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Articles

Theoretical Study of a Termolecular Mechanism for the Reaction of (Trimethylsilyl)thiazole with Carbonyl Compounds

Yun-Dong Wu,[*,†] Jeehiun K. Lee,[‡] K. N. Houk,[*,‡] and Alessandro Dondoni[§]

Department of Chemistry, The Hong Kong University of Science and Technology, Clear Water Bay, Kowloon, Hong Kong, Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90095, and Dipartimento di Chimica, Laboratorio di Chimica Organica, Universita, Ferrara, Italy

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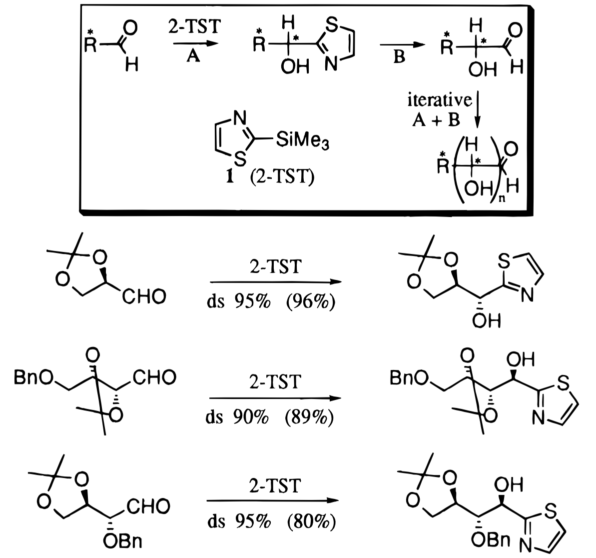
The mechanism of the addition of 2-silylthiazole to formaldehyde has been studied by *ab initio* calculations at the MP2/6-31+G*//6-31G* level. The reaction is predicted to occur by the concerted formation of an *N*-[(silyloxy)methyl]thiazolium-2-ylide intermediate followed by nucleophilic addition of the intermediate to another formaldehyde molecule. Loss of the first formaldehyde gives the addition product. An alternative mechanism involving 1,2-migration of the ylide to form 2-[(silyloxy)-methyl]thiazole is prevented because of the high activation energy of the 1,2-shift. A third mechanistic alternative involving the formation of an *N*-silylthiazolium-2-ylide through 1,2-silyl migration is also discounted due to a high activation energy.

Introduction

The reaction of 2-(trimethysilyl)thiazole (**1**, 2-TST) with aldehydes is the key step in a general method for the stereoselective chain elongation of aldehydes to form polyhydroxy compounds such as sugars,[1,2] several examples of which are shown in Scheme 1. The reaction formally involves the addition of the C_2−Si bond of **1** across the carbonyl group, but such a reaction is orbital-symmetry forbidden unless a pseudopericyclic mechanism[3] involving silicon occurs. We have carried out a theoretical study of the reaction of 2-silylthiazole with formaldehyde and predict a novel termolecular mechanism for this reaction. Our results are consistent with experimental results obtained in studies which were conducted while the calculations described herein were in progress.[2d] Experimental studies conducted while the present calculations were in progress have also uncovered evidence for a termolecular mechanism, through trapping of corresponding intermediates.[2d]

Scheme 1



Computational Methods

The calculations reported here were performed with GAUSSIAN 90[4a] and GAUSSIAN 92.[4b] Geometries were initially optimized with AM1,[5] and then with *ab initio* calculations using first the 3-21G and then the 6-31G* basis sets. Energies were also evaluated with 6-31+G* and MP2/6-31+G* calculations on the 6-31G* geometries. Vibrational frequencies were calculated with the 3-21G basis set. Free energies were calculated using the default thermochemical analyses (298.15 K, 1 atm) from RHF/3-21G frequency calculations.[4] The geometries of optimized species are given in Figures 1, 4, 5, and 6. When both structural formulas and calculated geometries are given, the latter are marked with primes.

[†] Hong Kong University of Science and Technology.

[‡] UCLA.

[§] Università di Ferrara.

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(1) Dondoni, A. *Pure Appl. Chem.* **1990**, *62*, 643 and references cited therein.

(2) (a) Dondoni, A.; Fantin, G.; Fogagnolo, M.; Medici, A.; Pedrini, P. *J. Org. Chem.* **1989**, *54*, 693. (b) Dondoni, A.; Fantin, G., Fogagnolo, M.; Pedrini, P. *J. Org. Chem.* **1990**, *55*, 1438. (c) Dondoni, A.; Fantin, G.; Fogagnolo, M.; Medici, A.; Pedrini, P. *J. Org. Chem.* **1988**, *53*, 1748. (d) Dondoni, A.; Douglas, A. W.; Shinkai, I. *J. Org. Chem.* **1993**, *58*, 3196. (e) Dondoni, A.; Scherrmann, M. C. *Tetrahedron Lett.* **1993**, *34*, 7319. (f) Dondoni, A.; Scherrmann, M. C. *J. Org. Chem.* **1994**, *59*, 6404. (g) Dondoni, A.; Perrone, D.; Semola, T. *Synthesis-Stuttgart* **1995**, *2*, 181. (h) Dondoni, A.; Perrone, D. *J. Org. Chem.* **1995**, *60*, 4749.

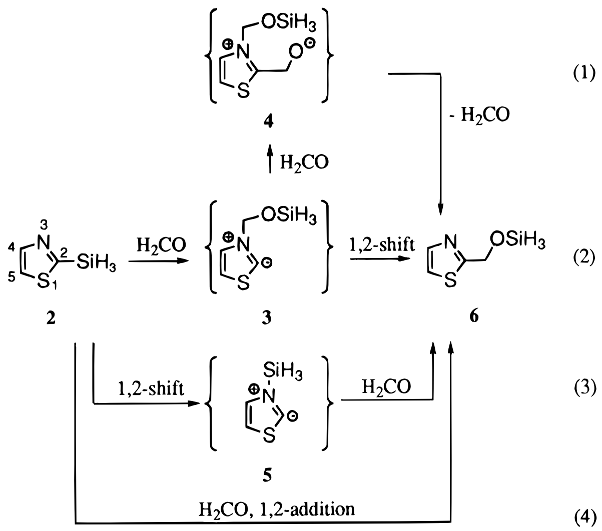
(3) Ross, J. A.; Seiders, R. P.; Lemal, D. M. *J. Am. Chem. Soc.* **1976**, *98*, 4325.

(4) (a) GAUSSIAN 90: Frisch, M. J.; Head-Gordon, M.; Trucks, G. W.; Foresman, J. B.; Schlegel, H. B.; Raghavachari, K.; Robb, M. A.; Binkley, J. S.; Gonzalez, C.; Defrees, D. J.; Fox, D. J.; Whiteside, R. A.; Seeger, R.; Melius, C. F.; Baker, J.; Martin, R. L.; Kahn, L. R.; Stewart, J. J. P.; Topiol, S.; Pople, J. A. Gaussian, Inc., Pittsburgh PA, 1990. (b) GAUSSIAN 92/DFT, Revision G.1: Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Wong, M. W.; Foresman, J. B.; Robb, M. A.; Head-Gordon, M.; Replogle, E. S.; Gomperts, R.; Andres, J. L.; Raghavachari, K.; Binkley, J. S.; Gonzalez, C.; Martin, R. L.; Fox, D. J.; Defrees, D. J.; Baker, J.; Stewart, J. J. P.; Pople, J. A. Gaussian, Inc., Pittsburgh PA, 1993.

(5) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F. *J. Am. Chem. Soc.* **1985**, *107*, 3902.

0022-3263/96/1961-1922$12.00/0

Scheme 2



Results and Discussion

Four possible mechanisms for the formation of **6** from **2**, the model system used in this study, are outlined in Scheme 2. We first considered the direct four-center reaction between 2-silylthiazole (**2**) and formaldehyde (mechanism 4). In spite of many trials with both 3-21G and 6-31G* basis sets, we were unable to locate a concerted transition structure for the insertion of formaldehyde into the C−Si bond of 2-silylthiazole to form 2-(siloxymethyl)thiazole. Upon constrained approach of the formaldehyde carbon to C_2 of **2**, the C_2−Si bond elongates and bends toward the C_2−N_3 bond, so that SiH_3 is stabilized by N_3. Full optimization leads to a transition structure for the 1,2 silyl shift and an isolated formaldehyde, which corresponds to an activation energy of 39 kcal/mol (*vide infra*). The activation energy for the four-center reaction would be expected to be even higher. Furthermore, a mechanism involving a four-center transition state should be symmetry-forbidden. In accord with this prediction, attempted constraints of both-forming CC and OSi bonds lead to high-energy structures. The direct four-center reaction was therefore discounted as a possible mechanism, while the other pathways shown in Scheme 2 were further explored.

A transition structure for the nucleophilic addition of N_3 of **2** to formaldehyde to form *N*-(siloxymethyl)thiazonium ylide (**3**) was located. This structure, **7**, shown in Figure 1, has an N−C forming bond length of 1.84 Å. The nitrogen attack angle is 104°, similar to that of other nucleophilic addition transition structures.[6] The addition is concerted with the migration of the silyl group, although the C−Si bond is only slightly elongated (1.94 Å compared to 1.89 Å in the starting material 2-silylthiazole; structure **2′**, *vide infra*). A transition structure with 180° rotation of the formaldehyde O away from Si could not be located, presumably because this geometry does not allow silyl group participation.

The transition structure **7** is only 4 kcal/mol higher in energy than the reactants at the best level of calculations. The estimated free energy of activation with thermal energy and entropy corrections is 14.6 kcal/mol at 298 K. This is mainly due to a large loss of entropy (−33 eu) in the transition state. Although this barrier is likely to be underestimated to some extent due to overestimation of correlation energy in transition structures by the MP2 calculations,[7] this reaction can occur readily. The optimized *N*-(siloxymethyl)thiazonium ylide (**3**) is shown by structure **3′**. The C_2NCO dihedral angle is 110°, close to perpendicular to the thiazole ring. The gauche effect causes the OSi bond to be gauche to the N−C bond.[8]

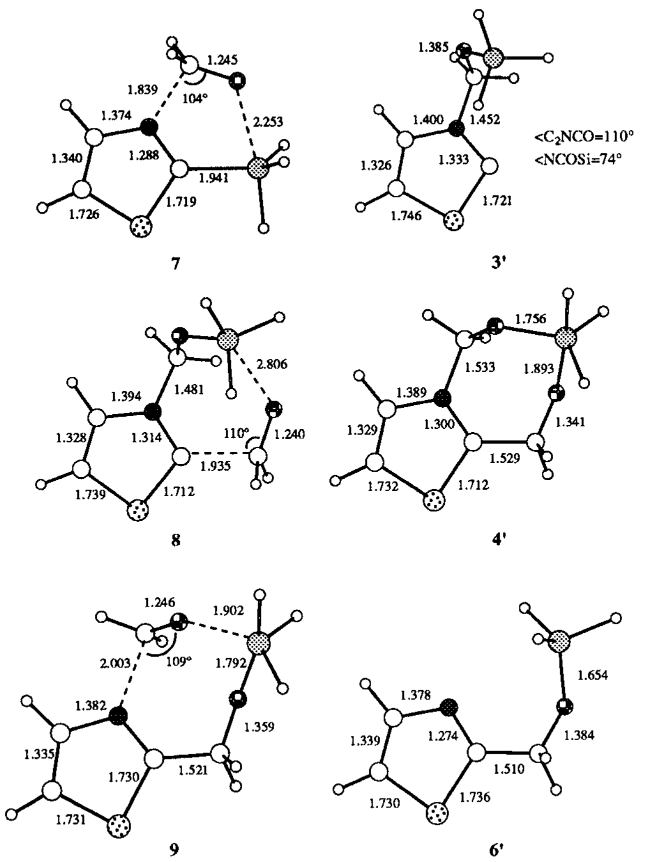


Figure 1. 6-31G* geometries of transition structure **7** and product **3′** of nucleophilic addition of N_3 of 2-silylthiazole to formaldehyde; of transition structure **8** and product **4′** of addition of **3′** to formaldehyde; and of transition structure **9** and product **6′** of loss of formaldehyde from **4′**. For atom numbering and identities, refer to **2**, Scheme 2.

The transition structure for the reaction of **3** with a second molecule of formaldehyde was then calculated (mechanism 1, Scheme 2). In the 6-31G* transition structure (**8**), the forming C---C bond length is only about 1.94 Å, which is significantly shorter than that in the transition structure of nucleophilic additions of ^{-}CN to carbonyl compounds.[6] Thus, the transition structure is late, and C_2 is only a weak nucleophile. There is a small attractive electrostatic interaction between the second carbonyl oxygen and the SiH_3 group, as indicated by the O−Si distance of 2.8 Å. The product of this reaction, **4**, is a cyclic structure, with a half-chair conformation (**4′**).

The calculated energy of the transition structure **8** with respect to two molecules of formaldehyde plus **2** is quite dependent upon basis sets, as shown in Table 1. The calculations with the 3-21G basis set significantly un-

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(6) (a) Wu, Y.-D.; Tucker, J. A.; Houk, K. N. *J. Am. Chem. Soc.* **1991**, *113*, 5018. (b) Kaufmann, E.; Schleyer, P. v. R.; Houk, K. N.; Wu, Y.-D. *J. Am. Chem. Soc.* **1985**, *107*, 5560. (c) Bachrach, S. M.; Streitwieser, A., Jr. *J. Am. Chem. Soc.* **1986**, *108*, 3946.

(7) For general discussions, see: (a) Jensen, F.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 3139. (b) Spellmeyer, D. C.; Houk, K. N. *J. Am. Chem. Soc.* **1988**, *110*, 3412.

(8) For a review, see: Kirby, A. J. *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*; Springer-Verlag: Heidelberg, 1983.

Table 1. Calculated Energies (au) of Structures 7, 3′, 8, 4′, 9, and 6. The Relative Energies (in Parentheses) of 7, 3′, and 6 Are Calculated with Respect to 2-Silylthiazole[a] (2) Plus Formaldehyde;[b] the Relative Energies of 8, 4′, and 9 Are Calculated with Respect to 2-Silylthiazole Plus Two Molecules of Formaldehyde. The Last Line Gives Estimated Relative Free Energies (kcal/mol) Calculated by the Correction of the MP2/6-31+G* Relative Energies with the 3-21G Thermal Energies and Entropies at 25 °C

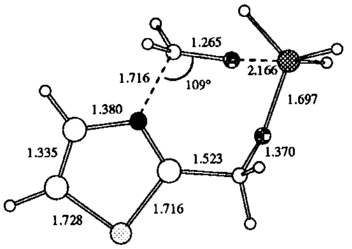
basis set	**7**	**3′**	**8**	**4′**	**9**	**6**
3-21G	−966.140 34 (3.4)	−966.179 35 (−7.5)	−1079.402 52 (−22.0)	−1079.429 33 (−38.8)	−1079.429 38 (−38.8)[d]	−966.219 91 (−46.6)
6-31G*	−971.211 85 (14.5)	−971.224 69 (−7.5)	−1085.097 39 (2.5)	−1085.121 61 (−12.0)	−1085.108 03 (−4.2)	−971.293 11 (−36.5)
6-31+G*//6-31G*	−971.221 93 (10.2)	−971.257 64 (−12.2)	−1085.111 16 (4.0)	−1085.134 08 (−10.4)	−1085.119 64 (−1.3)	−971.301 99 (−34.9)
MP2/6-31+G*//6-31G*	−972.29997 (3.8)	−972.31368 (−4.8)	−1086.49286 (−7.9)	−1086.52335 (−27.0)	−1086.50948 (−18.3)[e]	−972.36608 (−37.7)
estimated ΔG(298)[c]	14.6	9.4	23.9	6.3	14.6	−23.0

[a] For energies, see Table 2 (**2′**). [b] The energy of formaldehyde is: 3-21G, 113.22182; 6-31G*, 113.86633; 6-31+G*, 113.87114; MP2/6-31+G*, 114.17426. [c] The 3-21G ZPE (kcal/mol) and thermal energies (kcal/mol, 298 K), and entropies (cal/mol.K) are: formaldehyde, 18.2, 20.0, 52.1; 2-silylthiazole, 47.8, 50.2, 76.3; structure **7**, 65.9, 71.3, 95.8; structure **3′**, 69.6, 74.8, 93.7; structure **8**, 91.7, 97.8, 99.2; structure **4′**, 93.2, 98.8, 93.7; structure **6**, 70.0, 75.2, 93.8. [d] Energy value is for *apical* departure of formaldehyde (see text); unable to find the transition structure corresponding to equatorial formaldehyde departure. [e] Because equatorial transition state could not be found at 3-21G, the 6-31G* thermal energy and entropy were used. The 6-31G* ZPE (kcal/mol), thermal energy (kcal/mol, 298 K), and entropy (cal/mol.K) for structure **9** are: 92.3, 98.2, and 96.8.

derestimate the activation energy; our estimated free energy of activation considering thermal energy and entropy is about 24 kcal/mol. This energy barrier is mainly caused by a loss of 81 eu of entropy in the transition structure for this termolecular process.

The transition structure for the final step of this mechanism, **9**, is shown in Figure 1. The N−C bond has elongated to 2.00 Å and the O−Si bond has stretched to 1.902 Å as formaldehyde prepares to depart. Again, the calculated energy relative to two molecules of formaldehyde plus **2** is very dependent on basis sets (Table 1); the estimated free energy of activation is 14.6 kcal/mol. The main contribution to this energy barrier is enthalpic. Complete loss of formaldehyde leads to product **6′**; the overall reaction of the addition of one molecule of formaldehyde to **2** to form **6** is calculated to be 23.0 kcal mol^{-1} exothermic.

Another consideration in this last step is the geometry of departure of formaldehyde to yield product **6′**. Structure **9** is the transition state expected by direct O−Si cleavage from structure **4′**. This involves cleavage of an equatorial O−Si bond in the trigonal bipyramidal intermediate. It is well known that apical loss (or entry) of a leaving group (nucleophile) is favored in such nucleophilic substitution on Si.[9] Indeed, the transition states described earlier involving Si−O cleavage or formation (**7** and **8**) do have apical Si−O bonds. Structure **4′** can undergo a Berry-type pseudorotation[9] to generate an intermediate where the two oxygens in **4′** have "switched" positions, thereby placing the departing formaldehyde oxygen apical. The resulting transition state would be similar to **9** with the exception that the oxygen would leave apically rather than equatorially. To obtain an estimate of how much lower the barrier would be for oxygen apical departure, we found the transition structure corresponding to apical departure, **9**$_{\mathbf{ax}}$ (Figure 2). Structure **9**$_{\mathbf{ax}}$ is found to be 12.0 kcal/mol below **9** at our highest level of calculations. Thus, it is likely that **4′** will undergo a pseudorotation to a new intermediate possessing an apically oriented departing oxygen; the subsequent departure of formaldehyde through **9**$_{\mathbf{ax}}$ would be lower in energy than through **9**. The barrier to the initial pseudorotation, judging from other calculations of the pseudorotation of $SiH_3X_2^-$ compounds,[9b,c] will be less than 5 kcal/mol, provided the 7-membered ring does not cause too much strain. Therefore, a pseudorotation followed by apical departure of formaldehyde is possibly lower in barrier than the single-step, direct pathway through structure **9**. Since our interest is in showing the overall favorability, or disfavorability, of this termolecular pathway, whether the reaction proceeds through **9** or through an even lower energy pathway is not extremely important. The three steps of mechanism 1 are predicted to have very low free energies of activation (Figure 3), with the second step being the highest in energy; thus, the reaction by this mechanism should occur readily.



9$_{\mathbf{ax}}$

Figure 2. 6-31G* transition structure for the apical departure of formaldehyde to form product **6′**.

How would solvent influence the energies of these transition structures and intermediates? Since all of these species have some zwitterionic character, they should all be stabilized somewhat by solvent with respect to the nonpolar reactants. Therefore, this reaction mechanism has a sufficiently low activation energy to occur at room temperature, and the rate-determining step is the addition to the second molecule of aldehyde.

An alternative mechanism involves initial 1,2-shift of the silyl group of **2** to form the *N*-silyl ylide, **5**, an attractive intermediate due to the well-known stability of such ylides,[10] followed by nucleophilic addition of **5** to formaldehyde (mechanism 3, Scheme 2). The calculated geometries (6-31G*) of 2-silylthiazole (**2′**), *N*-silylthiazolium-2-ylide (**5′**), and the transition structure of 1,2-silyl shift (**10**) are shown in Figure 4, and the calculated energies of these structures are given in Table 2. In structure **2′**, the C_2−N bond is about 0.1 Å shorter than the N−C_4 bond, while the C_4−C_5 is a typical double bond. In structure **5′**, both C_2−N and N−C_4 bonds elongate, but C_4−C_5 shrinks slightly, indicating weaker conjugation. The transition structure (**10**) has a short N−Si distance

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[9] (a) Holmes, R. R. *Chem. Rev.* **1990**, *90*, 17−31. (b) Windus, T. L.; Gordon, M. S.; Burggraf, L. W.; Davis, L. P. *J. Am. Chem. Soc.* **1991**, *113*, 4356−4357. (c) Windus, T. L.; Gordon, M. S.; Davis, L. P.; Burggraf, L. W. *J. Am. Chem. Soc.* **1994**, *116*, 3568−3579.

[10] (a) Breslow, R. *Ann. N. Y. Acad. Sci.* **1962**, *98*, 445. (b) Schellenberger, A. *Ann. N. Y. Acad. Sci.* **1982**, *378*, 51. (c) Haake, P.; Nelson, R. M. *Ann. N. Y. Acad. Sci.* **1982**, *378*, 107. (d) Kluger, R. *Chem. Rev.* **1987**, *87*, 863.

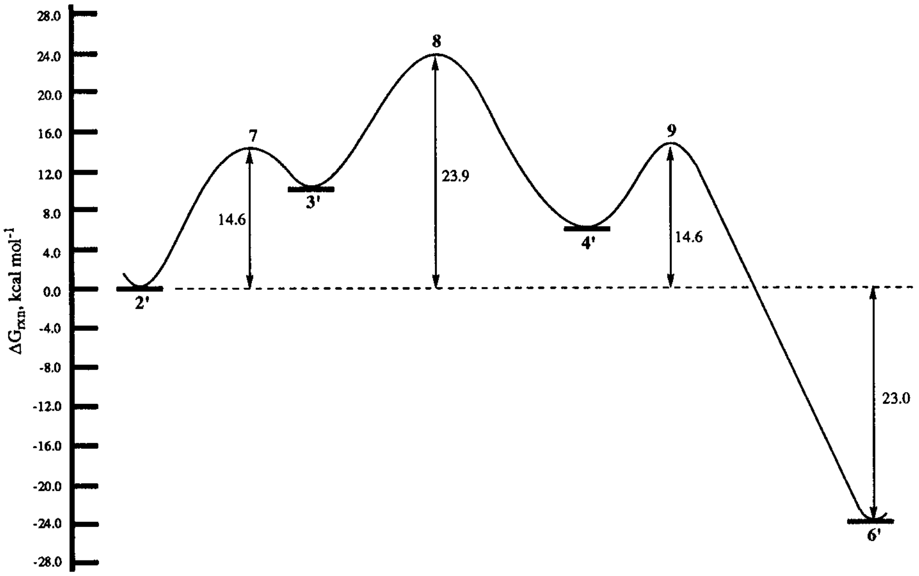

Figure 3. Energetics (ΔG_{rxn}) of the reaction of **2** with two molecules of formaldehyde to form **6** via mechanism 1, Scheme 2.

Table 2. Calculated Total Energies (au) and Relative Energies (in Parentheses, kcal/mol) of 2-R-thiazole (R = SiH_3, CH_3), 3-R-thiazolium Ylide, and Transition Structure of 1,2-Shift

R = SiH_3	**2′**	**5′**	**10**
3-21G	−852.923 88 (0.0)	−852.903 54 (12.5)	−852.860 54 (39.7)
6-31G*	−857.368 67 (0.0)	−857.336 86 (20.0)	−857.304 16 (40.5)
6-31+G*//6-31G*	−857.375 20 (0.0)	−857.345 21 (18.8)	−857.309 96 (40.9)
MP2/6-31+G*//6-31G*	−858.131 70 (0.0)	−858.090 58 (25.8)	−858.069 65 (38.9)
R = CH_3	**12**	**13**	**14**
3-21G	−603.197 36 (0.0)	−603.147 84 (31.1)	−603.012 36 (116.1)
6-31G*	−606.331 98 (0.0)	−606.274 16 (36.3)	−606.130 18 (126.6)
6-31+G*//6-31G*	−606.338 13 (0.0)	−606.282 46 (27.9)	−606.139 21 (124.8)
MP2/6-31+G*//6-31G*	−607.144 34 (0.0)	−607.080 47 (40.1)	−606.948 78 (116.4)

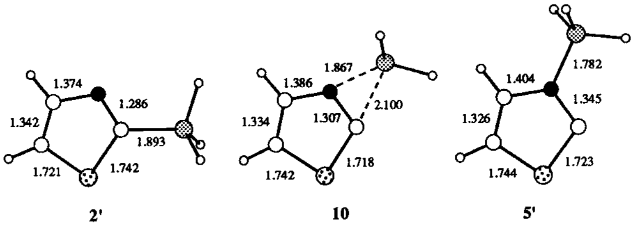

Figure 4. 6-31G* geometries of 2-silylthiazole, **2′**; *N*-silylthiazolium-2-ylide, **5′**; and the transition structure, **10**, for conversion between **2′** and **5′**. For atom numbering and identities, refer to **2**, Scheme 2.

of 1.87 Å. At the MP2/6-31+G* level, structure **5′** is calculated to be less stable than structure **2′** by about 26 kcal/mol. The calculated activation energy for the 1,2-SiH_3 shift is 39 kcal/mol for conversion of **2′** to **5′** and 13 kcal/mol for the **5′** to **2′** conversion. We also located the transition structure, **11**, for the addition of **5′** to formaldehyde (Figure 5). The free energy of this structure with respect to the reactants, formaldehyde plus **2′**, is estimated to be about 37 kcal/mol. Therefore, both steps of this mechanism have high activation energies, and this mechanism is unlikely to occur at room temperature.

Can the *N*-(siloxymethyl)thiazolium ylide intermediate, **3**, undergo a 1,2 shift to form the product **6** directly (mechanism 2, Scheme 2)? To model this, we calculated the 1,2 methyl shift reaction of *N*-methylthiazolium ylide to form 2-methylthiazole. The calculated structures are shown in Figure 6. *N*-Methylthiazolium ylide (**13**) is less stable than 2-methylthiazole (**12**) by about 40 kcal/mol, and the transition structure (**14**) is calculated to be less stable than **13** by 76 kcal/mol. Such a high activation energy for 1,2-methyl shift is similar to those of other 1,2-shifts in carbanionic species.[11] In fact, the reaction is most likely to occur in a stepwise fashion with homolytic N−C bond cleavage followed by C−C bond

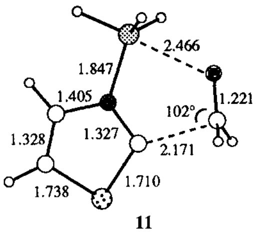

Figure 5. 6-31G* transition structure for the addition of **5′** to formaldehyde.

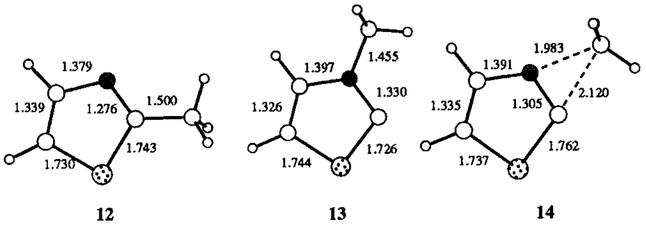

Figure 6. 2-Methylthiazole, **12**; *N*-Methylthiazolium-2-ylide, **13**; and the transition structure, **14**, for conversion between **12** and **13**. For atom numbering and identities, refer to **2**, Scheme 2.

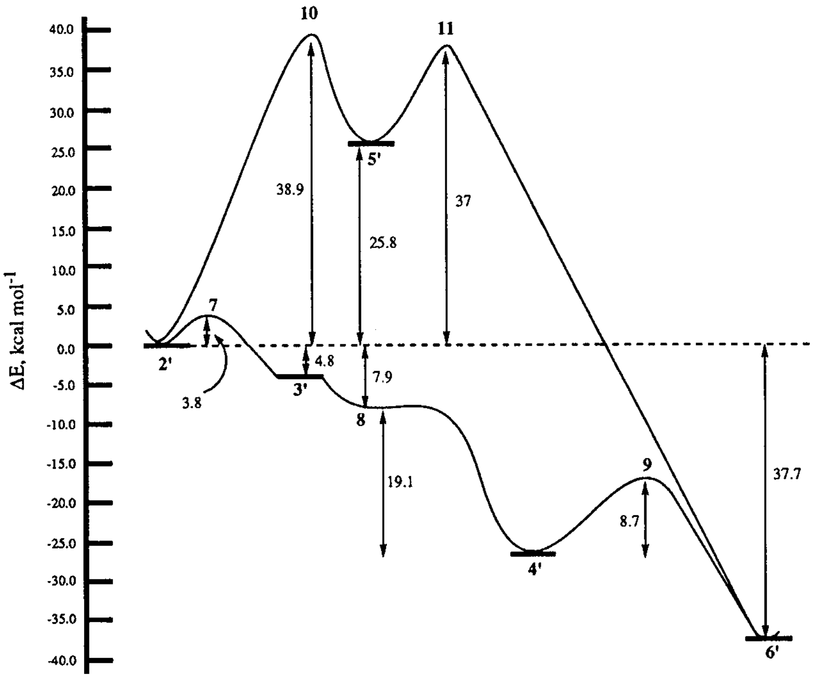

Figure 7. Energetics (MP2/6-31+G*//6-31G*) of mechanisms 1 and 3 (Scheme 2).

closure.[11] Therefore, this mechanistic pathway to product can be ruled out.

The energetics at MP2/6-31+G*//6-31G* of the possible mechanisms discussed herein are displayed pictorially in Figure 7. In summary, our calculations indicate that a direct four-center C−Si insertion of 2-silylthiazole to formaldehyde is forbidden due to an extremely high activation energy. As a result of relatively high activation barriers for 1,2-shifts, mechanisms 2 and 3 shown in Scheme 2 are also unlikely to occur under room temperature conditions (mechanism 2 is not shown in Figure 7 since calculations involved model compounds (*vide supra*); mechanism 3 is represented by curve **2′** → **10** → **5′** → **11** → **6**, Figure 7). The calculations predict that a termolecular mechanism involving one molecule of 2-silylthiazole and two molecules of formaldehyde (mechanism 1) has a sufficiently low activation energy (**2′** → **7** → **3′** → **8** → **4′** → **9** → **6′**, Figure 7). This mechanism involves fast formation of the *N*-(siloxymethyl)thiazolium ylide intermediate, **3**, followed by rate-determining nucleophilic addition to a second molecule of aldehyde to form intermediate **4**. The fast 1,6-silyl migration in **4** is accompanied by loss of a molecule of aldehyde to give the final product, **6**. In the case of a chiral aldehyde, the stereoselectivity is determined by the second nucleophilic addition to form the intermediate **4**. Such a mechanism is in agreement with experimental observations.[2d] While the present calculations were in progress, experiments were conducted in which NMR spectroscopy was used to follow the reaction of a series of aldehydes with 2-(trimethylsilyl)thiazole.[2d] It was found that the kinetics of the reaction of acetaldehyde with (trimethylsilyl)thiazole produce data which are consistent with a third-order mechanism, first order in the silylthiazole, and second order in acetaldehyde. It should be noted, however, that the acetaldehyde was used in excess, and the kinetics therefore also fit a second-order equation, which appears to be due to pseudo-second-order fitting. Furthermore, these experimental studies support our computational results by providing evidence, through trapping experiments, of a mechanism consistent with the intermediacy of **3** and **4**.[2d]

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[11] (a) Houk, K. N.; Li, Y.; Evanseck, J. D. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 682. (b) Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. *Ab initio Molecular Orbital Theory*; Wiley: New York, 1986.