On the Possibility of S_N2 Reactions at Nitrogen. Catalytic H–D Exchange in a Melt

Sir:

In a recent communication[1] Olah and coworkers reported on the possibility of an S_N2-type reaction occurring at a quaternary nitrogen based on results obtained from heating lithium deuteride (LiD) and ammonium trifluoroacetate ($NH_4O_2CCF_3$) in a melt (eq 1), Table I. To explain the production of D_2 and H_2 in this system reaction 2 was postulated to occur in competition with the expected acid–base reaction 3. This S_N2 reaction would be extremely interesting not only because it involves nitrogen, but also because it must compete with an extremely favorable acid–base reaction, it uses a poor nucleophile, and the reaction, as performed, must occur at the interface between the lithium deuteride powder and the melt. However, although this reaction will scramble isotopes, analysis of the data shows that it cannot account for the large portions of D_2 generated. Instead, we have found that H_2 and D_2 result from catalytic isotope exchange of the HD gas in a reaction which is highly dependent on melt conditions.

$$\begin{aligned}\mathrm{LiD} + 2\mathrm{NH_4O_2CCF_3} \rightarrow\ & \mathrm{NH_4OCOCF_3} \\ & + [85\%\ \mathrm{NH_3} + 15\%\ \mathrm{NH_2D}] \\ & + [66\%\ \mathrm{HD} + 21\%\ \mathrm{H_2} + 13\%\ \mathrm{D_2}] + \mathrm{LiOCOCF_3} \quad (1)\end{aligned}$$

Scheme I

$$\mathrm{D^-} + \mathrm{NH_4^+} \xrightarrow[k_2]{} \mathrm{NH_3D^+} + \mathrm{H^-} \quad (2)$$

$$\mathrm{D^-} + \mathrm{NH_4^+} \xrightarrow[k_3]{} \mathrm{HD} + \mathrm{NH_3} \quad (3)$$

For reaction according to Scheme I maximal isotope scrambling, and hence maximal D_2 production, will obtain when $k_2 \gg k_3$. Under these conditions one can calculate the percent D_2 produced from the initial isotopic content of 11% D (1 D to 8 H) to be $(0.11)^2 = 1.2\%$.[2] In other words the maximum amount of D_2 available through Scheme I, or any other scheme which scrambles deuterium into the ammonia pool, is an order of magnitude smaller than that observed. It is obvious that, in order to generate D_2 percentages in the range observed by isotopic scrambling, one must have a system which contains at least 36% ($(0.13)^{1/2}$) D. Enrichment on this level is achieved only in the HD fraction, and catalytic exchange of this gas could generate up to 25% D_2. Of the catalysts which exchange hydrogen gas, amide ion (NH_2^-),[3] which could be easily generated from LiD and NH_3,[4] is the most likely. Furthermore, amide ion can incorporate some protons from the ammonia pool during exchange, a result necessitated by the inequivalence of H_2 and D_2, and explain the production of NH_2D.

Our initial attempt to observe catalytic exchange was to react LiH with $NH_4O_2CCF_3$ under D_2, but analysis[5] of the products gave no evidence for HD. This result is compatible with the exchange mechanism if dissolution of gas into the melt is slow, a proposition which is supported by the predominance of deuterated ammonia in the gas phase rather than equal distribution between gas and melt, and exchange occurs before evolution. We then determined the isotopic ratio as a function of time and found it to be constant throughout the reaction, Table I. This result is incompatible with a two-step mechanism such as Olah's,[6] but it does agree with exchange before evolution. To establish the intermediacy of amide ion we treated LiD with 2 equiv of diisopropylammonium trifluoroacetate (I, mp 120 °C), pyridinium trifluoroacetate (II, mp 80 °C), triethylammonium trifluoroacetate[7] (III, mp <25 °C), and benzoic acid (IV, mp 120 °C). We were surprised to find that all systems exhibited some isotopic exchange, Table I. Only acid I produces more H_2 than D_2 as expected from the catalytic action of amide ion, but the exchange observed in the other systems must involve species heretofore unrecognized as catalysts for HD exchange. To determine the effect of melt conditions we treated LiD with solutions of $NH_4O_2CCF_3$, I, II, and IV in tetrahydrofuran. Isotopic exchange dropped significantly for the amines but was only halved for IV,[8] Table I, and the protio systems under D_2 did not produce HD.

Table I. Isotopic Content of the Hydrogen Gas[a]

	H_2, %	HD, %	D_2, %
$LiD + NH_4O_2CCF_3$[b]	21	66	13
LiD[c] + $NH_4O_2CCF_3$[d]			
Melt, early in reaction	18	70	11
Melt, late in reaction	20	70	10
THF	<5	95	<5
LiD + I[d]			
Melt	21	61	16
THF	<5	95	<5
LiD + II[d]			
Melt	12	77	12
THF	<5	95	<5
LiD + III			
Melt	9	83	8
LiD + IV			
Melt	26	51	24
THF	18	72	10

[a] All reactions were performed at least twice and used a twofold excess of acid over LiD. Melt reactions were prepared in a drybox and then placed into a preheated oil bath. Solutions of acid, 0.2 M, in tetrahydrofuran, freshly distilled from lithium aluminum hydride, were added to the LiD. [b] From ref 1. [c] Alfa Inorganics, 98% isotopic purity. [d] Twice recrystallized from acetone: ether and dried under vacuum.

In general the melt seems to enhance the reactivity of catalyst and substrate such that reactions of only minor importance in solution become predominant pathways in the melt. This could be the result of increased concentration at the LiD surface, an important consequence in the solution reactions, or changes in solvation, perhaps increasing the basicity of benzoate[3,9] or activating LiD, but, whatever the reason, melts alter the chemistry significantly.

Lastly, the previous results and the ones obtained here are fully accommodated by a classical exchange reaction and thus provide no evidence for reaction 2.

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References and Notes

(1) G. A. Olah, D. J. Donovan, J. Shen, and G. Klopman, *J. Am. Chem. Soc.*, **97**, 3559 (1975).
(2) This calculation neglects kinetic isotope effects and assumes a homogeneous system, whereas the actual system is a heterogeneous mixture of lithium hydride powder, gas, and melt. If kinetic isotope effects are included, one calculates that Scheme I could give the observed amounts of HD and D_2 if both H^- and D^- prefer D^+ over H^+ by ~5 to 1, an inverse isotope effect. However, this isotope effect must then obtain in the inverted reaction, $LiH + ND_4O_2CCF_3$, and would result in production of <1% H_2, whereas 18% is actually observed.[1]
(3) W. K. Wilmarth and J. C. Dayton, *J. Am. Chem. Soc.*, **75**, 4553 (1953); B. R. James, "Homogeneous Hydrogenation", Wiley, New York, N.Y., 1973, p 393.
(4) The original authors tested LiD under NH_3 for catalytic activity, but they did not use melt conditions.
(5) Separation was achieved with 15% $MnCl_2$ on Alcoa F1 alumina under conditions similar to those of G. F. Shipman, *Anal. Chem.*, **34**, 877 (1962), but employing a thermal conductivity detector, and mixtures of H_2 and D_2 did not show exchange.
(6) Even if $k_2 \gg k_3$, the heterogeneity allows gas to evolve before all of the LiD has reacted.
(7) This liquid was syringed onto the LiD.
(8) This reaction is very slow and produces a precipitate of lithium benzoate.

(9) Several anionic bases are known to catalyze H–D exchange of hydrogen: E. A. Symons and E. Buncel, *Can. J. Chem.*, **51**, 1673 (1973), and references therein. Surface phenomena may play a role in generating a microenvironment suitable for catalytic exchange which might not be duplicable in bulk solution. Also, the possibility of impurities should not be overlooked.

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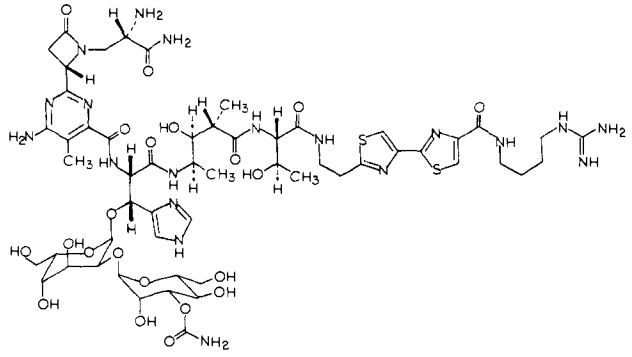
A Biomimetic Synthesis of the Bithiazole Moiety of Bleomycin

Sir:

The antibiotic bleomycin is of current interest because of its clinically useful anticancer activity.[1] As part of a total synthesis of bleomycin B_2 (**1**), we have been investigating the



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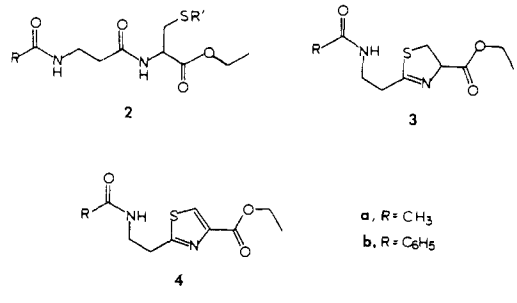
chemistry of the bithiazole moiety, the biosynthetic elaboration of which probably involves dehydrative cyclization of β-alanylcysteinylcysteine and dehydrogenation of the intermediate Δ^2-thiazolines.[2] Although the preparation of Δ^2-thiazolines from certain cysteinyl peptides has been reported not to be possible,[3] and no efficient methods have been recorded for the oxidation of complex Δ^2-thiazolines, we report herein a biomimetic synthesis of the bithiazole moiety of bleomycin. Since several other natural products contain single thiazoles or Δ^2-thiazoline groups,[4] this synthetic approach should also be of more general utility.

Although several agents previously employed for the preparation of simple thiazolines[5] failed to effect the conversion of dipeptide **2a**[6] to the corresponding thiazoline, treatment of

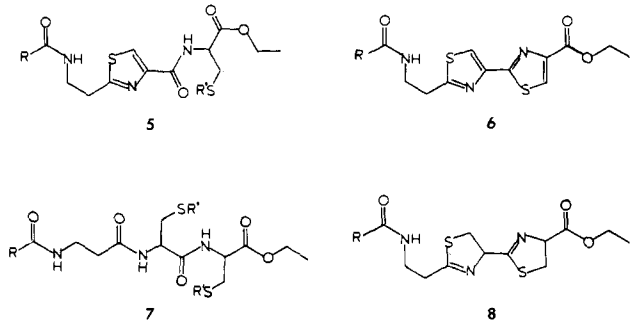


2 3 4

a, R = CH_3
b, R = C_6H_5

chloroform solutions of **2a** (R′ = H or $(C_6H_5)_3C$) with hydrogen chloride at 0 °C afforded ethyl 2-(2-acetamidoethyl)-Δ^2-thiazoline-4-carboxylate (**3a**), mp 156–158 °C, in yields up to 77% (purification by crystallization from benzene–chloroform–petroleum ether or distillation at 160 °C/(0.1 mm)), λ_{max} (1:1 HCl-C_2H_5OH) 267 nm. Of the reagents previously used for the oxidation of thiazolines,[7] only activated MnO_2 ($CHCl_3$, room temperature, 4 days) gave significant conversion of **3a** to **4a**; the latter was obtained as colorless crystals in 65% yield. A much better yield of **4a** (93%) was obtained by the use of NiO_2. In a typical experiment 293 mg (1.20 mmol) of **3a** and 762 mg of NiO_2[8] in 25 mL of $CHCl_3$ was shaken for 42 h. After filtration, concentration of the filtrate and crystallization of the residue (ether) gave **4a** in a good state of purity[9] as colorless needles: mp 83–84 °C; λ_{max} (C_2H_5OH) 236 nm; NMR ($CDCl_3$, $(CH_3)_4Si$) δ 1.45 (t, 3), 2.00 (s, 3), 3.28 (t, 2), 3.74 (m, 2), 4.42 (q, 2) 6.70 (br, 1), 8.09 (s, 1). Analogous conversion of **2b** to **4b** was also effected, although the transformation **2b** (R′ = H) → **3b** generally proceeded in somewhat lower yield than **2a** → **3a**.

Saponification of **4a** and **4b** (KOH, aqueous dioxane) gave the respective carboxylates in yields of 96 and 95%. While the carboxylate derived from **4a** had appreciable solubility only in water, and could not be condensed conveniently with *S*-tritylcysteine ethyl ester, condensation of the acid derived from **4b** with *S*-tritylcysteine ethyl ester (*N,N′*-dicyclohexylcarbodiimide, tetrahydrofuran) afforded tripeptide analogue **5b**



5 6 7 8

(R′ = $(C_6H_5)_3C$; 96%) as a white foam. Treatment with $AgNO_3$ (1.3 equiv, pyridine–methanol, 12 h) at room temperature gave the corresponding silver mercaptide (100%, R′ = Ag) as pale yellow crystals. The mercaptide was converted to mercaptan **5b** (100%, R′ = H) by treatment of a methanolic suspension of the silver salt with H_2S: NMR ($CDCl_3$, $(CH_3)_4Si$) δ 1.33 (t, 3), 1.47 (t, 1), 3.12 (dd, 2), 3.35 (t, 2), 3.88 (m, 2), 4.27 (q, 2), 4.98 (m, 1), 7.3–7.5 (m, 3), 7.7–8.2 (m, 3), 8.50 (t, 1), 8.96 (d, 1). Compound **5b** (R′ = H) was dissolved in $CHCl_3$ and treated with a slow stream of hydrogen chloride (36 h, room temperature). After concentration of the reaction mixture, the residue was partitioned between ethyl acetate and aqueous Na_2CO_3. Workup of the organic phase afforded a clear oil (90% recovery; λ_{max} (1:1 C_2H_5OH–HCl) 233 and 300 nm; presumably the thiazolylthiazoline) which was redissolved in $CHCl_3$ and shaken in the presence of MnO_2 or NiO_2[10] (5 days, room temperature). Workup gave a yellow oil which deposited colorless needles of the known[11] ethyl 2′-(2-benzamidoethyl)-2,4′-bithiazole-4-carboxylate (**6b**) from ethyl acetate–petroleum ether: yield 24%; mp 143–144 °C; λ_{max} (EtOH) 290 nm (log 4.17; NMR $CDCl_3$, $(CH_3)_4Si$) δ 1.46 (t, 3), 3.36 (t, 2), 3.93 (t, 2), 4.47 (q, 2), 7.35–7.9 (m, 6), 8.06 (s, 1), 8.19 (s, 1).

Having obtained the desired bithiazole (**6**) via stepwise dehydrative cyclization and oxidation, it was of interest to attempt the direct conversion of β-alanylcysteinylcysteine derivative **7** to **6** via bithiazoline **8**. Treatment of an ethanol-free $CHCl_3$ solution of **7a** (R′ = H)[12] with a slow stream of HCl (24 h, room temperature, followed by concentration under diminished pressure) afforded a water-sensitive residue having the UV spectrum (λ_{max} (1:1 C_2H_5OH–HCl) 266 nm (ε 9200)) expected of bithiazoline **8a**.[13] Attempted oxidation of the putative bithiazoline to **6a** (NiO_2, $CHCl_3$) gave instead the disulfide derived from **5a** (R′ = H), whose formation may pro-