like phenol **8**,[10] however, hydriodide **5**-H^+ is more likely to adopt a conformation similar to structure **5c**-H^+, in which an internal hydrogen



5-$H^{\oplus}$ 7 (2)

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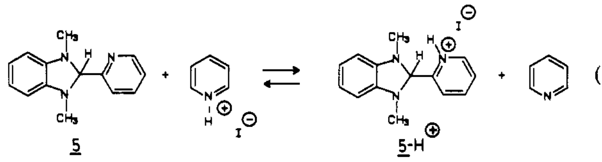
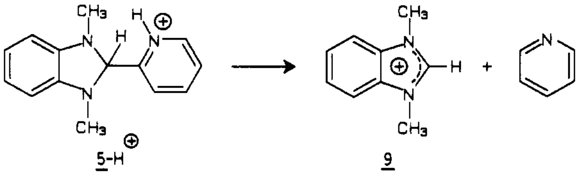
bond can be formed. We expected this hydrogen bond to be weak, since it is severely bent and since the nitrogens have poorly oriented, poorly convergent lone pairs. As a result, the acidic hydrogen should interact more strongly with the nitrogen of the pyridine ring and iodide[19a] than with the nitrogens of the dihydrobenzimidazole ring. Nevertheless, comparison of the infrared spectra of pyridinium iodide[19b] and hydriodide **5**-H$^+$ (hexachlorobutadiene mulls) provided evidence for additional hydrogen bonding in salt **5**-H$^+$. Pyridinium iodide shows a band at 2833 cm^{-1} due to nitrogen–hydrogen stretching, whereas the corresponding band of compound **5**-H$^+$ appears at a somewhat lower frequency (2800 cm^{-1}), indicating stronger hydrogen bonding. Furthermore, the chemical shift of the acidic hydrogen of hydriodide **5**-H$^+$ (δ 14.2, 0.02 M in CD_3CN) is larger than that of pyridinium iodide under comparable conditions,[19a] indicating again that hydrogen bonding is stronger in salt **5**-H$^+$. This additional hydrogen bonding is likely to be intramolecular, particularly in dilute solutions. When the concentration of hydriodide **5**-H$^+$ was further decreased to 0.002 M, the acidic hydrogen moved slightly upfield to δ 13.9, presumably because of increased dissociation of the ion pair.[19a]

Since hydriodide **5**-H$^+$ is primarily a pyridinium salt, its pK_a should closely resemble that of pyridinium. The ^1H NMR spectrum of a dilute solution prepared by mixing equimolar amounts of dihydrobenzimidazole **5** and pyridinium iodide (0.06 M, CD_3CN, 25 °C) showed well-resolved multiplets at chemical shifts that corresponded to a weighted average of those of compounds **5** and **5**-H$^+$.[20] We calculate that the equilibrium constant for the proton exchange of eq 3 is approximately 0.2. Despite the weak internal hydrogen bonding in salt **5**-H$^+$, dihydrobenzimidazole **5** is therefore slightly less basic in CH_3CN than pyridine. This reduced basicity is presumably due to the electron-withdrawing effect of the dihydrobenzimidazolyl group.



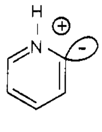
(3)

The internally hydrogen-bonded structure **5c**-H$^+$ does not juxtapose hydridic carbon–hydrogen and acidic nitrogen–hydrogen bonds and is therefore not ideal for the generation of molecular hydrogen, so we expected hydriodide **5**-H$^+$ to be relatively unreactive in the absence of oxidizing agents. We were therefore surprised to find that neat samples or samples dissolved in a variety of solvents decomposed when heated. This decomposition cleanly produces 1,3-dimethylbenzimidazolium iodide (**9**)[21] and pyridine (eq 4). For example, when solid hydriodide **5**-H$^+$ was warmed at 150 °C for 14 h, benzimidazolium iodide **9** was formed in 50% yield, and pyridine could be isolated in 68% yield as pyridinium iodide. No hydrogen could be detected.[22]



(4)

The fragmentation of eq 4 seems to indicate that the carbon–carbon bond between the dihydrobenzimidazole and pyridinium rings of hydriodide **5**-H$^+$ is more easily cleaved than the activated carbon–hydrogen bond. Heterolysis of the carbon–carbon bond would produce benzimidazolium iodide **9** directly. This hypothetical fragmentation would simultaneously produce pyridinium ylide **10**, which would then be converted into pyridine by tautomerization. Formation of ylide **10** is reasonable, since the same intermediate is known to be formed during the closely analogous thermal decarboxylation of 2-pyridinecarboxylic acid.[23] Ylide **10** cannot be eliminated from the preferred, hydrogen-bonded conformation **5c**-H$^+$ with stereoelectronic control,[24] so formation of the more reactive conformer **5d**-H$^+$ may precede fragmentation.



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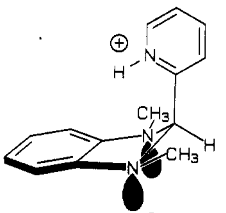
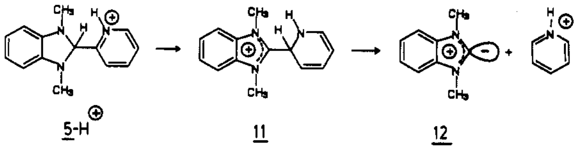


5d-H$^+$

A more subtle alternative mechanism for the decomposition of hydriodide **5**-H$^+$ is described in eq 5. In this sequence, fragmentation is triggered by a 1,2-hydride shift from the activated carbon–hydrogen bond to the adjacent pyridinium ring, producing intermediate dihydropyridine **11**. An analogous intermolecular hydride transfer is also conceivable. In either case, pyridinium is reduced to dihydropyridine, and dihydrobenzimidazole is oxidized to benzimidazolium. Since the reduction potential of benzimidazolium (−1.85 V vs SCE) is somewhat more negative than that of pyridinium (−1.45 V),[25] this redox reaction is thermodynamically feasible. Intramolecular hydride transfer would not necessarily be fast, however, since the activated carbon–hydrogen bond and the pyridinium ring are nearly coplanar in the preferred conformation **5c**-H$^+$.



(5)

Subsequent heterolysis of the carbon–carbon bond between the benzimidazolium and dihydropyridine rings of intermediate **11** would yield pyridinium and the known

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[19] (a) Odinokov, S. E.; Mashkovsky, A. A.; Nabiullin, A. A. *Spectrochim. Acta, Part A* **1983**, *39A*, 1065–1071. Ioganson, A. V.; Kiselev, S. A.; Rassadin, B. U.; Samoilenko, A. A. *Zh. Strukt. Khim.* **1976**, *17*, 629–637. (b) Cook, D. *Can. J. Chem.* **1961**, 2009–2024.

[20] Hine, J.; Li, W.-S. *J. Org. Chem.* **1975**, *40*, 1795–1800.

[21] Breslow, R. *J. Am. Chem. Soc.* **1958**, *80*, 3719–3726. Fischer, O.; Fussenegger, E. *Ber. Dtsch. Chem. Ges.* **1901**, *34*, 936.

[22] Thermolysis of hydriodide **5**-H$^+$ also produces traces of benzimidazolium iodide **7**, the result of the formal loss of molecular hydrogen (eq 2). However, careful attempts to trap hydrogen during the thermolyses by passing effluent gases into a mixture of *trans*-stilbene and palladium on charcoal were unsuccessful. Control experiments established that small, known amounts of hydrogen (1 mmol) could be trapped by this procedure in over 95% yield. We are therefore confident that the traces of benzimidazolium iodide **7** result from the rapid oxidation of hydriodide **5**-H$^+$ by adventitious oxygen.

[23] Dunn, G. E.; Thimm, H. F. *Can. J. Chem.* **1977**, *55*, 1342–1347.

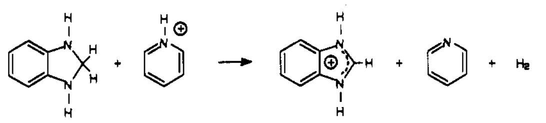
[24] Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon: Oxford, 1983.

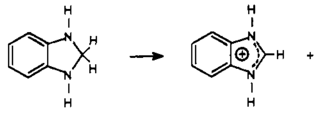
[25] Nelsen, S. F.; Clennan, E. L.; Echegoyan, L.; Grezzo, L. A. *J. Org. Chem.* **1978**, *43*, 2621–2628. Lizogub, A. V.; Pozharskii, A. F.; Sokolov, V. I. *Zh. Obshch. Khim.* **1976**, *46*, 680–687. Timofeeva, Z. N.; El'tsov, A. V. *Ibid.* **1967**, *37*, 2599–2602. Kellogg, R. M.; Piepers, O. *J. Chem. Soc., Chem. Commun.* **1982**, 402–404.

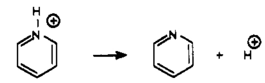
ylide **12**, which is responsible for the rapid base-catalyzed hydrogen–deuterium exchange at C_2 in 1,3-dimethylbenzimidazolium salts.[26] Proton transfer would then give the observed products, pyridine and benzimidazolium iodide **9**.

Both of the two alternative modes of decomposition are observed. However, the preferred mode in solution appears to be the one in which benzimidazolium iodide **9** and ylide **10** are formed directly by heterolysis of the carbon–carbon bond between the dihydrobenzimidazole and pyridinium rings of hydriodide **5**-H$^+$. This preference was revealed by heating deuterium-labeled hydriodide **5**-*d*-H$^+$ in CH_3CN at 60 °C for 9 days. No hydrogen–deuterium scrambling occurred in the starting material under these conditions,[27] and ^2H NMR spectroscopy showed that 70% of the label appeared in 1,3-dimethylbenzimidazolium-2-*d* iodide (**9**-*d*) and 30% in pyridine-2-*d*. Thermolysis in CD_3CN produced essentially identical results. The small amount of labeled pyridine indicates that formal transfer of deuteride from the activated carbon–deuterium bond of hydriodide **5**-*d*-H$^+$ does occur but is a minor reaction under these conditions, perhaps partly because it is opposed by a significant isotope effect. Furthermore, the exclusive formation of pyridine-2-*d* and the absence of the 3- and 4-isomers strongly suggest that the deuteride transfers are intramolecular, since intermolecular transfers would be expected to produce a mixture of isomers.[28,29]

We designed dihydrobenzimidazole **5** to bind protons and reduce them by an internal transfer of hydride from an activated carbon–hydrogen bond. The failure of hydriodide **5**-H$^+$ to react as expected is disappointing but very instructive. One of the origins of this setback is the high reactivity of other parts of the molecule, particularly the pyridinium ring and the carbon–carbon bond between the dihydrobenzimidazole and pyridinium rings. The carefully designed collaboration of the receptor site and the activated carbon–hydrogen bond is therefore thwarted by faster reactions elsewhere in the molecule. This suggests that the hydridic hydrogen of the activated carbon–hydrogen bond in hydriodide **5**-H$^+$ may not be sufficiently hydridic or the acidic hydrogen of the nitrogen–hydrogen bond may not be sufficiently acidic to allow an efficient mutual reaction. To test this possibility, we estimated ΔH for the generation of molecular hydrogen by breaking a similar reaction (eq 6) into the three hypothetical steps of hydride generation (eq 7), proton generation (eq 8), and recombination (eq 9). For deprotonation in the gas phase, ΔH_{298} is 220 kcal/mol, the proton affinity of pyridine.[30] Combination of hydride and a proton liberates 400 kcal/mol.[31] For the generation of hydride (eq 7), ΔH_{298} is approximately 200 kcal/mol, the calculated hydride affinity of benzimidazolium.[32] Consequently, we estimate that the overall reactions of eq 2 and 6 are endothermic by about 20 kcal/mol in the gas phase.[36] The preference of hydriodide **5**-H$^+$ for reactions other than the generation of hydrogen is therefore more easily understood.[38]


(6)


(7)


(8)

$$H^{-} + H^{+} \longrightarrow H_2 \qquad (9)$$

These thermodynamic obstacles may be compounded by kinetic problems. One is the preference of compound **5**-H$^+$ for conformation **5c**-H$^+$, in which the activated carbon–hydrogen and nitrogen–hydrogen bonds are not juxtaposed. Potentially reactive conformation **5a**-H$^+$ may be less readily accessible. Another possibility is that hydriodide **5**-H$^+$ is reluctant to yield molecular hydrogen because an acceptable trajectory for intramolecular protonation of the activated carbon–hydrogen bond cannot be achieved. Although the preferred trajectory for intermolecular versions of this reaction has not been established with certainty,[2c] the rigid, short, four-bond connection of the hydridic and acidic hydrogens in hydriodide **5**-H$^+$ may make intramolecular protonation insurmountably difficult.

Unforeseen reactions and inadequate understanding of mechanisms are obstacles that make the design of complex reagents for modifying bound substrates an enormously challenging problem. We are continuing to study compounds that bind protons and other reducible substrates close to an activated carbon–hydrogen bond but do not incorporate the undesirable features of dihydrobenzimidazole **5**. Our efforts are likely to lead to the discovery of new reactions, to a better knowledge of rates and mechanisms, and possibly to reagents of practical value.

Experimental Section

Infrared (IR) spectra were recorded on Perkin-Elmer Model 710B and 783 spectrometers. Bruker WH-90 and WH-400 spectrometers were used to obtain ^1H and ^2H nuclear magnetic

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[26] Elvidge, J. A.; Jones, J. R.; O'Brien, C.; Evans, E. A.; Turner, J. C. *J. Chem. Soc., Perkin Trans. 2* **1973**, 432–435.

[27] Simchen, G.; Rebsdat, S.; Kantlehner, W. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 875.

[28] van Bergen, T. J.; Mulder, T.; van der Veen, R. A.; Kellogg, R. M. *Tetrahedron* **1978**, *34*, 2377–2383.

[29] The preference for direct heterolysis of the activated carbon–carbon bond of deuterium-labeled hydriodide **5**-*d*-H$^+$ is not dramatic, and it can be overcome by minor changes in the experimental conditions. For example, pyrolysis of neat hydriodide **5**-*d*-H$^+$ at 150 °C for 10 h yielded mainly unlabeled benzimidazolium iodide **9**, the product of deuteride transfer. This may be due to small differences between the preferred conformations in solution and in the pure salt or to increased amounts of intermolecular deuteride transfer at higher concentrations of hydriodide **5**-*d*-H$^+$ in the melt.

[30] Hopkins, H. P., Jr.; Jahagirdar, D. V.; Moulik, P. S.; Aue, D. H.; Webb, H. M.; Davidson, W. R.; Pedley, M. D. *J. Am. Chem. Soc.* **1984**, *106*, 4341–4348.

[31] Bartmess, J. E.; Scott, J. A.; McIver, R. T., Jr. *J. Am. Chem. Soc.* **1979**, *101*, 6046–6056.

[32] Heats of formation were calculated by the standard MNDO procedure,[33] as implemented in the AMPAC Version 2.10 package of computer programs.[34] Geometries were optimized by the Davidon–Fletcher–Powell method. Hydride affinities were then calculated by using $\Delta H_f^\circ(H^-) = 34.7$ kcal/mol.[35]

[33] (a) Dewar, M. J. S.; Thiel, W. *J. Am. Chem. Soc.* **1977**, *99*, 4907–4917. (b) Dewar, M. J. S.; Thiel, W. *Ibid.* **1977**, *99*, 4899–4907.

[34] Quantum Chemistry Program Exchange (QCPE) Publication 506, Department of Chemistry, Indiana University, Bloomington, IN 47405.

[35] Kruppa, G. H.; Beauchamp, J. L. *J. Am. Chem. Soc.* **1986**, *108*, 2162–2169. Doering, W. v. E. *Proc. Natl. Acad. Sci. U.S.A.* **1981**, *78*, 5279–5283. Rosenstock, H. M.; Draxl, K.; Steiner, B. W.; Herron, J. J. *J. Phys. Chem. Ref. Data* **1977**, *6*, Suppl. 1.

[36] The actual values of ΔH may be distinctly different because of uncertainties introduced by the effect of condensed phases, variable errors in heats of formation of cations calculated by the MNDO procedure,[33a,37] and the use of dihydrobenzimidazole as a model for the more complex dihydrobenzimidazole **5**.

[37] Harris, J. M.; Shafer, S. G.; Worley, S. D. *J. Comput. Chem.* **1982**, *3*, 208–213.

[38] In contrast, formation of hydrogen from orthoformamide **1** and pyridinium is calculated to be *exothermic* by 10 kcal/mol. In this case, loss of hydride from compound **1** is endothermic by only 170 kcal/mol.[32]

resonance (NMR) spectra. Chemical shifts are reported in parts per million downfield from internal tetramethylsilane (δ). Low-resolution mass spectra were recorded on a V.G. Micromass 12-12 quadrupole spectrometer using chemical ionization (CI) mass spectrometry or on a Kratos MS-50 TA spectrometer using electron impact (EI) or fast atom bombardment (FAB) mass spectrometry. High-resolution mass spectra were recorded on a Kratos MS-50 TA spectrometer using electron impact (EI) mass spectrometry at 70 eV. Galbraith Laboratories, Knoxville, TN, performed all elemental analyses. Melting points were recorded on a Thomas-Hoover capillary apparatus and are not corrected. Acetonitrile was dried by distillation from P_2O_5, and benzene was dried by distillation from sodium. Solvents were deoxygenated by sparging with dry argon. All other reagents used were commercial products of the highest purity available.

2,3-Dihydro-1,3-dimethyl-2-(2-pyridinyl)-1*H*-benzimidazole (5). A mixture of *N,N'*-dimethyl-1,2-benzenediamine[4] (1.21 g, 8.88 mmol), freshly distilled 2-pyridinecarboxaldehyde (1.35 g, 12.6 mmol), and molecular sieves (4 Å, 1.3 g) was stirred in benzene (25 mL) at 25 °C under dry Ar. After 24 h, additional portions of aldehyde (0.144 g, 1.34 mmol) and molecular sieves (1.3 g) were added, and the mixture was stirred for 72 h. Then the mixture was washed at 0 °C with deoxygenated 10% aqueous NaOH, water, and brine. The organic phase was dried, solvent was removed by evaporation under reduced pressure, and the residue was decolorized with charcoal. Crystallization from water (90%)/methanol (10%) provided colorless needles of 2,3-dihydro-1,3-dimethyl-2-(2-pyridinyl)-1*H*-benzimidazole (**5**): 1.27 g, 5.64 mmol (63.5%); mp 55–56 °C; IR (KBr) 3060, 2955, 2860, 2800, 2740, 1605, 1590, 1575, 1500 (br), 1435, 1360, 1340, 1295, 1115 (br), 1015, 990, 775, 765, 750, 730, 660, 615 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.66 (s, 6 H), 5.11 (s, 1 H), 6.46 (m, 2 H), 6.73 (m, 2 H), 7.33 (t, 1 H), 7.79 (t, 1 H), 7.84 (d, 1 H), 8.61 (d, 1 H); mass spectrum (CI, isobutane), *m/e* 225, 210, 147; high-resolution mass spectrum (EI), calcd for $C_{14}H_{15}N_3$ 225.1266, found 225.1243, 225.1274.

1,3-Dimethyl-2-(2-pyridinyl)benzimidazolium Iodide (7). A stirred mixture of 2,3-dihydro-1,3-dimethyl-2-(2-pyridinyl)-1*H*-benzimidazole (**5**; 78 mg, 0.35 mmol) and K_2CO_3 (70 mg, 0.50 mmol) in methanol (2 mL) was treated at 25 °C with a solution of I_2 (95 mg, 0.37 mmol) in methanol (10 mL), added dropwise during 3 h. The resulting mixture was stirred at 25 °C for 48 h, and then volatiles were removed by evaporation under reduced pressure. The product was extracted with chloroform, and solvent was removed from the filtered extracts by evaporation under reduced pressure. Two recrystallizations of the residue from dichloromethane/benzene yielded colorless, analytically pure needles of 1,3-dimethyl-2-(2-pyridinyl)benzimidazolium iodide (**7**): 67 mg, 0.19 mmol (54%); mp 251.5 °C (lit.[7] mp 251–252 °C); IR (KBr) 1510, 1475, 1450, 1420, 980, 810, 740, 730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.13 (s, 6 H), 7.68 (t, 1 H), 7.76 (m, 4 H), 8.18 (t, 1 H), 8.88 (d, 1 H), 9.06 (d, 1 H); mass spectrum (CI, isobutane), *m/e* 210. Anal. Calcd for $C_{14}H_{14}IN_3$: C, 47.88; H, 4.02; N, 11.97. Found: C, 48.01; H, 4.29; N, 11.83.

2,3-Dihydro-1,3-dimethyl-2-(2-pyridinyl)-1*H*-benzimidazole-2-*d* (5-*d*). A solution of 1,3-dimethyl-2-(2-pyridinyl)benzimidazolium iodide (**7**; 63.1 mg, 0.180 mmol) in methanol-d_4 (2 mL) was treated with $NaBD_4$ (15.4 mg, 0.368 mmol), and the mixture was stirred for 2 h at 25 °C under N_2. Solvent was then removed by evaporation under reduced pressure, and the residue was extracted with hexane. Evaporation of solvent from the filtered extracts left an off-white residue of 2,3-dihydro-1,3-dimethyl-2-(2-pyridinyl)-1*H*-benzimidazole-2-*d* (**5-*d***): 19.4 mg, 0.0857 mmol (47.6%); IR (KBr) 3060, 2955, 2860, 2800, 1990 (br), 1600, 1595, 1570, 1495, 1390, 1310 (br), 1115, 1100, 1015, 990, 765, 750, 730, 655, 615 cm^{-1}; ^1H NMR (400 MHz, CD_3CN) δ 2.58 (s, 6 H), 6.44 (m, 2 H), 6.65 (m, 2 H), 7.38 (t, 1 H), 7.74 (d, 1 H), 7.84 (t, 1 H), 8.57 (d, 1 H); mass spectrum (CI, isobutane), *m/e* 226, 148; mass spectrum (EI), *m/e* 226, 148; high-resolution mass spectrum (EI), calcd for $C_{14}H_{14}DN_3$ 226.1328, found 226.1341.

Hydriodide 5-H$^+$ of 2,3-Dihydro-1,3-dimethyl-2-(2-pyridinyl)-1*H*-benzimidazole (5). A solution of 2,3-dihydro-1,3-dimethyl-2-(2-pyridinyl)-1*H*-benzimidazole (**5**; 60.2 mg, 0.267 mmol) in ether (3 mL) was stirred at 0 °C under N_2 and treated dropwise during 10 min with cold hydriodic acid (5%, 0.6 mL). The mixture was kept at 0 °C for an additional 45 min, and then the precipitated solid was separated by filtration under N_2, washed with cold ethanol (0.3 mL), and dried in vacuo at 0 °C. This yielded an analytically pure sample of hydriodide **5-H$^+$** as an orange solid: 78.3 mg, 0.222 mmol (83.1%); mp 144 °C; IR (KBr) 3020, 2920, 2850, 2800 (br), 1590, 1485, 1445, 1360, 1285, 1190, 1110, 1075, 1010, 990, 770, 755, 730 cm^{-1}; ^1H NMR (400 MHz, CD_3CN) δ 2.70 (s, 6 H), 5.53 (s, 1 H), 6.62 (m, 2 H), 6.80 (m, 2 H), 8.09 (t, 1 H), 8.17 (d, 1 H), 8.66 (t, 1 H), 8.75 (d, 1 H); mass spectrum (CI, isobutane), *m/e* 225, 210, 147. Anal. Calcd for $C_{14}H_{16}IN_3$: C, 47.61; H, 4.57; N, 11.90. Found: C, 47.48; H, 4.74; N, 11.79.

Pyrolysis of Hydriodide 5-H$^+$. Hydriodide **5-H$^+$** (48.8 mg, 0.138 mmol) was sealed in vacuo in a Pyrex tube and heated at 150 °C for 14 h. The tube was then chilled and opened, and the pyrolysate was extracted with ether (4 mL). After the ether extracts were treated with hydriodic acid (5%, 0.4 mL), removal of volatiles by evaporation in vacuo left a solid residue of pyridinium iodide (19.4 mg, 0.0937 mmol, 67.9%), which was identified by its IR and ^1H NMR spectra. Recrystallization of the ether-insoluble fraction of the pyrolysate from dichloromethane/benzene precipitated 1,3-dimethylbenzimidazolium iodide (**9**; 18.8 mg, 0.0686 mmol, 49.7%), which was identical by IR and NMR with an authentic sample.[21]

Hydriodide 5-*d*-H$^+$ of 2,3-Dihydro-1,3-dimethyl-2-(2-pyridinyl)-1*H*-benzimidazole-2-*d* (5-*d*). The preparation of labeled hydriodide **5-*d*-H$^+$** was analogous to the preparation of unlabeled hydriodide **5-H$^+$**: IR (KBr) 3030, 2945, 2870, 2810 (br), 2000 (br), 1600, 1495, 1450, 1320, 1295, 1200, 1115, 1090, 1070, 1015, 1000, 785, 775, 770, 735 cm^{-1}; ^1H NMR (90 MHz, CD_3CN) δ 2.74 (s, 6 H), 6.75 (m, 4 H), 8.12 (t, 1 H), 8.22 (d, 1 H), 8.68 (t, 1 H), 8.80 (d, 1 H); mass spectrum (CI, isobutane), *m/e* 226, 148.

Pyrolysis of Labeled Hydriodide 5-*d*-H$^+$. A solution of labeled hydriodide **5-*d*-H$^+$** (6.0 mg, 0.017 mmol) in CH_3CN (1 mL) was sealed in vacuo in an NMR tube and warmed at 60 °C for 9 days. The decomposition of compound **5-*d*-H$^+$** was followed by ^2H NMR spectroscopy.

Acknowledgment. This work was financially supported by the Natural Sciences and Engineering Research Council of Canada and by the Ministère de l'Éducation du Québec. In addition, we thank the Centre de Calcul, Université de Montréal, for a generous gift of computer time. We are grateful to Sylvie Bilodeau and Dr. M. T. Phan Viet of the Regional High-Field NMR Laboratory for recording our high-field NMR spectra and to Michael Evans and Christine Johnson for recording our mass spectra. We also thank Professor Maurice M. Kreevoy for valuable suggestions.

Registry No. **5**, 110569-76-1; **5-*d***, 110569-77-2; **5-H$^+$**, 110569-78-3; **7**, 51785-20-7; **9**, 7181-87-5.