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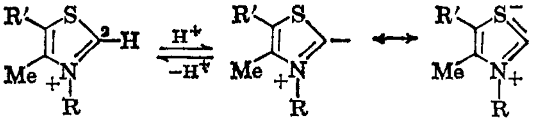
## The Deprotonation of Thiazole and Related Bases[1]

*Sir:*

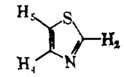
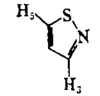
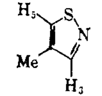
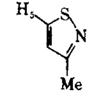
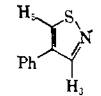
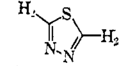
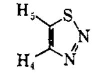
Breslow[2] has suggested that the lability of the 2 hydrogen of thiamine (I) and the stability of the ylide (II) resulting from its deprotonation might to some uncertain extent be caused by overlap of the anion in II with an unfilled d orbital of sulfur, as pictured in III. So far, attempts to assess the quantitative significance of such resonance effects in these systems have been uniformly unsuccessful because of sorting difficulties caused by the profusion of factors involved in the stabilization of II. The main obstacle is the positive charge in I and the absence of experimental evidence as to how it is distributed about the ring. We decided, therefore, to examine this d–$\sigma$ overlap—to test its geometrical likelihood in five-membered rings—by comparing the base-induced ionization rates of thiazole (IV) and a number of model bases. We especially hoped to utilize the isothiazole system (V) to separate out the overlap effect from other factors which stabilize these anions, because in this system (unlike IV) the nitrogen and sulfur should have their greatest influence on different protons, thus making it possible to use the nitrogen as an internal standard against which to measure the performance of the sulfur in the stabilization of $\alpha$ anions.[3]



I II III

In Table I the rates of base-induced deuterium incorporation of a series of S–N bases are listed. These compounds exchange $10^{5-10}$ times more slowly than the related N-alkyl cations.[1,4] From this table it is

Table I. Rates of H–D Exchange at 31°[a]

| | Compd | Ref | Proton | $k_2$, l./mole sec<br>$^{-}$OMe in MeOD[b] | $k_2$, l./mole sec<br>$^{-}$OD in $D_2O$[c] | Relative rate<br>MeOD | Relative rate<br>$D_2O$ |
|---|---|---|---|---|---|---|---|
| IV |  | *d* | $H_2$<br>$H_4$<br>$H_5$ | $5.6 \times 10^{-5}$<br>No exchange<br>$5.1 \times 10^{-5}$ | $5.8 \times 10^{-5}$<br>No exchange<br>$4.3 \times 10^{-5}$ | 1.00<br>$<10^{-6}$[e]<br>0.91 | 1.00<br>$<10^{-6}$[e]<br>0.74 |
| V |  | *f* | $H_3$<br>$H_5$ | No exchange<br>$3.9 \times 10^{-4}$ | Insoluble | $<10^{-7}$[e]<br>7.0 | |
| VI |  | *g* | $H_3$<br>$H_5$ | No exchange<br>$9.7 \times 10^{-5}$ | Insoluble | $<10^{-7}$[e]<br>1.7 | |
| VII |  | *f* | $H_5$ | $1.3 \times 10^{-4}$ | Insoluble | 2.3 | |
| VIII |  | *g* | $H_4$<br>$H_5$ | No exchange<br>$5.9 \times 10^{-4}$ | Insoluble | $<10^{-7}$[e]<br>10.5 | |
| IX |  | *h* | $H_2$ | | 0.36 | | 6200 |
| X |  | *i* | $H_4$<br>$H_5$ | | No exchange<br>1.8 | | $<10^{-2}$[e]<br>31,000 |

[a] Rates measured by nmr using probe as thermostat; reproducibility about 10%; at a given basicity reactions nicely first order over two half-lives. [b] Rates first order in substrate and first order in $^{-}$OMe. [c] Rates first order in OD$^{-}$; pD measured on a pH scale at 25° and uncorrected in calculations. Under widely varying buffer concentrations and buffer types at a single pD the variation in rate constant is less than a factor of 2. [d] J. McLean and G. D. Muir, *J. Chem. Soc.*, 383 (1942). [e] Rate at which substrate decomposes. [f] F. Hübenett, *et al.*, *Angew. Chem. Intern. Ed. Engl.*, **2**, 714 (1963). [g] See ref 4. [h] J. Goerdeler, J. Ohm, and O. Tegtmeyer, *Chem. Ber.*, **89**, 1534 (1956). [i] L. Wolff, H. Kopitzsch, and A. Hull, *Ann.*, **333**, 1 (1904).

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[1] This research was supported by the U. S. Public Health Service (GM 13980). Previous paper in series: R. A. Olofson and J. M. Landesberg, *J. Am. Chem. Soc.*, **88**, 4263 (1966).

[2] R. Breslow, *ibid.*, **80**, 3719 (1958).

[3] The application of these ideas hinges on two prior discoveries: (1) the observation by R. B. Woodward (*Harvey Lectures*, Ser. 59(1963–1964), 31 (1965) that the proton in the 5 position of 3,4-disubstituted isothiazoles can be exchanged with NaOMe in MeOD, and (2) the development of a general synthesis for 3-unsubstituted isothiazoles (R. A. Olofson, J. M. Landesberg, R. O. Berry, D. Leaver, W. A. H. Robertson, and D. M. McKinnon, *Tetrahedron*, **22**, 2119 (1966); J. M. Landesberg and R. A. Olofson, *ibid.*, **22**, 2135 (1966)). We wish to thank Professor Woodward for useful discussions and for communicating results to us prior to publication.

[4] R. A. Olofson, W. R. Thompson, and J. S. Michelman, *J. Am. Chem. Soc.*, **86**, 1865 (1964).

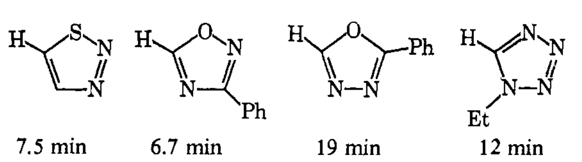

Figure 1. Half-time for exchange in 0.40 *N* piperidine in MeOD at 31° (substrates insoluble in $D_2O$ and rates too fast for NaOMe–MeOD).

evident that there is an extraordinary rate enhancement when a proton is on carbon next to sulfur, suggesting that d–σ overlap is a major factor in stabilizing these anions. The greatest surprise comes from the discovery that both $H_2$ and $H_5$ in thiazole (IV) deprotonate at about the same rate and that $H_5$ of isothiazole (V) exchanges even faster. From a comparison of IV and V it would seem that the only important factor is the sulfur effect, and superficially it makes little difference whether the ring nitrogen is α or β to the carbon bearing the exchanging proton. This is contrary to LCAO–MO calculations[5] or even a simple consideration of inductive effects.

However, inductive and electronegative atom effects are important in these systems. Electron-withdrawing substituents (VIII) increase the isothiazole (V) exchange rate, whereas electron-releasing substituents (VI, VII) slow it down. Addition of an extra β nitrogen gives the thiadiazoles (IX and X) which deprotonate $10^{3.5}$ faster than IV and V, respectively; also thiophene does not exchange with 2 *M* NaOMe in boiling MeOD. This suggests that bases which do not contain sulfur will exchange if the model substrate contains: (1) additional electron-withdrawing substituents, (2) more electronegative atoms, (3) more powerful electron-withdrawing atoms such as oxygen, or (4) these groupings placed more closely to the exchanging protons. The correctness of this postulate is verified with some selected examples in Figure 1, and it is seen what combinations of these factors will give an exchange rate equivalent to that of X.

The remarkable fact that $H_5$ in isothiazole is ionized more readily than $H_2$ in thiazole is repeated in the thiadiazoles where $H_5$ in X (a model for isothiazole with an extra β nitrogen) deprotonates faster than $H_2$ in IX (a model for thiazole also with an extra β nitrogen) and in the thiadiazolium salts: 3-ethyl-1,2,3-thiadiazolium cation (a model for isothiazole with extra β-N-alkyl, positively charged) deprotonates at C-5 faster than the 3-ethyl-1,3,4-thiadiazolium cation (a model for thiazole with extra β-N-alkyl, positively charged) deprotonates at C-5 ($k_2 \times 10^{-5}$ l./mole sec.; 4.6 to 1.8[1]).

These exchange rates do not depend much on the solvent–base system ($k_{H_2}/k_{H_5}$ for IV is 1.4 in NaOD–$D_2O$, 1.1 in NaOMe–MeOD, and 3.6 in KO-*t*-Bu-*t*-BuOD), thus lessening the possibility that the results may echo differences in steric effects, solvation effects, or electron-pair repulsion effects in the two molecular environments. We suspect these results may reflect a difference in the exact geometry (bond angles and bond lengths) of these heterocycles such as to increase the ease of d–σ overlap in the direction opposite to the nearest atom bearing a free electron pair in the plane of the ring, or they may reflect differences in some special multiatom overlap effect utilizing higher orbitals in the respective anions and the $sp^2$ electrons on the S and N. Experiments are being carried out to test these hypotheses.

(5) A. Adams and R. Slack, *J. Chem. Soc.*, 3061 (1959).

(6) (a) To whom inquiries should be addressed; Alfred P. Sloan Foundation Fellow, 1965–present; work done mostly at Harvard University; (b) National Institutes of Health Predoctoral Fellow, 1963–1964; (c) National Institutes of Health Predoctoral Fellow, 1962–1964.

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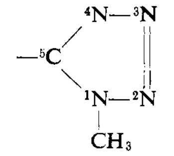
## A Nickel–Carbon Bond in Bis(1-methyl-5-tetrazolyl)nickel(II)

*Sir:*

We report the preparation and some properties of bis(1-methyl-5-tetrazolyl)nickel(II), which has a nickel–carbon bond at the 5-carbon atom, $Ni(C_2H_3N_4)_2$, where $C_2H_3N_4^-$ is



1-Methyltetrazole, prepared as in our previous studies,[1] was added under dry nitrogen to *n*-butyllithium and anhydrous tetrahydrofuran (THF) at −50°, and a gray solid, presumed to be 1-methyl-5-tetrazolyllithium, separated out. If the solution was warmed, butane was evolved, as verified by mass spectrography. To about 0.02 mole of a THF suspension of the tetrazolyllithium at about −50° was added about 0.01 mole of dichlorobis(triethylphosphene)nickel(II).[2] The mixture was stirred for 2 hr and was allowed to come to room temperature and stand for about 4 hr. A finely divided green solid was separated by centrifugation, washed with THF and acetone, and allowed to dry under a nitrogen atmosphere. A yield of 80% (based on the nickel) of bis(1-methyl-5-tetrazolyl)nickel(II), $Ni(C_2H_3N_4)_2$, was obtained. A very low yield of the compound was also obtained when anhydrous nickel chloride was used in place of the triethylphosphine complex.

Nickel was determined by the volumetric cyanide method[3] after the sample had been decomposed with 6 *M* HCl, evaporated to dryness, dissolved in a small amount of 2 *N* $H_2SO_4$, and then treated with concentrated ammonia. Because of fairly rapid decomposition in the atmosphere, satisfactory commercial C, H, and N analyses could not be obtained. However, the complex decomposes in ammonia to give $CN^-$, $CH_3OH$, and $N_3^-$, and thus the $CN^-$ could be determined. The decomposition products were determined by means of

(1) G. L. Gilbert and C. H. Brubaker, Jr., *Inorg. Chem.*, 2, 1216 (1963).

(2) K. A. Jensen, P. H. Nielsen, and C. T. Pedersen, *Acta Chem. Scand.*, 17, 1115 (1963).

(3) W. F. Hillebrand, G. E. F. Lundell, H. A. Bright, and J. I. Hoffman, "Applied Inorganic Analysis," 2nd ed, John Wiley and Sons, Inc., New York, N. Y., 1953, pp 414–415.