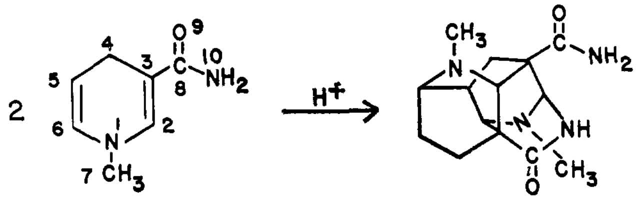
The "Dimeric Acid Product" of 1-Methyl-1,4-dihydronicotinamide

Sir:

The instability of the reduced forms of the coenzymes, NAD and NADP,[1] and of 1,3-disubstituted 1,4-dihydropyridine model compounds has been known for some time.[2,3] Anderson and Berkelhammer[4] have shown that the primary acid product[5] of 1-benzyl-3-acetyl-1,4-dihydropyridine arises from the addition of water to the 5,6 double bond, giving 1-benzyl-2-hydroxy-5-acetyl-1,4-dihydropyridine. In the course of some of the earliest studies on the dihydronicotinamide model compounds, Karrer, *et al.*,[3,6] discovered another kind of acid reaction which has received relatively little attention in the chemical literature in the intervening years. This acid product and its dihydronicotinamide parent have identical empirical formulas, and the two were originally thought to be double bond isomers.[7] Further work,[8–10] however, has shown these acid products to be "dimeric," each molecule containing the elements of two molecules of starting material.

This is a report of an X-ray crystallographic study of the dimeric acid product of 1-methyl-1,4-dihydronicotinamide, initiated to clarify the basic structure of this interesting class of molecules.



The material crystallizes in the monoclinic system: unit cell dimensions of a = 13.687, b = 13.448, c = 7.367 A and $\beta = 98° 58'$, four dimeric molecules per cell, $\rho_{\text{X-ray}} = 1.371$ g cm^{-3}, $\rho_{\text{meas}} = 1.368$ g cm^{-3}, space group $P2_1/n$. Unidimensionally integrated Weissenberg photographs were collected for the levels *hk*0 to *hk*6, and the intensities were measured with a scanning microdensitometer. Solution of the structure was readily achieved by application of the symbolic addition procedure.[11,12] Refinement has proceeded by full matrix least squares to an R factor of 0.049. A complete description of the determination will be published elsewhere.

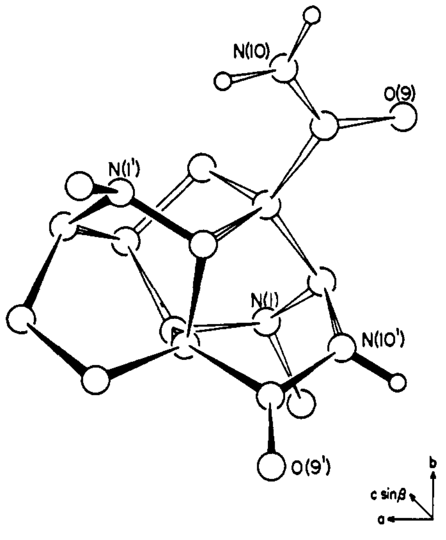


Figure 1. Perspective drawing of the "dimeric acid product" of 1-methyl-1,4-dihydronicotinamide. The unlabeled large circles are carbon and the smallest circles are hydrogen (shown for amide groups only).

A perspective drawing of the molecule is shown in Figure 1. As anticipated from the relatively rapid and mild conditions of synthesis, rupture of the dihydropyridine rings has not occurred. The "monomer" molecules are joined by one C–N (C(2)–N(10′)) and three C–C (C(3)–C(2′), C(5)–C(6′), and C(6)–C(3′)) bonds to form a distorted cage in which the two original six-membered rings are almost parallel but considerably offset. This produces a compact structure, with only the two methyl groups, one amide oxygen, and one carboxamide group as appendages, protruding from the body of the molecule. The unusually low thermal parameters of the atoms, less than those ordinarily found in organic crystals at room temperature, are probably a result of the cagelike nature of the structure. Most of the bond lengths and angles agree with anticipated values. C(6)–C(3′) and C(2′)–C(3′) (1.566 ± 0.003 and 1.572 ± 0.002 A) are significantly longer than normal carbon sp^3–sp^3 bonds (*ca.* 1.533 A[13]). However, each of the atoms is highly substituted (total of seven nonhydrogen substituents on the atoms composing each bond), and strong effects due to nonbonded interactions must be at least partially responsible for the increase. The C(2)–C(3) bond, for example, in 2,2,3,3-tetramethylbutane is 1.58 A.[14]

The structure of the "dimer" gives valuable support for the generally accepted mechanism of the primary acid reaction of 1,4-dihydropyridines[4,15] and for the position of protonation of tertiary vinylamines.[16] All four of the "intermonomeric" bonds are readily explainable on the basis of protonation or electrophilic attack at the 3 (or oxygen of the 3-carboxamido group) or 5 position of the 1,4-dihydronicotinamide followed by nucleophilic attack of the resulting iminium ion at the 2 or 6 positions. The formation of the C(5)–C(6′) bond is exactly analogous to a step proposed by Anderson and Berkelhammer[4] for the formation of an

(1) NAD and NADP are nicotinamide–adenine dinucleotide and nicotinamide–adenine dinucleotide phosphate.

(2) O. Warburg and W. Christian, *Biochem. Z.*, **274**, 112 (1934).

(3) P. Karrer, C. Schwartzenbach, F. Benz, and U. Solmssen, *Helv. Chim. Acta*, **19**, 811 (1936).

(4) A. G. Anderson, Jr., and G. Berkelhammer, *J. Am. Chem. Soc.*, 80, 992 (1958).

(5) The reaction leading to loss of the characteristic absorption of the parent at *ca.* 340–350 mμ and appearance of a new maximum at *ca.* 290–300 mμ is often called the primary acid reaction or primary acid-modification reaction.

(6) P. Karrer and F. J. Stare, *Helv. Chem. Acta*, **20**, 418 (1937).

(7) The reduced nicotinamides, now known to be the 1,4-dihydro isomers, were originally believed to be either the 1,2- or 1,6-dihydro isomers, and the "new" acid product was therefore assigned the 1,4-dihydro structure.

(8) H. Kuhnis, W. Traber, and P. Karrer, *Helv. Chim. Acta*, **40**, 751 (1957).

(9) H. L. Ammon, G. Berkelhammer, and A. G. Anderson, Jr., unpublished work.

(10) E. G. Krebs, G. W. Rafter, and S. Chaykin, unpublished work.

(11) I. L. Karle and J. Karle, *Acta Cryst.*, **16**, 969 (1963).

(12) A system of programs (PHASER) for the IBM 709–7090–7094 was used for the application of the symbolic addition procedure: H. L. Ammon, unpublished work.

(13) L. S. Bartell, *J. Am. Chem. Soc.*, **81**, 3497 (1959).

(14) S. H. Bauer and J. Y. Beach, *ibid.*, **65**, 1142 (1942).

(15) C. C. Johnston, J. L. Gardner, C. H. Suelter, and D. E. Metzler, *Biochemistry*, **2**, 689 (1963).

(16) See, for example, N. J. Leonard and A. S. Hay, *J. Am. Chem. Soc.*, **78**, 1984 (1956).

acid product of 1-benzyl-3-acetyl-1,4-dihydropyridine containing the elements of two molecules of the parent and one of water.

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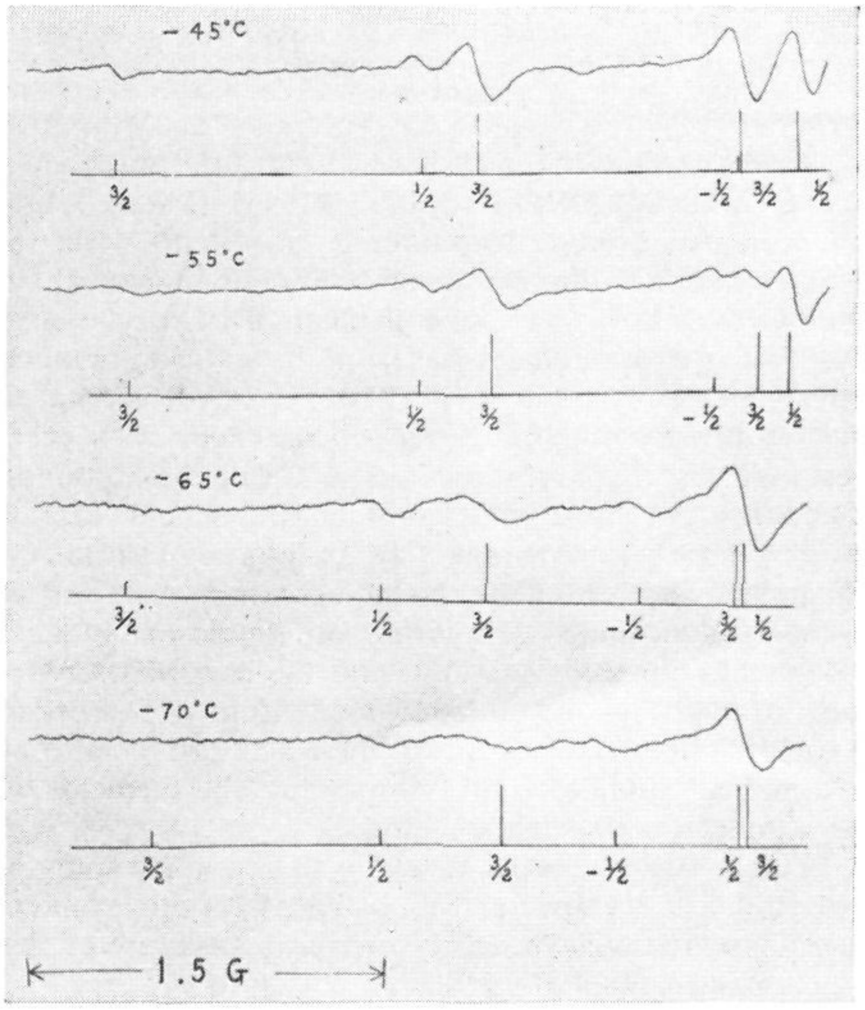

Figure 2. Temperature and M_Z^{Na} dependence of the line width of sodium anthracene.

Electron Paramagnetic Resonance Studies of Ion-Pair Equilibria[1]

Sir:

The temperature dependence of alkali metal splittings in aromatic anion radicals varies with the anion radical, the alkali metal, and the solvent.[2-5] There are, however, a number of systems in which the metal splittings change from the order of 1 gauss to almost 0 within a relatively small range of temperature. Sodium anthracene in 2-methyltetrahydrofuran (MTHF) and sodium 2,6-di-*t*-butylnaphthalene in tetrahydrofuran (THF) are such systems (Figure 1). We propose that a model involving an ion-pair equilibria can explain this sharp fall-off of metal splitting with temperature.

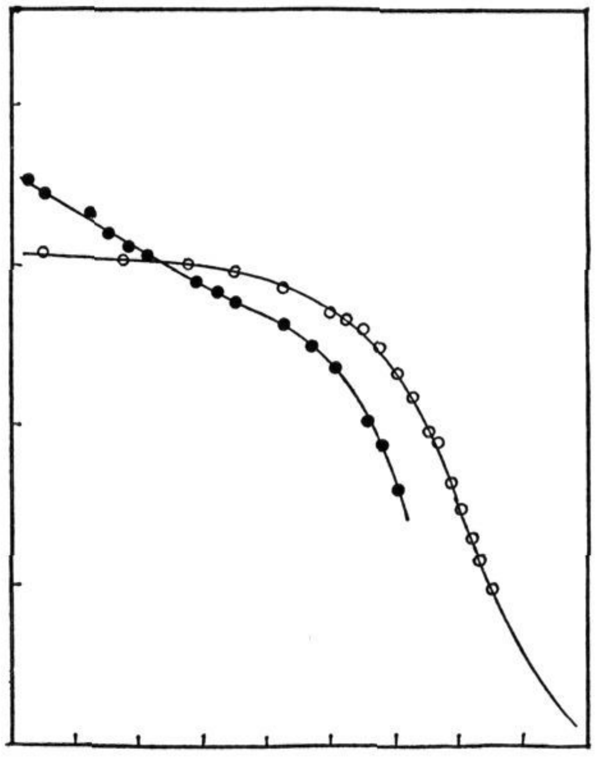

Figure 1. Temperature dependence of the sodium splittings: ○, sodium anthracene in MTHF and ●, sodium 2,6-di-*t*-butylnaphthalene in THF. The solid curve for anthracene in MTHF is the curve predicted by eq 1 with $\Delta H = -4.5$ kcal, $a_A = 1.55$ gauss, and $a_B = 0$.

Recently reported epr[6] and optical[7] spectra point out that two distinct types of ion pairs might exist. These ion pairs probably differ in their respective degrees of solvation and in the proximity of the alkali metal to the organic radical anion. One would expect different alkali metal splittings from two such species.

One possible method of interpreting the sharp temperature dependence of the alkali metal splitting is to consider a temperature-dependent rapid equilibrium between two structurally different ion pairs. We have investigated the temperature dependence of the line widths and the alkali metal splittings of sodium anthracene in MTHF and sodium 2,6-di-*t*-butylnaphthalene in THF, from 50 to −100° (Figure 1). The results obtained can be interpreted by the presence of a rapid equilibrium between two types of ion pairs, A and B.

We consider A and B to have two distinct coupling constants a_A and a_B. If P_A is the probability of finding form A and P_B the probability of finding form B, the equilibrium constant for interconversion of the two forms is given by

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(2) N. M. Atherton and S. I. Weissman, *J. Am. Chem. Soc.*, **83**, 1330 (1961).

(3) S. Aono and K. Oohashi, *Progr. Theoret. Phys.* (Kyoto), **30**, 162 (1963).

(4) B. J. McClelland, *Chem. Rev.*, **64**, 301 (1964).

(5) E. De Boer, *Rec. Trav. Chim.*, **84**, 609 (1965).

(6) N. Hirota, to be published.

(7) T. E. Hogen-Esch and J. Smid, *J. Am. Chem. Soc.*, **87**, 667 (1965).