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Topological Analysis of the Electron Density in Model Azolium Systems for Thiamin Structure−Function: Sulfur Is the Electron Sink and Positively Polarized Carbanions Act as Nucleophiles

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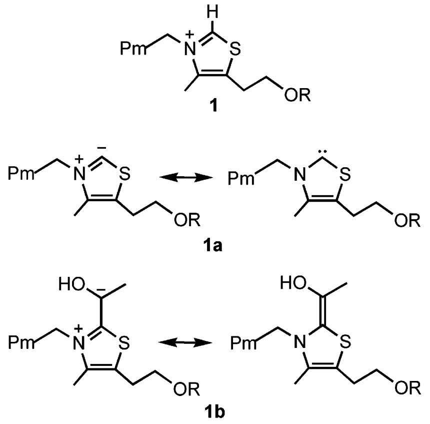
The mechanism of thiamin diphosphate-dependent enzyme reactions requires two carbanion intermediates **1a** and **1b**. Neither has been isolated nor detected, but resonance stabilization is assumed to occur with the thiazolium quaternary nitrogen being the electron sink. We have questioned the electronic nature of these carbanion intermediates and, in a broader sense, the role of sulfur in the thiazolium moiety. To address these issues the theory of atoms in molecules (AIM) was used to acquire quantitative electron distributions in thiazolium **2**, oxazolium **3**, and imidazolium **4** as cations and zwitterions. Among the heteroatoms, only sulfur acts as an electron sink. This is corroborated by a similar behavior in phosphorothioates. Further, the formal carbanion at C2 and Cα of the intermediates are positively charged and their nucleophilic character is explained with AIM theory by comparison with the σC^- of model **5a** and πC^- of model **6a**. C2 of **2a** excels in lone-pair coverage in the σ-plane, surpassing the σC^- in acyclic **5a** and other cyclic ylidenes, and hence, is a more effective nucleophile. The πC^- of **6a** reveals a depletion area centered in the σ-plane but shows lone-pair concentration above and below the plane. Unlike **6a,** the AIM properties, bond length, and bond order of **2b** indicate no lone-pair on Cα but essentially a double bond across C2−Cα. Thus, the nucleophilic behavior at Cα of **1b** is based on the enamine chemistry induced by an electrophile.

Introduction

Thiamin diphosphate (ThDP), **1**, is required in a broad range of metabolic reactions presented in many reviews and texts.[1,2,3] Notably ThDP is a cofactor in 2-oxoacid decarboxylase for decarboxylation, in acetolactate synthase for amino acid synthesis, and in transketolase for sugar chain shortening or extension.[1,2,3] The cornerstone in such enzymic actions is thiamin transketolation, the simplest example of which is the decarboxylation of pyruvic acid wherein the aceto group is transferred to hydrogen to form $HCOCH_3$. The mechanistic review by Jordan[3] and recent study by Perham et al.[4] have shown detailed understanding of these ThDP-dependent enzyme reactions. However, this mechanism is built upon two carbanion intermediates **1a** and **1b**, neither of which have been isolated nor directly detected, but inferred to exist along with their resonance forms, the carbene and enamine respectively,[5] as illustrated in Scheme 1. The assumption has always been that the positive charge on the thiazolium quaternary nitrogen atom serves as the electron sink to reduce the negative charge load on C2 in **1a** or Cα in **1b**. Reasonable as Scheme 1 appears, there is no assurance that such a resonance pathway actually occurs resulting in the stabilization of the carbanions present in **1a** and **1b**. The fundamental question concerns the stability and electronic nature of these carbanion intermediates and hence the role of sulfur in the azolium moiety: whether sulfur is critical or replaceable by another heteroatom like oxygen or nitrogen in order for the carbanions to perform as nucleophiles. To address these issues we have acquired quantitative electron distribution data on several model azolium systems using Bader's[6,7] theory of atoms in molecules (AIM). The topology of the Laplacian of the electron density of azolium models—thiazolium **2**, oxazolium **3**, and imidazolium **4** of Scheme 2—was examined both at the cationic and zwitterionic intermediate levels, viz. the ylidene and the exocyclic α-carbanion. Our results, based on the nature of accumulated bonded and nonbonded charge concentrations and the properties of the atom as a well-defined quantum mechanical entity within a molecule, provide a unique picture of these essential species in thiamin chemistry.

SCHEME 1: Thiamin Diphosphate Intermediates



Pm = 5-(4-amino-2-methyl)-pyrimidyl
OR = diphosphate

Methods

The equilibrium geometries of the molecules of this study were fully optimized, and determined to be stationary states by

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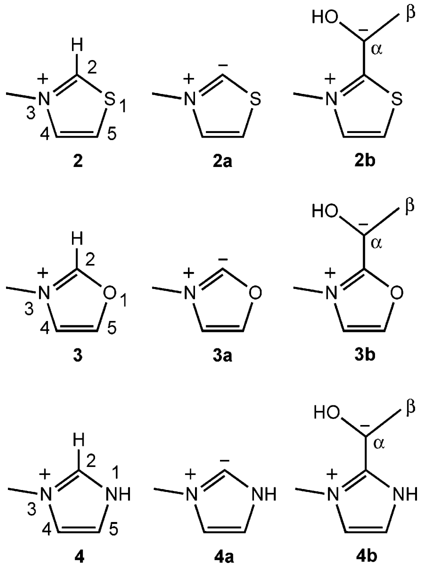
SCHEME 2: Azolium Models



normal-mode frequency analysis, using density functional theory (DFT) with the B3LYP functional[8,9] and the 6-31G(d,p) basis set, as implemented in Gaussian98.[10] The resultant electron density obtained from the wave function of all optimized structures was analyzed with AIM theory.[6,7] AIM focuses on the properties of the topology of the electron density and its Laplacian, obtained either by experiment or by calculation. In this analysis, an atom in a molecule is rigorously defined as a quantum mechanical entity bounded by a three-dimensional surface of zero flux in the gradient of the electron density ρ. As such the net charge on an atom can be obtained by integration of the electron density ρ over this volume of space. A chemical bond between two atoms is distinguished by a path of maximal electron density between the nuclear attractors with a (3,−1) critical point (saddle point) on the interatomic surface joining the two atoms. The properties of the bond critical point (BCP) serve to categorize different types of chemical bonds. The covalent bond is a shared interaction with generally large values of the electron density, $\rho(r_{cp})$, at the BCP. The Laplacian, $\nabla^2\rho(r_{cp})$, which may be written in terms of the eigenvalues of the Hesssian of ρ as $\nabla^2\rho = \lambda_1 + \lambda_2 + \lambda_3$, where $\lambda_1 \leq \lambda_2 \leq \lambda_3$, is also generally large and negative at this point.[6,7,11] Covalent bonding thus is dominated by contraction of electron density at the BCP in the plane perpendicular to the bond path (BP) (i.e., $|\lambda_1 + \lambda_2| > \lambda_3$). In this case, the electronic charge is concentrated between nuclei and thus shared.

Examination of the topological properties of the Laplacian of the total electron density can also uncover regions of valence shell charge concentration (VSCC) where the electron density is curving inward in all directions.[6,12] These regions are characterized by the presence of (3,−3) critical points (CPs) where all eigenvalues λ_i of the Hessian of the Laplacian are negative. These CPs may or may not be directed toward bonded atoms. In the latter case, the accumulations of charge map onto the chemist's idea of nonbonded lone-pairs.[6,12] VSCCs may be further characterized by their spherical surface area[6,12] about the nucleus and radial thickness outward of the nucleus as given by μ_3, the curvature of $\nabla^2\rho$ perpendicular to the surface of this sphere.[6,12] A larger value of μ_3 is indicative of a more compacted radial concentration of charge.

The π-type concentration of electron density is evident in double, or partially double, bonds in the distortion from circular symmetry of the inward curvature of ρ about the bond axis. For like atoms, the value of $\epsilon = (\lambda_1/\lambda_2) - 1$ at the BCP is a good measure of this ellipticity.[12,13]

TABLE 1: Distribution of Integrated AIM Atomic Charges (e) on the Atoms of the Heterocyclic Azolium Cation Series

	thiazolium cation **2** X=S	oxazolium cation **3** X=O	imidazolium cation **4** X=N
X1	0.56	−1.06	−1.29
C2	0.38	1.29	1.14
H2	0.16	0.19	0.15
N3	−1.27	−1.28	−1.28
H3	- -	- -	0.51
C_n[a] (4, 5, N−Me)	0.47, −0.12, 0.36	0.44, 0.51, 0.37	0.46, 0.47, 0.38
H_n[a] (4, 5, N−Me[b])	0.13, 0.15, 0.23	0.15, 0.17, 0.25	0.13, 0.14, 0.22
net charge[c]	1.05	1.03	1.03

[a] C_n, H_n are the carbons and hydrogens in a neighboring position to the azolium NC(H)X series of atoms. [b] Sum of the integrated charges on all hydrogens of the methyl group. [c] Net charge: sum of the integrated charges on all the atoms of the 1+ cations.

Estimates of bond order, n, may be obtained from empirical fits of an equation of the form $n = \exp[A\rho(r_{cp}) - B]$ to the values of $\rho(r_{cp})$ calculated for standard single, double and triple bonds.[6,7,13] For carbon−carbon bonds, we find $A = 6.87$ and $B = 1.68$ with $\rho(r_{cp})$ calculated at B3LYP/6-31G(d,p) for ethane ($n = 1$), ethene ($n = 2$), and acetylene ($n = 3$) used as reference standards. For carbon−nitrogen bonds, we find $A = 5.55$ and $B = 1.48$ with $\rho(r_{cp})$ calculated at the same level for methylamine ($n = 1$), the CH_2NH imine ($n = 2$), and HCN ($n = 3$) as standards.

AIM analysis was performed with the AIM2000 program[14] using wave functions generated with the Gaussian electronic structure package.

Results and Discussion

Sulfur Is the Electron Sink in Thiamin. The AIM charges for all the atoms of the azolium cations **2**, **3**, and **4** are shown in Table 1. The net charge q, the sum of all integrated atomic charges, is essentially +1.0e, with overall integration error of no more than the unaccounted for 0.03−0.05e. The quaternary N3 atom in these azolium cations, customarily assigned a formal +1 charge, turns out to bear more than one full negative charge (−1.27e to −1.28e). This dichotomy between formal and real charge is not an isolated incidence. Calculation of atomic charges in nitrogen ylides like $H_3N^+{-}^-CH_2$ showed nitrogen to be negative (−0.94e) despite bearing a formal positive charge.[15] Also, the N^+ atoms of protonated pyrimidine bases always display substantial negative charges.[16] We have found by AIM analysis that the quaternary nitrogen of H_4N^+ has a negative charge of −1.13e, with each hydrogen atom bearing a positive charge of +0.53e. This phenomenon is clearly a result of electronegativity (χ) differences in the bonding atoms, where for reference here $\chi(H) = 2.1$, $\chi(C) = 2.5$, $\chi(S) = 2.5$, $\chi(N) = 3.0$, and $\chi(O) = 3.5$. Indeed, the inductive electronegativity effect manifests itself throughout the azolium cation series. Thus, even the nominally neutral O1 of oxazolium **3** and N1 of imidazolium **4** are negatively charged to the extent of about −1.1e to −1.3e. On the other hand, the lower electronegativity of sulfur relative to nitrogen causes S1 of thiazolium **2** to lose electron density, thereby acquiring a partial positive charge of 0.56e.

The combination of the inductive effects of nitrogen and sulfur confer in **2** a much smaller positive charge of 0.38e on C2, which is only about one-third of that found on C2 in **3** and **4**. Such a difference in the positive charge load on C2 is consistent with the relative electrophilic reactivity of C2 in the

TABLE 2: Distribution of Integrated AIM Atomic Charges (e) on the Azolium Ylidene Series

	thiazolium ylidene **2a** X=S	oxazolium ylidene **3a** X=O	imidazolium ylidene **4a** X=N
X1	0.18	−1.09	−1.28
Δq(X1)[a]	−0.38	−0.03	0.01
C2	0.32	0.94	0.84
Δq(C2)[b]	−0.06	−0.35	−0.30
N3	−1.26	−1.30	−1.27
C_n (4, 5, N-Me)	0.39, −0.16, 0.40	0.37, 0.49, 0.42	0.38, 0.39, 0.43
H_n (4, 5, N-Me[c])	0.04, 0.06, 0.07	0.06, 0.07, 0.06	0.04, 0.04, 0.04
net charge[d]	0.04	0.03	0.01

[a] Δ*q*(X1) = charge on ylidene heteroatom X minus charge on azolium heteroatom X. [b] Δ*q*(C2) = charge on ylidene C2 minus charge on azolium C2. [c] Sum of the integrated charges on all hydrogens of the methyl group. [d] Net charge: sum of the integrated charges on all the atoms of the neutral ylidenes.

TABLE 3: Distribution of Integrated AIM Atomic Charges (e) on the Azolium Exocyclic Carbanion Series

	thiazolium exo-carbanion **2b** X=S	oxazolium exo-carbanion **3b** X=O	imidazolium exo-carbanion **4b** X=N
X1	0.11	−1.09	−1.13
Δ*q*(X1)[a]	−0.45	−0.03	0.16
C2	0.25	0.82	0.73
Δ*q*(C2)[b]	−0.13	−0.47	−0.41
N3	−1.14	−1.11	−1.13
C_α,C_β in $HOC_\alpha C_\beta$	0.50, 0.43	0.51, 0.43	0.48, 0.43
O in $HOC_\alpha C_\beta$	−1.11	−1.12	−1.12
C_n (4, 5, N-Me)	0.47, −0.15, 0.43	0.38, 0.48, 0.43	0.37, 0.40, 0.43
H_n (4, 5, N-Me[c])	0.03, 0.06, 0.06	0.04, 0.07, 0.04	0.03, 0.04, 0.03
net charge[d]	0.16	0.11	0.13

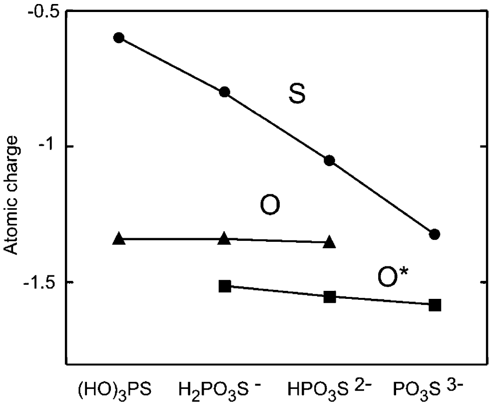
[a] Δ*q*(X1) = charge on carbanion heteroatom X minus charge on azolium heteroatom X. [b] Δ*q*(C2) = charge on carbanion C2 minus charge on azolium C2. [c] Sum of the integrated charges on all hydrogens of the methyl group. [d] Net charge: sum of the integrated charges on all the atoms of the exocyclic carbanion intermediates.

azolium systems. It has been shown that the equilibrium acidity of thiazolium cations like **2** cannot be measured in basic aqueous solution because of hydroxide attack at C2 followed by ring opening.[17] In this context, the corresponding oxazolium cations show greater acidity and even faster rates of ring hydrolysis.[18] The lability of the oxazolium ring due to a strongly electrophilic C2 would thus be a disadvantage for thiamin catalyst. Additionally, the carbon and hydrogen atoms neighboring to the NC(H)X moiety share in the positive load of these azolium cations, the only exception being C5 of **2**, that is bonded to sulfur, and has a slight negative charge of −0.12e.

Table 2 lists the AIM atomic charges of all the atoms in the ylidene models **2a**, **3a**, and **4a** of the first zwitterion intermediate **1a**. The net charges are close to zero, with overall integration error of no more than the unaccounted for 0.01−0.04e. The quaternary N3, with a formal charge +1, continues the trend of the cation series in bearing a negative load of about −1.3e (the *same* as that found in the cation series **2**, **3**, and **4**). Likewise, the charges of the other heteroatom O1 of **3a** and N1 of **4a** remain essentially unchanged from the values found for the cationic species with Δq(X1) = −0.03e and +0.01e, respectively. However, S1 of **2a** has become much less positive, gaining 0.38e. Thus, among all the heteroatoms of the azolium ylidenes, only sulfur acts as an electron sink. The deprotonated C2 in the sulfur analogue turns out to bear a positive charge 0.32e, which is only slightly less positive (Δ*q*(C2) = −0.06e) than in the corresponding cation. On the other hand, the C2 conjugate base carbons of **3a** and **4a** are much more positive (0.94e and 0.84e, respectively), after a pick up of ∼5 times more electron density (Δ*q*(C2) = −0.35e and −0.30e, respectively) than the corresponding C2 of the thiazolium ylidene.

The charge distribution trend set by the first intermediate ylidenes is reinforced by those of the second carbanion intermediate, the exocyclic α-carbanion models. As shown in Table 3, all the azolium nitrogen and oxygen atoms, including the exocyclic hydroxyl oxygen, carry a negative charge of about −1.1e. Again, sulfur is the only significant heteroatom electron sink (Δ*q*(S1) = −0.45e). The positive character of C2 is retained across the series as seen in their positive charges and the negative values of Δ*q*(C2). Interestingly all the exocyclic Cα atoms acquire a positive charge of about 0.5e. By convention, Cα should be a formal carbanion after decarboxylation. The remaining carbon and hydrogen atoms in these zwitterions are found to share the balance of positive charge load, except C5 of the thiazolium system noted above.

Sulfur Is the Electron Sink in Phosphorothioates. The role of sulfur as electron sink in thiamin is corroborated by a similar inquiry into a series of phosphorothioates of increasing net anionic charge: $(HO)_3PS$, $H_2PO_3S^-$, HPO_3S^{2-}, and PO_3S^{3-}. The question is which of the congeners, sulfur or oxygen, has the greater ability to stabilize the growing negative charge. Liang and Allen[19] showed by ab initio electronic structure calculations that sulfur does not form double bonds in these anions and hence may be negatively charged. We have obtained AIM charges for phosphorothioic acid and its anions in order to ascertain whether sulfur in this series behaves as the electron sink like sulfur in thiamin. Figure 1 is a plot of the AIM charges of oxygen and sulfur atoms in the phosphorothioates series. Here O* refers to singly coordinated oxygens and O to those oxygens also bonded to hydrogen. Across the series, the charge loads remain quite constant for the phosphorus and oxygen atoms: phosphorus is positively charged (about 2.9e to 3.1e), O* negatively charged (about −1.5e to −1.6e), and O also negative (−1.34e to −1.35e). The major variant is that of sulfur which bears an increasingly larger electron load, from −0.60e in the overall neutral conjugate acid to −1.32e in the 3− anion. That sulfur is negatively charged even in the conjugate acid form is because it is bonded only to phosphorus, which has a lower electronegativity of $\chi = 2.1$. Thus, it appears that sulfur is a capable electron sink irrespective of whether the atom is nominally neutral (thiamin series) or negatively charged (phosphorothioate series).



	$(HO)_3PS$	$H_2PO_3S^-$	HPO_3S^{2-}	PO_3S^{3-}
S	-0.60	-0.80	-1.05	-1.32
O*		-1.51	-1.55	-1.58
O	-1.34	-1.34	-1.35	
P	3.01	2.89	2.97	3.09

Figure 1. Integrated AIM atomic charges (e) in a series of phosphorothioates of increasing net negative charge. O* refers to singly coordinated oxygens and O to those oxygens also bonded to hydrogen.

TABLE 4: Integrated AIM Charges (e) and Geometric Parameters for $(CH_3)_2N{-}CH{=}^{+}N(CH_3)_2$ (5) and $(CH_3)_2N^{-}C{=}N^{+}(CH_3)_2$ (5a)

	cation **5**	ylidene−carbene **5a**
N, N	−1.22	−1.21
C	1.28	0.94
H	0.10	- -
Me−C[a]	1.53	1.59
Me−H[b]	0.56	−0.06
net charge	1.04	0.05
C−N bond length (Å)	1.324	1.354
∠NCN (deg)	131.0	119.8

[a] Sum of integrated charges on all methyl carbons. [b] Sum of integrated charges on all methyl hydrogens.

Positively Charged Carbanions Are Polarized To Act as Nucleophiles. The positive charge on, yet nucleophilic character of, the formal carbanion at C2 and Cα in the azolium series needs to be explained. Traditionally, these carbanions are distinguished in orbital terms as two different types: C2 has a σ lone-pair (σC^-) in the ylidene (first carbanion intermediate **1a**), and Cα has a π lone-pair (πC^-) in the exocylic α-carbanion (second carbanion intermediate **1b**). For comparison we have calculated integrated AIM charges for σC^- in $(CH_3)_2N^-$-$C{=}N^+(CH_3)_2$ (**5a**) and πC^- in $^-CH_2NO_2$ (**6a**). The zwitterion ylidene **5a** is also a resonance structure which behaves similar to the singlet diaminocarbenes reviewed recently by Bertrand et al.[20] Its stability is attributed to significant nitrogen lone-pair density transferred into the formally empty p-orbital on the central carbon perpendicular to the N−C:−N plane. The resultant ylidene is nucleophilic by virtue of the outwardly extended, in-plane σC^- lone-pair.[20] The πC^- model **6a** is the conjugate base of CH_3NO_2. This carbanion is stabilized by both inductive withdrawing and resonance effects of the nitro group and is often used as a nucleophile in Aldol-type reactions.

Table 4 lists the atomic charges, bond lengths and angles for $(CH_3)_2N^-C{=}N^+(CH_3)_2$ (**5a**) along with its conjugate acid $(CH_3)_2NCH{=}N^+(CH_3)_2$ (**5**). These atomic charges resemble those reported in Tables 1 and 2 for the imidazolium cation **4** and its ylidene **4a**. In particular, the amino nitrogen bears a negative charge of about −1.2e in both the ammonium cation and its conjugate base, the ylidene−carbene. The diaza carbon is highly positive in the two forms, 1.28e and 0.94e, respectively. The angle subtended at the central carbon, ∠NCN, narrows considerably from 131° in the cation to 120° in the conjugate base. The corresponding angles in the cyclic imidazolium **4** and **4a** follow the same trend with ∠NCN = 108 and 101°, respectively. As this angle becomes more acute by making use of more p-orbital concentration on the carbon, the C−N bonds are lengthened by 30 pm in the acyclic and 32 pm in the cyclic model. According to Bent's rule,[21] atomic s-character concentrates in orbitals directed toward electropositive substituents. Lone-pair electrons are regarded as limiting situations pointing to virtual, extremely electropositive atoms. Thus, more s-orbital electron density results on the ylidene carbons of **4a** and **5a**, stabilizing the σC^- lone-pairs. Furthermore, the angle constraint of the five-membered ring serves to enhance the s-character and carbanion stability of **4a**.

TABLE 5: Integrated AIM Charges (e) and Bond Lengths for CH_3NO_2 (6) and $^-CH_2NO_2$ (6a)

	CH_3NO_2, **6**	$^-CH_2NO_2$, **6a**
C	0.31	0.35
N	0.44	0.07
O[a]	−0.91	−1.34
H[b]	0.17	−0.08
net charge	0.01	−1.00
C−N bond length (Å)	1.499	1.342

[a] Sum of the integrated charges on both oxygens. [b] Sum of the integrated charges on all hydrogens.

For comparison with a π−type carbanion, Table 5 summarizes the atomic charges and C−N bond lengths of $^-CH_2NO_2$ (**6a**) and its conjugate acid CH_3NO_2 (**6**). The center of interest is the carbon bonded to nitrogen of the nitro group. The nitro group is the expected electron sink for the conjugate base carbanion. This is confirmed by the change in the charge load of NO_2 from the conjugate acid to the carbanion: the charge on nitrogen goes from 0.44e to 0.07e and that on both oxygens from −0.91e to −1.34e, suggesting a powerful inductive withdrawing effect of the nitro group. A π-type resonance is also noted. The C−N bond length of 1.499 Å in **6** is relatively long due to repulsion of positive charges on the adjacent carbon (0.31e) and nitrogen (0.44e) atoms. Double bond character in the form of the enolate appears to develop, as the C−N bond of **6a** becomes shorter (1.342 Å). The shorter C−N bond length accentuates the inductive withdrawing influence of nitrogen, making the carbanion carbon of **6a** even more positive (0.35e) than its conjugate acid carbon.

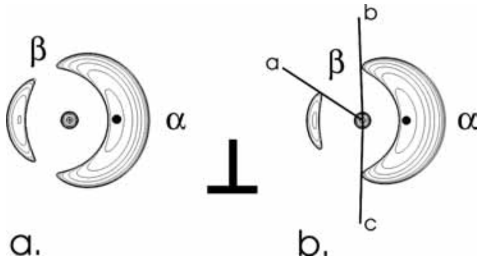


Figure 2. Contour plot of the Laplacian of the electron density showing regions of charge concentration in a plane perpendicular to (a) the five-membered ring and approximately bisecting the N3−C2−S1 bond angle of the thiazolium ylidene **2a** and (b) the plane and bisecting the N−C−N bond angle of the acyclic diaminocarbene **5a**. The dark circle on each carbon is the (3,−3) critical point of the lone-pair concentration in the valence shells of the two carbon atoms. These points both lie in the σ-plane of the respective molecules. Lines of charge depletion are not shown for clarity. Two angles, the lone-pair extension angle α and the valence depletion angle β, are defined by the rays (a, b, and c) emanating from the nucleus in part b. [6,22]

In all these cases, the carbanion carbons bonded to nitrogen are actually positively charged. This raises the question of how such a positive carbon can behave as nucleophile. The origin of nucleophilicity of the thiamin−C2 carbanion may be understood by analyzing the Laplacian of the electron density of C2 as shown in Figure 2a for the thiazolium ylidene **2a**. This is a view of the Laplacian of the electronic density of C2 in a plane perpendicular to the ring plane and roughly bisecting the N−C−S bond angle for the ylidene structure. For clarity, only the regions of valence shell charge concentration (VSCC) are shown. The most pronounced feature is the extended crescent shaped lobe of nonbonded, lone-pair concentration on the carbon pointing outward of the five-membered ring. As originally shown by MacDougall and Bader,[22] this feature is a consequence of back-polarization mainly from the more electronegative nitrogen attached, thereby conferring nucleophilic properties to the ylidene carbon. (This adjustment on carbon in the direction opposite to that of the charge transfer to the more electronegative nitrogen is necessary to counterbalance the loss of excess potential energy associated with this charge.[6,22] Otherwise the energy of the carbon atom would increase dramatically. Concentration of the repolarized density outward of the C2−N3 bonding region restores the balance of kinetic and potential energy components in the Laplacian and also maintains the zero

TABLE 6: Properties of the (3,−3) VSCC Lone-Pair on the C2 Carbon Across Thiamin Analogues with a Comparison to the Tetramethyldiamine Ylidene−Carbene

	thiazolium ylidene **2a**	oxazolium ylidene **3a**	imidazolium ylidene **4a**	diamino ylidene−carbene **5a**
ρ (au)	0.31	0.32	0.32	0.33
$\nabla^2\rho$ (au)	−1.23	−1.37	−1.29	−1.40
μ_3 (au)	−15.11	−16.34	−15.70	−16.37
d (au)[a]	0.87	0.87	0.87	0.87
area (Å^2)	1.73	1.23	1.65	1.34
α	213°	172°	207°	181°
β	20°	45°	42°	53°

[a] *d* is the distance of the (3,−3) VSCC critical point from the carbon nucleus, α is the angle approximating the extent of the lone-pair concentration on a sphere of radius *d* centered at the nucleus cutting through the lone-pair VSCC, and β is the exposure angle of charge depletion about the nucleus.

flux condition of the overall atomic electronic density within the carbon atomic basin.) The plot in Figure 2a is reminiscent of the electronic density in carbon monoxide, where its positively charged carbon end—not the oxygen end—preferentially acts as the nucleophile.[6,23]

For comparison, the Laplacian plot of the σC^- in the model diaminocarbene-ylidene $(CH_3)_2N^-C{=}N^+(CH_3)_2$ (**5a**) is shown in Figure 2b. There is great resemblance between the two plots in Figure 2 indicating lone-pair concentration directed outward in the σ-plane. To provide quantitative analysis of the nucleophilicity of these ylidene−carbene carbons, the AIM properties of the (3,−3) lone-pair critical point on C2 in the azolium models as well as on the acyclic diaminocarbene **5a** were calculated and are given in Table 6. We consider first a comparison between the imidazolium ylidene **4a** and its acyclic analogue, the diaminocarbene **5a**. Many topological properties are close in value including the electron density (0.32 au, 0.33 au), Laplacian (−1.29 au, −1.40 au), and the distance of the critical point from the carbon nucleus (0.87 au). However, the geometric parameters suggest a wider reach in the σ-plane of the lone-pair of the cyclic ylidene **4a** than of the open chain analogue **5a** (surface area 1.65 vs 1.34 Å^2; extension angle α 207° vs 181°). The thickness of the charge concentration, as measured by the radial curvature $|\mu_3|$ (15.70 vs 16.37 au) is also greater for the lone-pair of the imidazolium C2. (Recall that a larger value of $|\mu_3|$ indicates greater curvature and hence a more compacted concentration of charge). These comparisons are consistent with the ∠NCN, C−N bond lengths, and s-character discussed above for **4a** and **5a**. Consider next the thiazolium ylidene **2a**. While the electronic properties, ρ and $\nabla^2\rho$, of **2a** are comparable to **4a**, **2a** excels in lone-pair coverage and hence is a more effective nucleophile. The surface area (1.73 Å^2) of the cap of lone-pair concentration, angle α (213°) and radial thickness ($|\mu_3| = 15.11$ au) are the largest of all cyclic ylidenes. Apparently, the combined effect of nitrogen and sulfur attached to the σC^- is optimal for lone-pair coverage. Quite the opposite are the properties of the lone-pair density in the oxazolium **3a** which exhibits the smallest area and α angle. The highly electronegative nitrogen and oxygen atoms in **3a** are ill-fitted to the task. It should be noted that the C2 carbon of thiazolium **2a** also has the smallest β angle (20°), making it the least likely to undergo electrophilic attack or self-coupling.

The AIM properties of a conjugating π−carbanion such as the carbanion carbon in $^-CH_2NO_2$ (**6a**) are in a different class. In contrast to the σ-plane carbanions, the Laplacian plot of the C−N bond in **6a**, shown in Figure 3 in a view perpendicular to the molecular plane, reveals a depletion area centered in the σ-plane of the carbon terminus. Thus, the carbon σ-plane is devoid of any nucleophilic activity. On the other hand, two (3,−3) lone-pair critical points on carbon are clearly indicated in the π-plane joined with nitrogen through contours of partial π-bonding. This distinct lone-pair concentration with critical points above and below the plane of the molecule makes the carbon atom stick out as a πC^- anionic center. As such, this is a partially conjugating πC^- model for comparison with the carbanion at the exocyclic Cα in **1b**. The contour maps of the C2−Cα bond and the four atoms attached thereto in **2b** are shown in Figures 4 (σ-plane) and 5 (π-plane), respectively. Figures 4 and 5a are consistent with a C2−Cα carbon−carbon double bond, with considerable and uniform concentration of charge in the π-plane. Unlike the π-plane profile for $^-CH_2NO_2$ (**6a**) shown in Figure 3, there is no evidence of the presence of a lone-pair on Cα. There is no evidence of conjugative interaction of the out of plane lone-pairs of oxygen in the enol Cα-O bond (Figure 5b) when viewed perpendicular to the C2−Cα π-plane. There are however two distinct (3,−3) lone-pair critical points on N3 which can allow π-overlap with C2 (Figure 5c). It should be noted that lone-pair concentrations on the nitrogen atom displayed in Figure 5c are along the C2−N3 bond in a plane approximately ±15° to the normal of the ring plane. This tilt is due to a slight pyramidalization about the nitrogen center in the optimized structure of **2b**. Also evident is the contraction of both σ- and π-electron density into the atomic basin of nitrogen in the C2−N3 bond, consistent with an

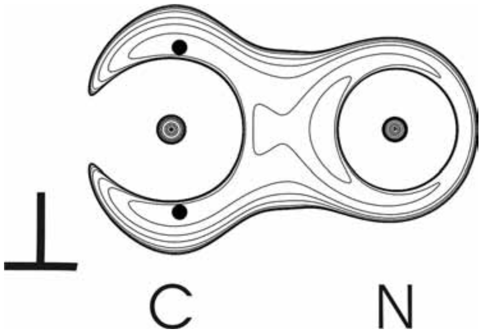


Figure 3. Contour plot of the Laplacian of the electron density showing regions of charge concentration perpendicular to the molecular plane and along the C−N bond of the nitromethane carbanion **6a**. The two dark circles above and below the carbon atom are (3,−3) critical points representing the maxima of valence shell charge concentration and are indicative of a well-defined lone-pair concentration of this πC^- carbanion. Only lines of charge concentration are shown for clarity.

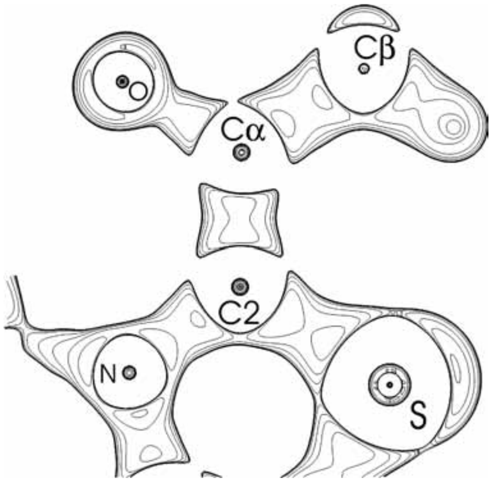


Figure 4. Contour plot of the Laplacian of the electron density showing regions of charge concentration in the plane of the >C2═Cα< double bond of the thiazolium exo-carbanion **2b**.

TABLE 7: Properties of the C2−Cα Bond of the Exocyclic Carbanion Analogues with a Comparison to the C−N Bond of the $^-CH_2NO_2$ Carbanion

C2−Cα or C−N (**6a**) (3,−1) bond critical point; bond order and length	thiazolium exo-carbanion **2b** X=S	oxazolium exo-carbanion **3b** X=O	imidazolium exo-carbanion **4b** X=N	nitromethane carbanion **6a**
$\rho(r_{cp})$ (au)	0.33	0.34	0.33	0.32
$\nabla^2\rho(r_{cp})$ (au)	−0.93	−0.97	−0.93	−0.20
ϵ	0.59	0.68	0.64	
bond order	1.86	1.90	1.83	1.34
bond length (Å)	1.351	1.348	1.355	1.342

enamine. Furthermore, the estimated bond order of this bond is only 1.15, compatible with the enamine structure. Finally the sulfur atom, shown in a tilted view in Figure 5d and a bisected angle view in Figure 5e, displays two lone-pair concentrations. They point outward in a "rabbit ear" fashion, making an angle of approximately 20° to the normal of the ring plane at the sulfur nucleus. However, since only one (3,−3) critical point per lone-pair can be identified, the sulfur atom is not configured for π-bonding. Therefore, this analysis says that **2b** is more a covalent than a zwitterionic structure, with a carbon−carbon double bond. By inference, the traditional term "resonance stabilized intermediate" is aptly used for **1b**. This result is corroborated by a recent cryocrystallographic study [24] of a trapped exocyclic thiazolium α-carbanion intermediate, formed by transketolase with the mimetic β-hydroxypyruvate donor substrate, demonstrating enamine electronic character.

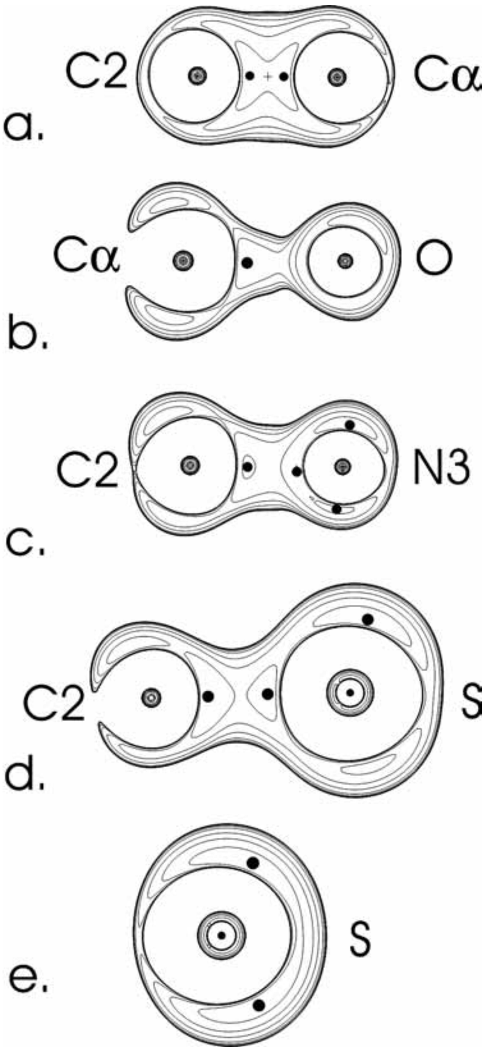


Figure 5. Contour plot of the Laplacian of the electron density of the thiazolium exo-carbanion 2b showing the extent of conjugation in planes: (a) perpendicular to the >C2=Cα< double bond along the axis of the >C2=Cα< double bond, (b) perpendicular to the >C2=Cα< double bond plane and along the Cα−O bond, (c) tilted from the ring plane normal by approximately ±15° so as to capture the two nonbonded (3,−3) critical points on N3 along the C2−N3 bond, (d) tilted from the ring plane normal by approximately 20° so as to capture one of the two lone-pair concentrations on S1 along the C2−S1 bond, and (e) perpendicular to the ring plane and bisecting the C2−S1−C5 angle so as to capture both of the lone-pair charge concentrations on the S1 atom. Dark circles represent bonding and nonbonding (3,−3) VSCC critical points.

A more detailed presentation of the AIM properties of these formal πC^- carbanions is given in Table 7 to support this argument. There is little difference in the values of ρ (0.33 au to 0.34 au) and $\nabla^2\rho$ (−0.93 au to −0.97 au) at the C2−Cα bond critical points for the azoliums, all pointing to considerable covalency. The value of $\rho(r_{cp})$ for the C−N bond in the nitromethane carbanion **6a** is also comparable, but the value of $\nabla^2\rho(r_{cp})$ of −0.20 au at this point is considerably smaller, befitting a shared interaction with an ionic component. Other properties of the C2−Cα and C−N bonds are also listed in Table 7. The ellipicity, ϵ, at the bond critical point is a good topological measure of double bond character (π conjugation or hyperconjugation) across a formally single bond. This is strictly true only for bonds between like atoms or atoms with similar electronegativities. Values of ϵ of about 0.6 across the azolium exo-carbanion are consistent with the C2−Cα double bond. So are the bond lengths of about 1.35 Å. Empirical relationships discussed in the Methods section for estimating the bond order of carbon−carbon and carbon−nitrogen bonds also yield essentially double bond character for C2−Cα (1.83 to 1.90), whereas the C−N bond of the nitromethane carbanion reference exhibits some partial double bond character (1.34) due to negative hyperconjugation.[25] Considering the established π-bond character of the azolium models **2b**−**4b**, it can be projected that the nucleophilic behavior at Cα of **1b** is based on the enamine chemistry induced by an electrophile, but not as a carbanion with lone-pair density in the π-plane like that of nitromethane conjugate base **6a**.

Conclusions

The assumption that the formal positive charge on the thiazolium nitrogen serves as the electron sink to stabilize the carbanion intermediates **1a** and **1b** is not validated. The quaternary N3 atom in azolium cations or zwitterions and other ammonium nitrogens, which are customarily assigned a formal charge of +1, turn out to bear more than one full negative charge. The trend is also found in all the other azolium nitrogen and oxygen atoms. Among these heteroatoms, only sulfur acts as an electron sink: sulfur of ylidene **2a** gains 0.38e and sulfur of the exocyclic α-carbanion **2b** gains 0.45e relative to the initial thiazolium cation. Thus, sulfur is a capable electron sink when it is a formally neutral atom as found in the thiamin series. We have further corroborated this role when sulfur is negatively charged in a series of phosphorothioates.

The positive charge on, yet nucleophilic character of, the formal carbanion at C2 (σC^-) and Cα (πC^-) in the azolium series is explained by analyzing the Laplacian of the electron density, AIM and other properties. Thus, C2 of **2a** features an extended crescent shaped lobe of lone-pair concentration in the σ-plane, conferring nucleophilic properties to the ylidene carbon. This resembles a similar plot of the σC^- in the model diaminocarbene-ylidene **5a**. The geometric parameters and thickness of the radial curvature of the charge concentration suggest a wider reach in the σ-plane of the lone-pair of the cyclic ylidene **4a** than of the open chain analogue **5a**. Among the azolium ylidenes, **2a** shows the largest surface area in the angular sweep of lone-pair concentration, extension angle α, and radial thickness. The oxazolium **3a** exhibits the smallest area and extension angle.

In contrast to the σ-plane carbanions, a conjugating πC^- model **6a** reveals a depletion area centered in the σ-plane but lone-pair critical points on carbon are indicated in the π-plane along with partial π-bond contour. The contour maps of the C2−Cα bond in **2b** are consistent with a carbon−carbon double bond, and unlike **6a**, there is no evidence of the presence of a lone-pair on Cα. Bond length, bond order and AIM properties, including ellipticity, of C2−Cα also point to essentially double bond character. By inference the traditional term “resonance stabilized intermediate” is aptly used for **1b**. Hence it can be projected that the nucleophilic behavior at Cα of **1b** is based on its enamine chemistry.

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Supporting Information Available: Tables of the coordinates of the optimized stationary states of all numbered molecules discussed in this article. This material is available free of charge via the Internet at http://pubs.acs.org.

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