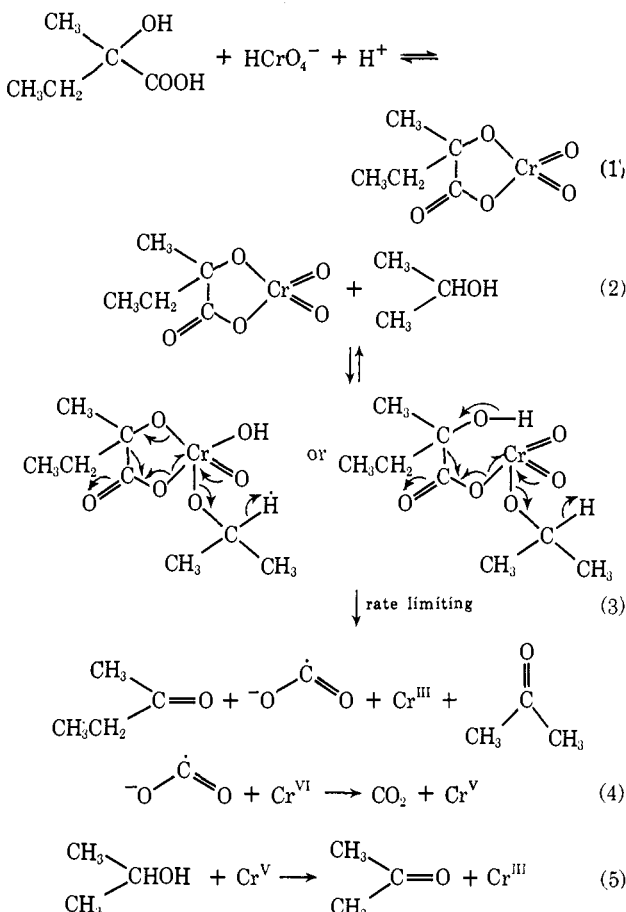


**Table I.** Products of Cooxidation of Isopropyl Alcohol and 2-Hydroxy-2-methylbutyric Acid

[Isopropyl alcohol], M	[Hydroxy acid], M	[Acrylonitrile], M	[HClO <sub>4</sub> ], M	Cr(VI), mmol	Acetone, mmol	Methyl ethyl ketone, mmol	CO <sub>2</sub> , mmol
0.780	0.617	0.0	0.628	1.57	1.61	0.72	0.69
0.780	0.617	0.396	0.628	1.57	1.60	1.54	0.0

**Scheme I**

$10^{-3} \text{ sec}^{-1}$  for  $\alpha$ -hydroxyisobutyric acid and  $k = 8.25 \times 10^{-3} \text{ sec}^{-1}$  for 2-hydroxy-2-methylbutyric acid. These rate constants are 4.5 and 6.2 times greater than the sums of the rate constants for the two substrates ( $1.28 \times 10^{-3}$  and  $1.33 \times 10^{-3} \text{ sec}^{-1}$ ), respectively. Similar rate accelerations have been obtained for citric acid and also for secondary hydroxy acids like malic, *meso*-, and *d*-tartaric acids and to a somewhat lesser extent for glycolic and lactic acids.<sup>4</sup>

The products obtained in the chromic acid oxidation of a mixture of isopropyl alcohol and 2-hydroxy-2-methylbutyric acid in the absence and in the presence of acrylonitrile used as a free-radical scavenger<sup>5</sup> are given in Table I.

In both cases both substrates undergo oxidation and the isolated products account for all chromium(VI) used. However, in the presence of acrylonitrile no carbon dioxide was produced, and acetone and methyl ethyl ketone were formed in a 1:1 ratio. The suppres-

(5) Acetone and methyl ethyl ketone were separated as the 2,4-dinitrophenylhydrazones by column chromatography,<sup>6</sup> on a 1:1 mixture of Bentonite (Fisher) and infusorial earth (Fisher) with chloroform and chloroform-ethanol (1:1) as eluents. The compounds were identified by comparison with authentic samples. Carbon dioxide was determined manometrically in a Warburg apparatus.<sup>3</sup>

(6) J. A. Elvidge and M. Whalley, *Chem. Ind. (London)*, 589 (1955).

sion of the carbon dioxide formation in the presence of the free-radical scavenger indicates that all CO<sub>2</sub> is formed *via* a free-radical intermediate.

The mechanism of the chromic acid oxidation of a mixture of isopropyl alcohol and 2-hydroxy-2-methylbutyric acid can best be represented by Scheme I. The rate-limiting step (reaction 3) consists of a decomposition of the termolecular complex into a chromium(III) species, one molecule of acetone, one molecule of methyl ethyl ketone, and a free-radical  $\cdot\text{CO}_2^-$ . In the presence of acrylonitrile this free radical is trapped and removed from the reaction chain. In the absence of the free-radical scavenger the radical is oxidized by chromium(VI) to carbon dioxide (reaction 4). The chromium(V) species formed in this reaction then reacts with isopropyl alcohol to give another molecule of acetone (reaction 5),<sup>7</sup> leading thus to an overall product ratio of acetone:methyl ethyl ketone:carbon dioxide of 2:1:1.

The large number of compounds capable of accelerating the reduction of chromic acid by isopropyl alcohol<sup>4</sup> and the composition of the reaction products reported in this communication strongly indicate that three-electron cooxidations may represent a rather general and important new class of oxidation reactions.

(7) In principle, chromium(V) could also react with 2-hydroxy-2-methylbutyric acid to give another molecule of methyl ethyl ketone and of carbon dioxide. However, since the rate of the chromium(VI) oxidation of 2-hydroxy-2-methylbutyric acid is much lower than that of isopropyl alcohol and since relative reactivities of chromium(VI) and chromium(V) have been found to be quite similar,<sup>8</sup> chromium(V) is likely to react almost exclusively with isopropyl alcohol.

(8) K. B. Wiberg and H. Schäfer, *J. Amer. Chem. Soc.*, 91, 933 (1969).

Fariza Hasan, Jan Roček\*

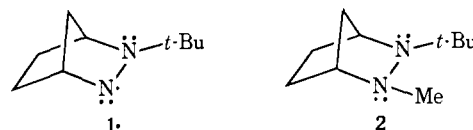
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### Electrochemical Estimation of the Acidity of a Trialkylhydrazine

Sir:

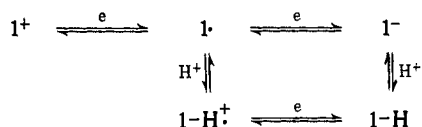
We reported that bicyclic hydrazyl 1 $\cdot$  is formed upon electrochemical reduction of the related diazenium salt 1<sup>+</sup> and that it is stable on a time scale of seconds at room temperature in acetonitrile.<sup>1</sup> We wish to point out here that electrochemical experiments on the diazenium ion (1<sup>+</sup>)-hydrazine (1-H) interconver-



sion require that the trialkylhydrazine 1-H is a remarkably weak acid. The cycle shown in Scheme I con-

(1) S. F. Nelsen and R. T. Landis, II, *J. Amer. Chem. Soc.*, submitted for publication.

Scheme I



nects the hydrazyl radical  $1\cdot$  and the hydrazine  $1\text{-H}$  by proton and electron transfers. Breslow and Chu<sup>2</sup> have pointed out the power of such cycles in measuring acidities and, by using the formal step  $\text{RH} \rightleftharpoons \text{ROH}$ , have applied them to the measurement of the relative acidities of hydrocarbons. For the cycle of Scheme I

$$\begin{aligned}
 pK_a(1\text{-H}) &= pK_a(1\text{-H}^+) + \\
 &(1/0.059)\{E^0(1\text{-H}, 1\text{-H}^+) - E^0(1^-, 1\cdot)\}
 \end{aligned}$$

where  $pK_a(1\text{-H})$  refers to the equilibrium  $1\text{-H} \rightleftharpoons 1^- + \text{H}^+$ . Direct measurement of  $E^0(1\text{-H}, 1\text{-H}^+)$  is complicated by the fact that  $1\text{-H}\cdot^+$  deprotonates to  $1\cdot$  before diffusion away from the electrode surface, forming  $1\cdot$  at an electrode which is far anodic of its  $E^0$  value for oxidation to  $1^+$ , resulting in rapid removal of  $1\text{-H}\cdot^+$ , and leading to an irreversible-appearing oxidation wave and no observable rereduction wave on the back scan. The peak potential observed for the oxidation wave in cyclic voltametry experiments was  $E_p = -0.08$  V vs. sce in acetonitrile which must be cathodic (more negative) of the true  $E^0$  values.<sup>3</sup> We contend that **2**, which lacks an NH proton and therefore gives the stable  $2\cdot^+$  cation in an electrochemically reversible oxidation, serves as a reasonable model. We observe  $E_{1/2}(2, 2^+) = +0.17$  V and suggest that, if anything, **2** ought to be somewhat more easily oxidized than  $1\text{-H}$ , because of the inductive effect of the methyl group, and so  $E^0(1\text{-H}, 1\text{-H}^+)$  ought to be  $\geq +0.17$  V, but in any event is certainly greater than 0.1 V.

Significantly,  $1\cdot$  is very difficult to reduce. Scanning a  $1^+$  solution to  $-2.5$  V and back showed no reduction wave beyond the  $1^+ + e \rightarrow 1\cdot$  wave, although the oxidation wave for  $1\cdot \rightarrow 1^+ + e$  was still observed, demonstrating that the standard potential  $E^0(1^-, 1\cdot) \leq -2.5$  V. Thus, the radical  $1\cdot$  is as difficult to reduce as naphthalene.

A cycle such as that of Scheme I will normally be useful for measuring  $pK_a$  values for radical ions, which have been obtained by flash photolysis<sup>4</sup> or pulse radiolysis<sup>5</sup> techniques and esr spectroscopy.<sup>6</sup> Electrochemistry is a poor tool for such measurements, since four rate constants must be measured accurately to obtain  $pK_a$  values of radical ions;<sup>7</sup> such has rarely, if ever, been done. In our case, however, nothing is known

(2) R. Breslow and W. Chu, *J. Amer. Chem. Soc.*, **91**, 5182 (1969); **92**, 2165 (1970); **95**, 411 (1973).

(3) R. S. Nicholson and I. Shain, *Anal. Chem.*, **36**, 722 (1964).

(4) For an example of  $pK_a$  measurements in the hydrouroquinone system, see E. J. Land, G. Porter, and E. Strachand, *Trans. Faraday Soc.*, **57**, 1885 (1971); and for analine radical cation, see E. J. Land and G. Porter, *J. Chem. Soc.*, 2027 (1963).

(5) E. Hayon and M. Simic, *J. Amer. Chem. Soc.*, **94**, 42 (1972).

(6) R. W. Fessenden and P. Neta, *J. Phys. Chem.*, **76**, 2857 (1972), were able to estimate  $pK_a$  for  $\text{Me}_2\text{NH}\cdot^+$  by esr experiments using continuous radiolysis, since the esr spectrum of the protonated form was observed in acid and of the unprotonated form in base. Similar experiments using electrolysis of  $1^+$  have failed, and the esr spectrum of  $1\cdot$  has not yet been observed, possibly because the equilibrium constant for  $1\text{-H}\cdot^+ + 1\cdot \rightleftharpoons 1\text{-H} + 1^+$  is so large.

(7) For a discussion of the experimental problems, cast as a measurement of the rate of dissociation of acetic acid (a simpler case), see R. R. Schroeder and I. Shain, *J. Phys. Chem.*, **73**, 197 (1969).

about  $pK_a$  values for hydrazines, but  $pK_a$  of  $\text{N}_2\text{H}_4\cdot^+$  has been determined to be  $7.1 \pm 0.1$  by Hayon and Simic<sup>5</sup> using pulse radiolysis, and we argue that  $pK_a$  of  $1\text{-H}\cdot^+$  cannot be many pK units different from this figure, although there are both steric and inductive differences in the two compounds. We assert that  $pK_a(1\text{-H}\cdot^+) > 0$  is a conservative estimate.

The cycle in Scheme I shows, then, that  $pK_a(1\text{-H}) > 0 + (1/0.059)(0.1 - (-2.4)) > 42$ . This is an astonishingly high value for  $pK_a$ ,<sup>8</sup> considering that the conventional experimental value for ammonia is 33 and that for methane 40.<sup>9</sup> Deprotonation of  $1\text{-H}$  increases lone pair-lone pair interactions seriously, and we suggest that this effect is important in destabilizing  $1^-$ . The amide  $1\text{-Li}$  is formed when *tert*-butyllithium is added to a THF solution of 2,3-diazanorbornene at  $-78^\circ$  and is present in the solution, since quenching with methyl iodide gives **2**. This extremely basic hindered amide could prove useful as an unusually strong base.

**Acknowledgment.** We thank the National Science Foundation for financial support, and Professor D. H. Evans of this department for frequent discussions.

(8) Following Breslow and Chu,<sup>2</sup> we have used electrochemical measurements in a nonaqueous solvent. The solvent effect on  $E^0(1\cdot, 1^+)$  is small. We observe  $E_{1/2}$  for  $1^+$  reduction in water to be  $-0.75 \pm 0.01$  in water buffered at pH 10-13. Increasingly rapid scan rates must be used to observe the reoxidation wave at lower pH values, because of protonation and reduction to  $1\text{-H}$  rapidly removing  $1\cdot$ . Since  $E_{1/2}(1\cdot, 1^+)$  is  $-0.72$  in acetonitrile,<sup>1</sup> the solvent effect on this step is certainly negligible.

(9) The value of 40 for methane is probably too low, and 55-60 might be a more reasonable estimate.

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## Structure of Cytochalasin E, a Toxic Metabolite of *Aspergillus clavatus*

Sir:

*Aspergillus clavatus* collected from mold-damaged rice in a Thai household, where a young boy died of an unidentified toxicosis, produced a highly toxic mixture of metabolites. We previously described the two major, but nontoxic, metabolites kotanin and desmethylkotanin,<sup>1</sup> and now report isolation and characterization of the toxin which has absolute stereostructure **1**.

*A. clavatus* was grown on rice and the toxin isolated by extractive and chromatographic techniques: mp  $206\text{-}208^\circ$  dec;  $[\alpha]^{25}_D -25.6^\circ$  (methanol) after recrystallization from acetone-hexane; *m/e* (found) 495.2258, calcd for  $\text{C}_{28}\text{H}_{33}\text{NO}_7$  495.2257.<sup>2</sup> The substance is neutral and has ir absorptions typical of  $\gamma$ -lactams. One tertiary hydroxyl group was revealed by ir absorption at  $3475\text{ cm}^{-1}$  and one exchangeable proton at  $\delta$  5.0 (singlet in  $\text{DMSO-}d_6$ ). Intense ir bands at  $1765$ ,  $1660$ , and  $1720\text{ cm}^{-1}$  are consistent with a vinyl

(1) G. Büchi, D. H. Klaubert, R. C. Shank, S. M. Weinreb, and G. N. Wogan, *J. Org. Chem.*, **36**, 1143 (1971). The organism was incorrectly identified as *A. glaucus*.

(2) The high-resolution mass spectrum was measured in the National Institutes of Health supported facility at Massachusetts Institute of Technology (Grant FR 00317) under the direction of Professor K. Biemann.