Quantum-Chemical Considerations on the Acidity of Thiamin Pyrophosphate and Related Systems

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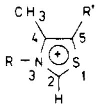
Abstract: The H–D exchange reactions of 1,3-azolium cations have been studied by the semiempirical CNDO/2 method with optimization of all geometrical parameters, in order to explain the rate enhancement for the 1,3-thiazolium cations. The following results are obtained: (a) stabilization of a carbanion by the adjacent sulfur atom is not due to (d–p) conjugation; (b) the 1,3-thiazolium conjugate base is stabilized with respect to the other conjugate bases by the greater polarizability of sulfur; (c) the smaller amount of energy necessary for the 1,3-thiazolium cation, with respect to the other cations, to use the penultimate σ MO gives an explanation for the unique rate enhancement.

Introduction

Thiamin pyrophosphate is the coenzyme for a number of biochemical reactions including the nonoxidative decarboxylations of α-keto acids, oxidative decarboxylations of α-keto acids, and formation of α-ketols (acyloins). A number of theories have been put forward to explain the catalytic role of thiamin pyrophosphate in these reactions. Breslow[1] has proposed a mechanism involving the loss of the aromatic proton at position 2 of the thiazolium ring (**1**), with the consecutive formation of a zwitterion (ylide structure). The arguments in favor of this mechanism are supported by the lability of the proton at position 2 of the thiazolium ring, which is demonstrated with the aid of infrared and nuclear magnetic resonance data,[1a,b] and the kinetics for the exchange reaction with D_2O. The work of Haake et al.[2] on the rate constants of deuterioxide-catalyzed generation of cations with deuterium on position 2 (**2**, X = NH, O, S) shows that for 3,4-dimethyl-1,3-oxazolium, 3,4-dimethyl-1,3-thiazolium, and 1,3,4-trimethyl-1,3-imidazolium cation the relative rate constants are $10^{5.5}$:$10^{3.5}$:1, respectively. A study on N-methylated 1,3-azolium 5-carboxylates (**3**) indicates that the 5-ylides[2a] (**4**) are generated at relative rates of $10^{5.4}$:$10^{3.0}$:1 for **3c, 3b,** and **3a,** respectively. *In order to explain the differences in rates and thus in activation energies, it was assumed that the structure of the activated complex closely resembles the intermediate zwitterions.*[2a,b] The similarity of both ^{13}C–2H and ^{13}C–5H coupling constants[2b] in homologous 1,3-imidazolium and 1,3-thiazolium cations indicates that hydrogens at position 2 and 5, respectively, have similar potential acidity in the cations. On the other hand, the observed H–D exchange is much faster for the 1,3-thiazolium cation than for the 1,3-imidazolium cation. In order to get more fundamental insight into the activated complex and the kinetic acidity, we studied, in particular, the HOMOs (highest occupied molecular orbital) and lower lying occupied MOs of the conjugate bases and cations, respectively. The calculations were performed with the CNDO/2 method including geometry optimization (GEOMO).



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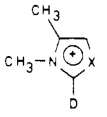
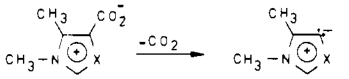


2 a X = NCH3
b X = S
c X = O



3 **4**

a X = NCH3
b X = S
c X = O

Until now theoretical contributions were only focused on the thermodynamic acidity. It appeared that polarization of the σ bonds is principally responsible for stabilization of the 1,3-thiazolium ylide.[7] An additional stabilization effect of sulfur on carbanions has usually been ascribed to the possibility of $(d-p)\pi$[3-5] or $(d-p)\sigma$[5] back-bonding of the lone pair of the carbanion into the vacant d orbitals of sulfur. However, ab initio calculations[6] performed on simpler sulfur- or oxygen-containing anions show that stabilization of a carbanion by an adjacent sulfur atom is not due to $(d-p)\pi$ bonding but to the greater polarizability of sulfur with respect to oxygen. The systems investigated are shown in Figure 1, with X is oxygen, nitrogen, sulfur, and phosphorus. Although no H–D exchange rates are available for 1,3-phosphazolium systems, the cation and related ylides are examined in order to gain a better insight into the effect of d-orbital participation.

Method of Calculation

Semiempirical molecular orbital calculations are performed on the systems shown in Figure 1, using the GEOMO program[8] including geometry optimization. The GEOMO program performs LCAO calculations with any usual semiempirical formalism (CNDO, INDO, MINDO). The algorithms in this program permit use of parametrization and allow direct minimization of energy with respect to any geometric parameter. For our purpose we use the CNDO/2 method.[9] In this method the Slater AOs of all valence electrons are used as a basis set. The geometry of the 1,3-thiazolium, 1,3-imidazolium, and 1,3-oxazolium system determined by Sax et al.,[10] Rerat,[11] and Albano et al.,[12] respectively, was used for the calculations. For the 1,3-phosphazolium cation and ylide the geometrical parameters were taken from phosphole[13] and the 1,3-imidazolium system. All internal parameters in the structures were optimized.

Results and Discussion

In order to gain insight into the thermodynamic and kinetic acidity for the 1,3-azolium cations, we considered in more detail the d orbital participation, the bonding, and electron density. In the H–D exchange reaction the formation of the conjugate base[14] is the rate-determining step; thus for the kinetic acidity these aspects were aimed at the HOMO and penultimate occupied MO of the cations.

d-Orbital Conjugation. Computations with and without inclusion of 3d orbitals on the sulfur and phosphorus atoms have been performed on compounds **5c,d, 6c,d,** and **7c,d,** in order

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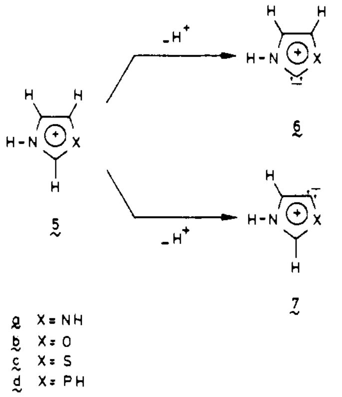

Figure 1. Systems investigated.

Table I. Calculated Energy Differences between Ylides and Cations

compd	basis set	total energy, au	ΔE_r,[a,b] au	ΔE_r,[a,c] au
5a	sp	−48.118 92		
6a	sp	−47.488 97	0.629 95	
7a	sp	−47.434 44		0.674 48
5b	sp	−54.054 14		
6b	sp	−53.480 88	0.573 26	
7b	sp	−53.421 15		0.632 99
5c	spd	−46.520 22		
5c	sp	−46.246 68		
6c	spd	−45.900 95	0.619 27	
6c	sp	−45.626 71	0.619 97	
7c	spd	−45.861 65		0.668 57
7c	sp	−45.577 96		0.668 72
5d	spd	−43.277 87		
5d	sp	−42.880 92		
6d	spd	−42.634 74	0.643 13	
6d	sp	−42.236 41	0.644 51	
7d	spd	−42.597 55		0.680 32
7d	sp	−42.200 79		0.680 13

[a] $\Delta E_r = E_{\text{ylide}} - E_{\text{cation}}$. [b] Formation of conjugate base on position 2. [c] Formation of conjugate base on position 5.

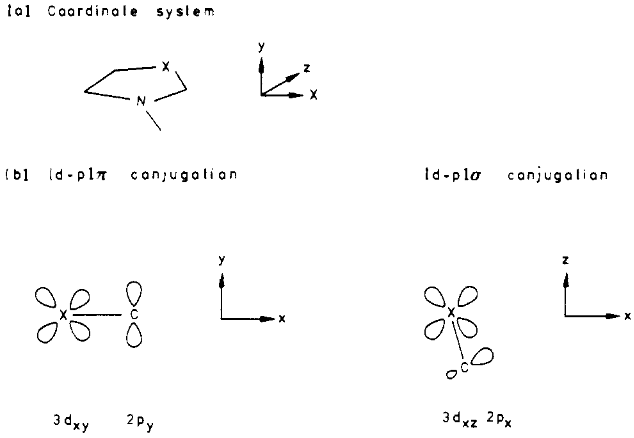

Figure 2. The nature of (p-d)π and (p-d)σ conjugation in the conjugate bases of 1,3-azolium systems with X = S, PH and C = C_2, C_5.

Table II. Optimized Bond Lengths of 1,3-Thiazolium and 1,3-Phosphazolium Cations and Conjugate Bases, Computed Both with and without Inclusion of d Orbitals in the Basis Set

	bond length, Å			
compd	C_2-X spd[a]	C_2-X sp[a]	C_5-X spd[a]	C_5-X sp[a]
5c	1.680	1.685	1.689	1.691
6c	1.709	1.711	1.698	1.695
7c	1.680	1.682	1.713	1.721
5d	1.704	1.709	1.742	1.744
6d	1.722	1.730	1.748	1.749
7d	1.712	1.713	1.756	1.761

[a] Basis set.

Table III. Coefficients of C2p and X3d Orbitals Which Are Appropriate for (p-d)π and (p-d)σ Interaction in the HOMO and Penultimate Occupied MO[a]

		coefficients[b]	
compd	MO	X3d[c]	C2p[d]
6c	HOMO	0.065 (xz)	0.532 (x)
	POMO	0.041 (yz)	−0.278 (y)
6d	HOMO	−0.069 (xz)	−0.627 (x)
	POMO	0.081 (yz)	−0.337 (y)
7c	HOMO	0.071 (yz)	−0.375 (y)
	POMO	−0.091 (xz)	−0.631 (x)
7d	HOMO	0.081 (yz)	−0.420 (y)
	POMO	−0.079 (xz)	−0.577 (x)

[a] POMO: penultimate occupied MO. [b] Symbols in parentheses refer to type of basis function. [c] X = S, P. [d] C2p refers to C_2 in **6** and to C_5 in **7**.

to test the role of d orbitals in carbanion stabilization by sulfur as compared to nitrogen and oxygen. The results in Table I show that d orbitals have no effect on the proton affinities of **6** and **7**, or conversely on the C-H acidity of the cations **5**. The introduction of d orbitals just renders the basis set more flexible but lowers the energy of the cation and conjugate base by the same amount.

Optimized bond lengths of the 1,3-thiazolium and 1,3-phosphazolium cations and conjugate bases are shown in Table II. It is noteworthy that the same bond lengths are obtained with the two basis sets (sp and spd). So this geometrical parameter is probably not sensitive to the presence or absence of d-type functions. The fact that the bonds in the conjugate bases are longer than in the cations suggests the absence of (p-d)π conjugative effects, because such effects are expected to be manifested by a decrease in bond length.[15] The contribution of the d-type functions to the MOs of **6c,d** and **7c,d** has been assessed by consideration of the coefficient matrix and charge distribution in these conjugate bases. In the coordinate system shown in Figure 2 one (p-d)π and one (p-d)σ interaction are possible on symmetry grounds, viz., $(C2p_y\text{-}X3d_{yz})\pi$ and $(C2p_x\text{-}X3d_{xz})\sigma$. For the presence of (p-d)π and (p-d)σ conjugation it is necessary that the coefficients of $C2p_y$, $X3d_{yz}$ and $C2p_x$, $X3d_{xz}$, respectively, are nonzero. Table III lists the coefficients of the C2p and X3d functions in the two highest occupied molecular orbitals. The HOMO of the 1,3-thiazolium conjugate base is essentially the carbon lone pair orbital and would have been expected to exhibit the greatest (p-d)σ interaction. The $(C2p_y\text{-}S3d_{yz})\pi$ interaction appears in the penultimate occupied MO. In case of the 1,3-phosphazolium conjugate base $(C2p_y\text{-}P3d_{yz})\pi$ interaction occurs in the HOMO and $(C2p_x\text{-}P3d_{xz})\sigma$ interaction in the penultimate occupied MO. The data of Table III indicate that the HOMO has the greatest (p-d)σ interaction in case of **6c** and **7c** and the greatest (p-d)π interaction for **6d** and **7d**. However, it is clear that the proper d-orbital coefficients are substantially smaller than those of the C2p orbitals in the MOs, so that (p-d)π and (p-d)σ conjugation can hardly be considered to constitute an essential basis for the explanation of the properties of the 1,3-thiazolium cation. The net orbital populations of $X3d_{xy}$ and $X3d_{xz}$ are respectively in **6c** 0.057 and 0.070, in **6d** 0.048 and 0.059, in **7c** 0.062 and 0.058, and in **7d** 0.067 and 0.051.

Table IV. σ and π Electron Densities[a]

	5a		**6a**		**7a**		**5b**		**6b**		**7b**	
atom	σ	π	σ	π	σ	π	σ	π	σ	π	σ	π
X_1	3.527	1.48	3.460	1.578	3.498	1.467	4.411	1.615	4.433	1.674	4.464	1.571
C_2	2.862	0.92	3.492	0.65	2.845	1.024	2.845	0.826	3.454	0.586	2.803	0.971
N_3	3.527	1.48	3.460	1.578	3.531	1.492	3.551	1.461	3.477	1.578	3.569	1.43
C_4	2.883	1.06	2.889	1.096	2.802	1.201	2.906	1.042	2.919	1.068	2.0899	1.239
C_5	2.883	1.06	2.889	1.096	3.512	0.815	2.824	1.055	2.829	1.094	3.456	0.790
H_2	0.899				0.991		0.885				0.997	
H_5	0.906		0.997				0.900		1.002			

	5c		**6c**		**7c**		**5d**		**6d**		**7d**	
atom	σ	π	σ	π	σ	π	σ	π	σ	π	σ	π
X_1	4.039	1.756	4.195	1.907	4.316	1.737	3.327	1.482	3.429	1.655	3.525	1.467
C_2	3.048	0.841	3.543	0.572	3.025	0.900	2.949	1.000	3.343	0.764	2.951	1.033
N_3	3.541	1.419	3.479	1.518	3.530	1.444	3.454	1.528	3.412	1.551	3.410	1.587
C_4	2.893	0.953	2.854	0.972	2.809	1.068	2.897	0.902	2.862	0.957	2.832	0.986
C_5	3.014	1.032	2.977	1.033	3.436	0.849	2.979	1.085	3.075	1.073	3.369	0.926
H_2	0.892				0.984		0.900				0.993	
H_5	0.870		1.047				0.871		0.957			

[a] In electron units.

Table V. Mulliken Overlap Population[a]

	5a		**6a**		**7a**		**5b**		**6b**		**7b**	
bond	σ	π	σ	π	σ	π	σ	π	σ	π	σ	π
C_2-X	0.720	0.144	0.693	0.139	0.712	0.136	0.629	0.110	0.591	0.104	0.613	0.104
C_2-N_3	0.720	0.144	0.693	0.139	0.683	0.143	0.722	0.158	0.684	0.153	0.721	0.160
N_3-C_4	0.673	0.091	0.670	0.077	0.642	0.083	0.663	0.078	0.679	0.072	0.631	0.0760
C_4-C_5	0.798	0.211	0.801	0.223	0.845	0.232	0.810	0.228	0.819	0.234	0.843	0.236
C_5-X	0.673	0.091	0.670	0.077	0.694	0.108	0.560	0.060	0.570	0.056	0.599	0.074

	5c[b]		**6c**[b]		**7c**[b]		**5d**[b]		**6d**[b]		**7d**[b]	
bond	σ	π	σ	π	σ	π	σ	π	σ	π	σ	π
C_2-X	0.801	0.196	0.744	0.189	0.705	0.200	0.871	0.282	0.842	0.266	0.875	0.275
	(0.175)	(0.077)	(0.182)	(0.087)	(0.178)	(0.081)	(0.193)	(0.126)	(0.213)	(0.115)	(0.131)	(0.112)
C_2-N_3	0.715	0.145	0.697	0.146	0.714	0.144	0.715	0.107	0.710	0.119	0.718	0.104
N_3-C_4	0.673	0.090	0.677	0.084	0.652	0.080	0.676	0.104	0.664	0.095	0.659	0.098
C_4-C_5	0.793	0.203	0.830	0.215	0.861	0.216	0.799	0.195	0.818	0.201	0.859	0.214
C_5-X	0.776	0.136	0.708	0.121	0.738	0.132	0.815	0.197	0.789	0.175	0.779	0.187
	(0.110)	(0.076)	(0.102)	(0.077)	(0.074)	(0.074)	(0.197)	(0.080)	(0.217)	(0.075)	(0.213)	(0.081)

[a] σ, π: total overlap population in σ and π bond, respectively. [b] In parentheses total (σ-d) and (π-d) overlap.

These are too small to permit chemical significance to be attached to (p-d)π and (p-d)σ conjugation. *Thus the overall conclusion is that 3d orbitals on sulfur and phosphorus in 1,3-azolium systems act as polarization functions rather than as independent valence orbitals.* Aldrich et al.[7] draw the same conclusion based on the calculated destabilization energies and 3d orbital populations. In the following discussion only the computations with d-type functions employed on sulfur and phosphorus will be considered.

Bonding and Electron Densities. Tables IV and V show the electron densities and the overlap population in the 1,3-azolium cations and conjugate bases. In the cations both the sulfur and phosphorus atom have positive character, whereas the nitrogen and oxygen atom are nearly neutral. The partial positive charge on sulfur is also found by Jordan[16] in a theoretical study on 2-(α-hydroxyethyl)thiamin. Upon deprotonation sulfur gains the largest amount of electron density. None of the products formed has a classical ylide structure as was recently found by Aldrich et al.[7] in calculations with the ARCANA semiempirical molecular orbital method. The calculated charges on the C_2, C_4, and C_5 atoms in **6c** correlate with the ^{13}C chemical shifts as measured by Gallo and Sable.[17] In Table VI the calculated net charges of the proton-like atoms at the carbon 2 and nitrogen atom are given with the corresponding acidic and basic p*K*s. The calculated net charges correlate very well with the p*K* values. The correlation coefficients of the H_2 charges vs. the acidic p*K* and the H_3 charges vs. the basic p*K* are −0.96 and −0.99, respectively. Small differences between the charges of the H_2 protons are also found in the study of Aldrich et al.[7] As is expected on symmetry considerations, the data in Table V indicate that π bond density remains nearly the same upon generation of the conjugate base. The π bonds are, however, shifted from C_2 to X in **6** and from C_5 toward C_4 in **7** (Table IV). The σ bonds C_2-X and C_2-N_3 of the 1,3-azolium systems show loss of electron charge density upon deprotonation of C_2. The electron density is transferred from the (N_3-C_2)σ bond to C_2, whereas that of the (C_2-X)σ bond is shifted to X. It is found that the polarization of the (C_2-X)σ bond is stronger

Table VI. Calculated Net Charges of H_2 and H_3 and Corresponding p*K*s

compd	net charge H_2	p*K*[a]	net charge H_3	p*K*[b]
5a	0.1004	17	0.1951	7.52
5b	0.1151	12	0.2054	1.03
5c	0.1077	14	0.2024	3.07

[a] Acidic p*K* as measured by Haake and Bausher.[20] [b] Basic p*K* as computed by Haake et al.[2b]

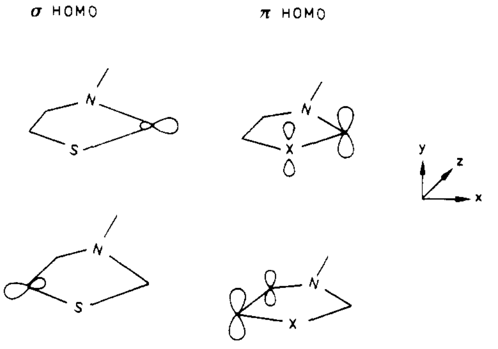

Figure 3. The HOMOs of the conjugate bases (X = O, NH, PH).

(for X = PH or S) relative to the (C_2–N_3)σ bond. The (C_2–X)σ bond is more polarized for X = S or PH than for X = O or NH, respectively.

Upon generation of a negative charge at C_5, the (C_4–C_5)σ bond shows an increase of electron charge density, whereas the (C_5–X)σ bond shows a decrease when X is a second-row atom and an increase when X is a first-row atom. Upon deprotonation, σ electron density shifts from C_4 to C_5, from C_5 to X (X = O, S, PH), and from X to C_5 (X = NH). The change in polarity in the (C_5–X)σ bond is greater for X = PH or S than for X = O (cf. the (C_2–X)σ bond upon deprotonation at C_2). The above results can be ascribed to the much greater polarizability[18a] of both the sulfur (3.45 $Å^3$) and phosphorus (4.42 $Å^3$) atoms with respect to the carbon (1.75 $Å^3$), oxygen (0.73 $Å^3$), and nitrogen (1.04 $Å^3$) atoms. The total overlap population of the C_2–X bond decreases upon generation of the conjugate base. The overlap population decreases along the series of atoms X = S, PH, O, NH. This is in line with the greater polarizability[18b] of the C–S bond (1.88 $Å^3$) with respect to the C–O bond (0.81 $Å^3$) and the C–N bond (0.57 $Å^3$). The larger decrease in overlap population of the C_2–S bond indicates that this bond is more weakened than the others. In the present systems a decrease in overlap population is accompanied by a lengthening of the bond (Table III for X = S, PH; Table VII for X = NH, O).

The data in Table I show that the relative thermodynamic acidity (i.e., formation of a carbanion) has the same trend as the kinetic acidity (i.e., rate of H–D exchange of the cation), but the correlation is rather poor. Thus the greater polarizability of sulfur as well as the S–C bond, which affords stabilization of the conjugate base of the 1,3-thiazolium cation with respect to the others, does not completely account for the relatively small difference in H–D exchange between the 1,3-oxazolium and 1,3-thiazolium cation. In order to get better insight into the features which also determine the kinetic acidity, our study was aimed at the MOs of the cations and conjugate bases. The difference in energy on generation of a carbanion at C_2 or C_5 is consistent with the relative H–D exchange rates of the hydrogen atoms at C_2 and C_5 ($1{:}10^{-4}$) as measured by Olofson et al.[5]

Use of a HOMO and Penultimate MO Description for the Transition State. The H–D exchange in 1,3-azolium systems is assumed to occur via an ylide on position 2. *Since it is fairly reasonable to assume that the transition state closely resembles the conjugate base structure,*[2a,b] *we describe the character of the transition state by using the HOMO and penultimate occupied MO of the conjugate base.* The calculations show that only conjugate bases on positions 2 and 5 of the 1,3-thiazolium cation have a HOMO with predominant σ contribution, whereas the HOMOs of the other conjugate bases mainly possess a π contribution. The σ HOMO (Figure 3) of the 1,3-thiazolium conjugate bases is principally the carbon lone pair orbital on the C_2 and C_5 atom. The π HOMO of the other conjugate bases is in the C_2 zwitterion chiefly located on the C_2 atom and to a minor extent on X, whereas in the C_5 zwitterion a similar situation is found for C_5 and C_4, respectively. The penultimate occupied MO is in the latter cases a σ HOMO, i.e., the carbon lone pair orbital.

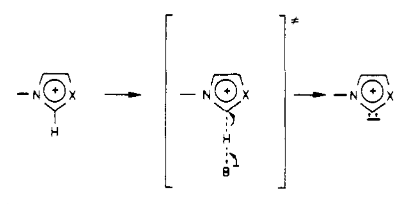

Figure 4. Activated complex for proton abstraction of 1,3-azolium cations.

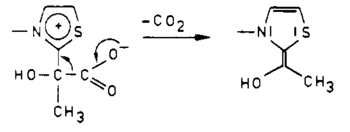

Figure 5. Decarboxylation of pyruvate anion.

Table VII. Optimized Bond Lengths of 1,3-Imidazolium and 1,3-Oxazolium Cations and Conjugate Bases

compd	bond length, Å	
	C_2–X	C_5–X
5a	1.350	1.392
6a	1.362	1.393
7a	1.352	1.400
5b	1.322	1.371
6b	1.340	1.372
7b	1.324	1.383

Estimation of the Activation Energy. *As mentioned before, it was proposed that deprotonation of the cations and deuteration of the conjugate bases take place in the plane of the 1,3-azolium systems (Figure 4). This assumes that a σ MO is representative for the H–D exchange reaction only.* All cations have a HOMO with predominant π character, whereas the penultimate occupied MO has σ character, which is appropriate for the description of the H–D exchange of position 2. For the deprotonation of the C_5 atom a lower lying σ MO is suitable, which is principally located on the atomic orbitals of H_5 and C_5. The energy differences between the π HOMO and the appropriate σ MO are shown in Table VIII. Thus, extra energy will be necessary in order to use the lower lying occupied σ MO. An approximation for the amount of activation energy in the H–D exchange reactions may be the energy difference between the conjugate base and the cation *and* an additional term for the energy difference between the π HOMO and the proper σ MO of the cation. The calculated activation energies (Table VIII) are in excellent agreement with the observed H–D exchange rates. The correlation coefficients for the relative k_{exp} vs. E_a for the exchange of the H_2 and H_5 atom are 0.96 and 0.97, respectively. From the ^{13}C–H coupling constants of the 1,3-azolium cations it was expected[2b] that the 1,3-thiazolium cation would have a much lower exchange rate than the 1,3-oxazolium cation and a similar rate as the 1,3-imidazolium cation. Therefore we presume that the smaller amount of energy necessary for the 1,3-thiazolium system to employ the appropriate σ MO will be responsible for the relatively small difference in exchange rate (factor of 100) between the 1,3-oxazolium and 1,3-thiazolium cation. Although it is beyond the scope of this study, we examined the LUMO (lowest unoccupied molecular orbital) of the cations in order to gain insight into the reactivity of the 1,3-thiazolium cation as electron acceptor in the biochemical decarboxylation reactions (Figure 5). The LUMO of the 1,3-thiazolium cation

Table VIII. Calculated Activation Energies and Relative Rates for the Deprotonation of the C_2 and C_5 Atoms in 1,3-Azolium Systems

	ΔE,[a] au	E_a,[b] au	rel k_{calcd}[c]	rel k_{exptl}[d]
1,3-imidazolium C_2	0.1203	0.7503	$\ll 1$	1
1,3-oxazolium C_2	0.1139	0.6872	2.0×10^5	$10^{5.5}$
1,3-thiazolium C_2	0.0731	0.6923	1.0×10^3	$10^{3.5}$
1,3-phosphazolium C_2	0.1010	0.7441	<1	
1,3-imidazolium C_5	0.2191	0.8936	<1	1
1,3-oxazolium C_5	0.2316	0.8646	10^5	$10^{5.4}$
1,3-thiazolium C_5	0.2022	0.8708	2.5×10^2	$10^{3.0}$
1,3-phosphazolium C_5	0.2172	0.8975	<1	

[a] Energy difference between π HOMO and appropriate σ MO in cation. [b] Activation energy: $E_a = \Delta E + \Delta E_r$ (ΔE_r, see Table I). [c] Relative rates, calculated from the activation energies ($T = 33$ °C). [d] Relative rates as measured by Haake et al.[2a,b] (pH 4–5, $T = 33$ °C).

has the most negative energy value with respect to the other 1,3-azolium cations. This means that decarboxylation will occur most rapidly with thiamin pyrophosphate as catalyst.

Conclusion

This study shows that 3d orbitals of sulfur and phosphorus have no effect on the formation and acidity properties of carbanions adjacent to these heteroatoms. The 1,3-thiazolium conjugate base is stabilized with respect to the other conjugate bases by the greater polarizability of the sulfur atom. The relatively faster H–D exchange rate of the 1,3-thiazolium cation can be explained by the small amount of energy this cation needs to utilize the appropriate σ MO with respect to the other cations.

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On the Thermal Rearrangement of Cyclobutylidene to Methylenecyclopropane. Intermediacy of a Novel Nonclassical Carbene[1]

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Abstract: The reaction of cyclobutylidene to methylenecyclopropane represents a ring contraction rearrangement in which a three-membered ring is generated from a four-membered ring. The quantum-mechanical investigation of its singlet state ($^1\sigma^2$) by the MINDO/3 method reveals that the reaction is initiated by an electrophilic attack of the empty p AO at the carbene site C_1 to the CH_2 group C_3. Thus it takes up a bicyclobutane-like structure. In this species, which corresponds to a nonclassical carbene, electron density is shifted toward the carbene site. In a second step it can easily undergo rearrangement to methylenecyclopropane. In this process the bond fission is controlled by orbital symmetry. For the total reaction an activation enthalpy of 8 kcal/mol is computed. When correction terms for the ring strain are added, this represents an upper limit for the reaction.

Cyclobutylidene (**1**, X = CH_2) derived from the thermal cleavage of cyclobutanone tosylhydrazone[2] rearranges to methylenecyclopropane (**2**). To a minor extent cyclobutene (**3**) is formed by hydrogen shift from C_2 (or C_4) to C_1. Subsequent ring opening in **3** yields the butadiene **4**. The ring-contraction reaction has been used as a synthetic route to homofulvenes.[3] The rearrangement has also been observed in the reaction of cyclobutylidene derivatives containing heteroatoms, such as X = SO_2[4] and X = O, NH.[5]

No details are yet known for the mechanism of the very common ring-contraction reaction, **1** to **2**. In order to reveal a mechanistic concept and to examine the experimental ob-

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