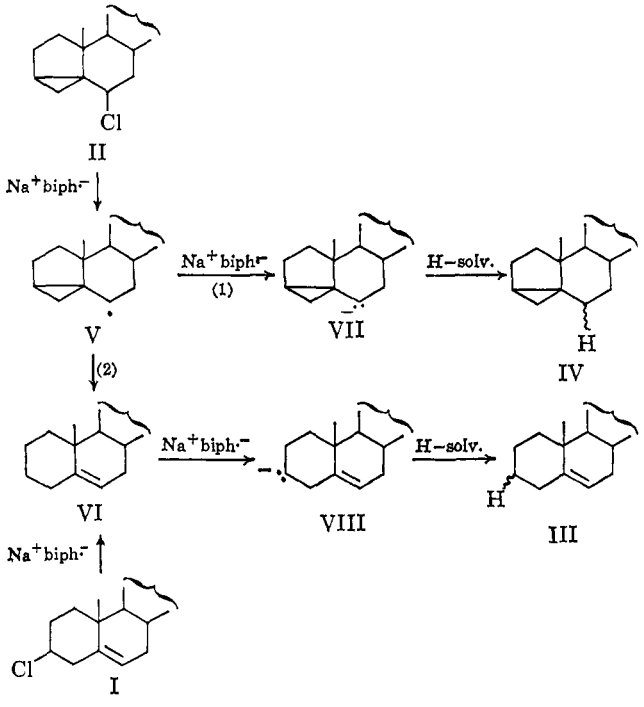
The radical V would appear to have three important choices: (a) it may abstract a hydrogen atom from the surrounding medium to give the cyclocholestane IV, (b) it may be reduced by another molecule of radical anion to form the corresponding carbanion VII, or (c) it may rearrange to the allylcarbinyl radical VI, which may have similar choices. That choice a is unimportant is shown by the lack of dependency of the product ratio on the hydrogen atom donor ability of the medium. Competition between the other choices is required to rationalize our results. The reaction sequence proposed is outlined in scheme I.

Scheme I



It would be predicted from this sequence that increased radical anion concentration should favor conversion of the radical V to the carbanion VII over its isomerization to the radical VI, as is observed, and the dependence upon concentration also requires that the rearrangement occurs at the radical stage rather than at the carbanion stage. Thus, if all radical V were reduced to carbanion VII, a decrease in radical anion concentration should not lead to increased amounts of III.

The strong temperature dependence of the product ratio IV/III is a reflection of the difference in activation energies between the electron-transfer reaction and the rearrangement reaction. That reaction 2 has an activation energy is an interesting confirmation of our conclusions regarding the nonexistence of nonclassical homoallylic free radicals.

The fact that no rearrangement occurred in the reduction of I (III being the sole product) suggests that radical VI is more stable than V, so that the reverse of reaction 2 is not observed. Attempts to trap carbanions VII and VIII by rapid carbonation of the reaction mixtures yielded none of the possible carboxylic acids. Carbanions VII and VIII must abstract protons from solvent very rapidly.

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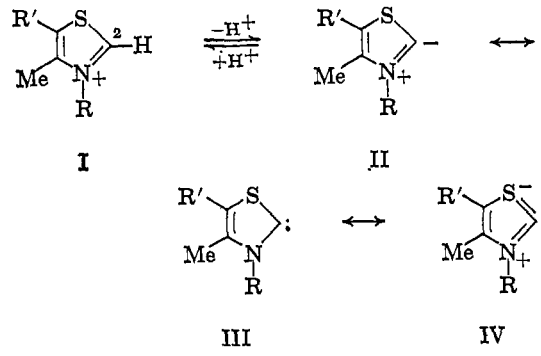
Hydrogen–Deuterium Exchange in Some Heterocyclic Cations Containing Nitrogen and Sulfur

Sir:

The importance in the mechanism of thiamine action of ionization at C_2 of the thiazolium ring (I) has been rigorously established by Breslow and others.[1] The

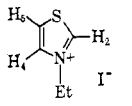
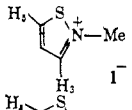
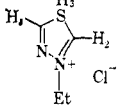
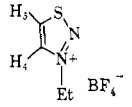
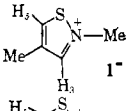
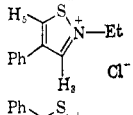
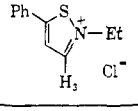


factors causing the lability of H_2 and their quantitative significance are, however, not well understood. Recently we showed by a study of the rates of deprotonation of a series of azoles and azolium salts (in which the number of nitrogens and the positioning of the positive charge were varied) that coulombic and inductive effects are major rate-enhancing factors:[2] that the positive charge in I should be worth *ca.* 10^{10} in rate and the α nitrogen *ca.* 10^5. We now wish to amplify our initial conclusions to include sulfur–nitrogen systems as necessary background for a later consideration of the importance of the carbene structure (III) and d–σ overlap (IV)[3] in the stabilization of II.

Two other groups have rationalized the acidity of I. Hafferl[4] discovered that 3,4-dimethylthiazolium iodide (V) and N,N′-diphenylimidazolinium chloride (VI) exchange at almost the same rate and concluded that III is an important rate-enhancing factor whereas IV is not. These authors, however, chose a poor model (the N,N′-dimethylimidazolium cation deprotonates 10^3 times more slowly than VI) and relied on some misinterpreted data of Wanzlich.[5] Haake[6] compared the exchange rates, nmr chemical shifts, and $J_{C^{13}-H}$ for the 3,4-dimethyloxazolium cation (VII) and V (rates 40:1; $J_{C^{13}-H}$ = 247:218 cps), and concluded that high s character in the C–H bond was a dominant factor. The use of $J_{C^{13}-H}$ as a measure of s character

(1) R. Breslow, *J. Am. Chem. Soc.*, 80, 3719 (1958), and other papers; F. H. Westheimer, *Advan. Enzymol.*, 24, 467 (1962).
(2) R. A. Olofson, W. R. Thompson, and J. S. Michelman, *J. Am. Chem. Soc.*, 86, 1865 (1964), and unpublished results.
(3) R. A. Olofson, J. M. Landesberg, K. N. Houk, and J. S. Michelman, *ibid.*, 88, 4265 (1966).
(4) W. Hafferl, R. Lundin, and L. L. Ingraham, *Biochemistry*, 2, 1298, (1963).
(5) D. M. Lemal, R. A. Lovald, and K. I. Kawano, *J. Am. Chem. Soc.*, 86, 2518 (1964).
(6) P. Haake and W. B. Miller, *ibid.*, 85, 4044 (1963).

Table I. Rates of H–D Exchange at 31°

	Compd	Ref	Proton	Rate (k_2), l./mole sec[a]	Calcd pD for $t_{1/2}$ = 10 min[a]	Relative rate
VIII		*b*	H_2	9.8×10^5	5.07	1.000
			H_4	Ring cleaves faster	*c*	$<10^{-4}$
			H_5	*c*	~8–10	$\sim 10^{-4}$
IX		*d*	H_3	Ring cleaves faster	(pD ~10)	...
			H_5	7.3×10^2	8.20	7×10^{-4}
X		*e*	H_2	2.6×10^9 [f]	1.66[f]	3×10^3
			H_5	1.8×10^5	5.81	2×10^{-1}
XI		*e*	H_4	4.2×10^3	7.44	4×10^{-3}
			H_5	4.6×10^5	5.40	5×10^{-1}
XII		*d*	H_3	1.6×10^1	9.86	2×10^{-5}
			H_5	3.0×10^2	8.58	3×10^{-4}
XIII		*e*	H_3	2.1×10^2	8.74	2×10^{-4}
			H_5	6.5×10^3	7.25	7×10^{-3}
XIV		*e*	H_3	1.7×10^2	8.83	2×10^{-4}

[a] Rates measured by nmr; reproducibility is about 15%. Rate = k_2(substrate)($^-$OH); some variation with buffer concentration and buffer type. At given pD, exchange is nicely first order over two half-lives; pD measured on a pH scale at 25° and is uncorrected in calculations. [b] T. Ugai, S. Tanaka, and S. Dökawa, *J. Pharm. Soc. Japan*, **63**, 296 (1943). [c] Ring cleaves in carbonate solution but pD cannot be kept constant (decreases 13 to 7), H_5 exchanges competitively with ring opening. No evidence for exchange of H_4 prior to ring cleavage. [d] F. Hübenett, *et al.*, *Angew. Chem. Intern. Ed. Engl.*, **2**, 714 (1963). [e] New compound; satisfactory analytical data obtained (X: hygroscopic solid (tetrafluoroborate salt: mp 78–79°); XI: mp 70–71°; XIII: mp 167–168°; XIV: mp 164–165°). [f] Assumed base is $^-$OH but here water and buffer anions also act as bases.

in related systems has been criticized,[7] and a simple correlation is not substantiated with other substrates.[8] These authors also did LCAO–MO calculations on V and VII and concluded that d–σ overlap might contribute to the lability of H_2 in thiamine; however, the futility of such calculations as predictive aids in these systems can be demonstrated.[3]

In Table I the rates of deuterium incorporation of a number of five-membered positively charged nitrogen- and sulfur-containing heteroaromatic salts are listed. Note that thiazolium salts exchange more rapidly than isothiazolium salts and that replacement of a carbon in the thiazolium or isothiazolium cation by nitrogen (to yield the thiadiazolium salts X and XI) increases the deprotonation rate 10^{3-4}, paralleling our studies of azolium salts.[2] In those substrates where an internal comparison of the exchange rates of two protons can be made (especially VIII,[9] X, and XI), the special importance of coulombic and electronegative atom effects is further substantiated. Electron-withdrawing substituents (phenyl) increase the deprotonation rate whereas electron-releasing substituents (methyl) decrease the rate (by inductively stabilizing or destabilizing the incipient carbanion) at both H_3 and H_5 in isothiazolium salts (IX, XII–XIV) (see Table I).

H_2 in the thiazolium cation VIII is lost 10^4 times faster than H_2 in the related 1,3-dimethylimidazolium cation ($k_2 = 3 \times 10^2$ l./mole sec)[2] and *both* protons of the isothiazolium cations XII and IX are lost faster than H_3 of the 1,2-dimethylpyrazolium cation ($k_2 = 9 \times 10^{-3}$ l./mole sec).[2] From the decrease in electronegativity on replacing N by S the opposite prediction would be made. This result suggests that another effect such as d–σ overlap (see ref 3) is also operative. Note that the exchange rate of protons on carbon next to sulfur is invariably greater than the exchange rate of protons on carbon next to nitrogen where internal comparisons may be made (IX, XI–XIII). This again requires postulation of d–σ overlap or another special factor since both electronegative atom and coulombic effects (most of the positive charge should be on the nitrogen; compare ease of protonating a Schiff base (model for $=N^+-$) *vs.* ease of protonating a thio ketone (model for $=S^+-$)) would lead one to predict the opposite.

Preliminary experiments hint that the relative exchange rates found here are also paralleled in other processes which generate carbanions on the heterocyclic ring (*i.e.*, decarboxylation) and that it may ultimately be possible to formulate a simple semiempirical equation from which the rate of any process which yields a carbanion on a heteroaromatic ring can be accurately predicted.

(7) G. J. Karabatsos and C. E. Orzech, *J. Am. Chem. Soc.*, **86**, 3574 (1964).

(8) Thiazole exchanges H_2 (τ 1.02) and H_5 (τ 2.42) at about the same rate but H_4 (τ 2.08) does not exchange ($<10^{-7}$); also 1,2,3-thiadiazole exchanges at C_5 ($J_{C^{13}-H}$ = 192.0 cps) but not at C_4 ($J_{C^{13}-H}$ = 190.3 cps).

(9) It is possible that deprotonation in VIII may be occurring *via* the enamine resulting from reversible addition of OD^- at C_2. Decarboxylation at C_5 does, however, occur more rapidly than at C_4. This pathway cannot generally be operative since it often would require ready OD^- addition at N (XI).

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

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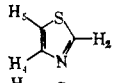
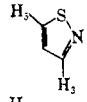
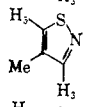
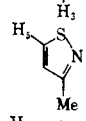
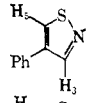
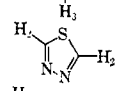
The Deprotonation of Thiazole and Related Bases[1]

Sir:

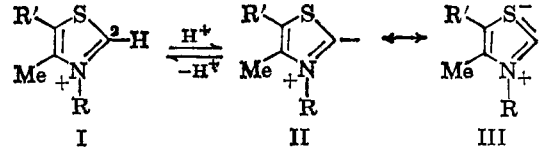
Breslow[2] has suggested that the lability of the 2 hydrogen of thiamine (I) and the stability of the ylide (II) resulting from its deprotonation might to some uncertain extent be caused by overlap of the anion in II with an unfilled d orbital of sulfur, as pictured in III. So far, attempts to assess 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–σ 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 α anions.[3]

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



I II III

(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).