Thermodynamic Results for Geometrical Isomerism in Silyl Ketene Acetals

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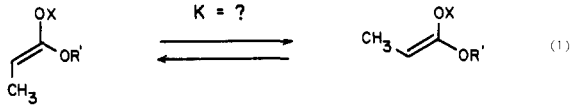
Ketene acetals and ester enolate anions occupy an important position among reactive reagents available to the chemist for stereospecific carbon–carbon bond formation.[1,2] Despite the frequent appearance of ester enolate anions and silyl ketene acetals in synthetic sequences, a unified explanation of the factors that influence both the stereochemistry of these molecules and the stereochemical outcome of ester deprotonation is lacking.[3]

Although the ketene acetals illustrated in eq 1 are widely

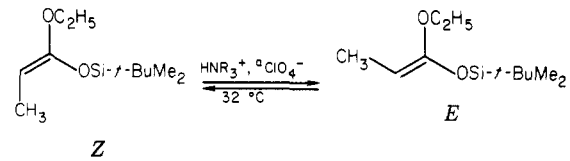


used for organic synthesis, the result of thermodynamic equilibration has never been determined for any of these systems. Experimental determinations of these equilibria are undeniably relevant in efforts to understand observed selectivities in the formation and reactions of these species,[4] and we now report the results for geometrical isomerization of silyl ketene acetals. Inasmuch as lithium ester enolates in tetrahydrofuran solution may be subject to steric and electronic forces similar to those present in silyl ketene acetals, these results may bear on geometrical selection in ester deprotonations.[5]

Results and Discussion

In the presence of trialkylammonium perchlorates, isomerization of *O*-trialkylsilylated methyl ketene acetals (eq 1, X = trialkylsilyl) was readily achieved.[7] Isomerization was not observed in CCl_4 but was quite fast in CD_2Cl_2 (Table I). The intriguing result in these equilibria is that the predominant silyl ketene acetal isomer is the one wherein the vinylic alkyl group is *adjacent* to the (trialkylsilyl)oxy group (Table II). An explanation for this phenomenon which would require that the alkoxy group be considered to be sterically larger than the (trialkylsilyl)oxy group is not tenable; as the size of the alkoxy group is increased, the ratio of isomers approaches unity. Comparisons among the various congeners in Table II indicate that the size or electron demand of the *O*-alkyl group is much more important than the size of the vinylic alkyl group in controlling these equilibria.

Table I. Solvent Effect on Isomerization



solvent	τ[b]	E/Z[c]
CCl_4	>72 h	d
$CDCl_3$	90 min	9:91
CD_2Cl_2	10 min	9:91

[a] 0.1 molar equiv. [b] Time required to reach 50:50 E/Z ratio. All experiments started with ~95% pure E isomer. [c] Equilibrium ratio (±3%). [d] No isomerization was observed. Perchlorate partially soluble.

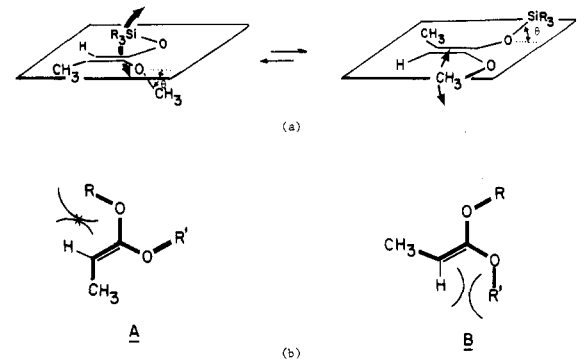
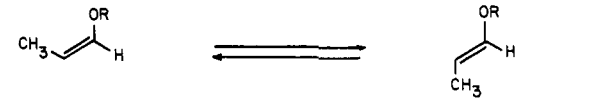


Figure 1. Illustration of conformational isomers for E and Z forms (A, B, respectively) of a silyl ketene acetal. The oblique view (a) illustrates possible displacements from the olefinic plane. The angle θ is likely to be small.[10] In (b) are shown planar projections emphasizing the "pinwheel" shape and the steric effects in these conformers.[12]

These results comprise the first available information concerning the thermodynamic stability of isomers of the type shown in eq 1. These data should be compared to those of Taskinen, who found a thermodynamic preference for (*Z*)-alkylpropenyl ethers[8] (eq 2). The results reported here parallel Taskinen's



measurements; as the alkoxy group increases in size, the isomer having the alkoxy group adjacent to the vinyl proton is less favored.

To understand the present results, it is necessary to consider possible ground-state conformations for silyl ketene acetals. Ketene acetals are clearly analogous to vinyl ethers, about which much is known. There are two conformational minima for methyl vinyl ether. The most stable conformer is the planar *s*-cis conformer.[9,10] Durig has shown that the second, slightly less stable

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(3) Speculation on the factors controlling ester deprotonation have been recorded. For example: (a) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868–2877. (b) See ref 1b. (c) Narula, A. S. *Tetrahedron Lett.* **1981**, *22*, 4119–4122.

(4) Fataftah, Z. A.; Kopka, I. E.; Rathke, M. W. *J. Am. Chem. Soc.* **1980**, *102*, 3959–3960.

(5) Ester enolate anions probably exist as ion pair aggregates in solution.[6] The coordinated lithium ion is analogous to a trialkylsilyl group in that both are sterically large, relatively electropositive substituents.

(6) Amstutz, R.; Schweizer, W. B.; Seebach, D.; Dunitz, J. *Helv. Chim. Acta* **1981**, *64*, 2617–2621. House, H. O.; Gall, M.; Olmstead, H. D. *J. Org. Chem.* **1971**, *36*, 2661. Jackman, L. M.; Szeverenyi, N. *J. Am. Chem. Soc.* **1977**, *99*, 4954. Jackman, L. M.; Lange, B. C. *Tetrahedron* **1977**, *33*, 2737–2769.

(7) Silyl ketene acetals were prepared according to ref 3a by using lithium diisopropylamide in THF at −78 °C. The ratio of isomers obtained by this procedure was consistently within a few percent of a 95:5 (E/Z) ratio.[1,3]

(8) Taskinen, E.; Liukas, P. *Acta Chem. Scand., Ser. B* **1974**, *B28*, 114–120.

(9) (a) Owen, N. L.; Sheppard, N. *Trans. Faraday Soc.* **1964**, 634. (b) Owens, N. L.; Seip, H. M. *Phys. Lett.* **1970**, *5*, 164. (c) Samdal, S.; Seip, H. M. *J. Mol. Struct.* **1975**, *28*, 193–203.

(10) Durig, J. R.; Compton, D. A. C. *J. Chem. Phys.* **1978**, *69*, 2028–2035.

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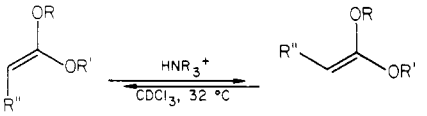
Table II. Isomerization of Trialkylsilyl Ketene Acetals



R[a]	R'	R''	E/Z[b]		^{1}H NMR data: vinylic H	allylic H(R'')	other
t-BuMe$_2$Si	CH_3	CH_3	5:95	E	3.64, q	1.46, d	3.52, s, OCH_3
				Z	3.44, q	1.49, d	3.43, s, OCH_3
t-BuMe$_2$Si	C_2H_5	CH_3	9:91	E	3.73, q	1.46, d	3.85, q, OCH_2CH_3
				Z	3.43, q	1.48, d	3.67, q, OCH_2CH_3
t-BuMe$_2$Si	i-C_3H_7	CH_3	29:71	E	3.78, q	1.46, d	4.34, h, $OCH(CH_3)_2$
				Z	3.48, q	1.48, d	4.12, h, $OCH(CH_3)_2$
t-BuMe$_2$Si	t-C_4H_9	CH_3	d	E	3.97, q	1.48, d	1.33, s, $OC(CH_3)_3$
				Z	3.99, q	1.49, d	1.27, s, $OC(CH_3)_3$
t-BuMe$_2$Si	i-C_3H_7	i-C_3H_7	27:73[c]	E	3.63, d	2.52, m	4.32, h, $OCH(CH_3)_2$
				Z	3.31, d	2.52, m	4.09, h, $OCH(CH_3)_2$
t-BuPh$_2$Si	i-C_3H_7	CH_3	28:72	E	3.59, q	1.33, d	4.57, h, $OCH(CH_3)_2$
				Z	3.44, q	1.65, d	3.92, h, $OCH(CH_3)_2$
TES	i-C_3H_7	CH_3	25:75	E	3.80, q	1.49, d	4.37, h, $OCH(CH_3)_2$
				Z	3.44, q	1.52, d	4.15, h, $OCH(CH_3)_2$

[a] t-BuMe$_2$Si = *tert*-butyldimethylsilyl; t-BuPh$_2$Si = *tert*-butyldiphenylsilyl; TES = triethylsilyl. [b] Final ratio (±3%) as determined by ^{1}H NMR and capillary VPC analysis. [c] Solvent was CD_2Cl_2. [d] Afforded isobutylene under isomerization conditions.

conformer has a dihedral angle of about 144°, in contrast to 180° for an antiperiplanar arrangement. A barrier of 5–6 kcal/mol separates these two minima.[10,11] In accord with this, it is reasonable to suppose that silyl ketene acetals will assume planar or nearly planar conformations. For isomers of the silyl ketene acetals in question, while suitably sized oxygen substituents adjacent to the vinylic proton can approach the preferred *s*-cis conformation, the vinylic alkyl group will force the other oxygen substituent to occupy a position approximately antiperiplanar to the olefinic bond. This is illustrated in Figure 1.[12]

It should be noted that the same effects that stabilize the *s*-cis conformation of methyl vinyl ether (vide supra) will stabilize the *Z* isomer of silyl ketene acetals (B, Figure 1) relative to the *E* isomer (A). Stabilizing interactions between the trialkylsilyl group and the π-bond in A are evidently less important and are likely to be insignificant compared to the considerable steric repulsion encountered in any conformation placing a large group in the *s*-cis position.[8] Thus both steric repulsion and the *s*-cis effect will act to make B more stable than A.

This simple explanation, which accommodates well the experimental observations reported here, incorporates two reasonable hypotheses concerning ketene acetals: First, it is assumed that, as is the case for vinyl ethers, in the absence of overriding steric constraints, ketene acetals will take up planar or nearly planar conformations. Second, it is assumed that the same effects which stabilize the *s*-cis conformer of methyl vinyl ether will favor *s*-cis conformers of ketene acetals. Only the "pinwheel"like conformers shown in Figure 1 will allow for planar or nearly planar ketene acetals and avoid impossibly severe $A_{1,3}$-type interactions. Of the two possible "pinwheel" conformers, B is clearly preferable. Isomer B will have less severe steric compression than does A, and B will also allow the energetic advantage of the *s*-cis interaction with the smaller substituent to come into play.

To summarize, the relative thermodynamic stabilities for geometrical isomers of several silyl ketene acetals derived from propanoate esters have been determined. In each case, the more stable isomer is that in which the ester alkoxy group is adjacent to the unsubstituted vinylic site. The observation that increases in the size of the ester alkoxy group lead to diminished equilibrium ratios is of interest from a theoretical and practical viewpoint.

Experimental Section

Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded on a Varian EM-390 spectrometer. Chemical shifts are reported as δ values in parts per million relative to tetramethylsilane as internal standard. Capillary VPC analysis was performed on a Varian 3700 instrument equipped with a 0.25 mm (i.d.) glass column, 25 m in length, wall coated with Carbowax 20M. Injection port temperatures (split ratio 400:1) were typically held at 20 °C above the column oven temperature.

Dichloromethane and diisopropylethylamine were distilled from calcium hydride immediately before use. Chloroform and chloroform-*d* were filtered through alumina (activity I) immediately prior to use. Perchloric acid was used as obtained commercially, without further treatment. Ether refers to diethyl ether, which was distilled from sodium metal in the presence of benzophenone ketyl.

Diisopropylethylammonium Perchlorate. To an ice-cooled solution of 5.4 mL (31 mmol) of diisopropylethylamine in 60 mL of a 4:1 mixture of dry dichloromethane:ether under nitrogen was added, dropwise, 2.5 mL (30 mmol) of perchloric acid (70%). After 15 min, 3–5 g of anhydrous $MgSO_4$ was added, and the resulting slurry was stirred vigorously for 1 h. (Additional dry CH_2Cl_2 was added as required to redissolve any precipitated salt.) Filtration under nitrogen and removal of volatile components under reduced pressure afforded a semicrystalline paste, which crystallized on trituration with 50 mL of dry ether. The crystals were washed with two 50-mL portions of dry ether and dried under vacuum for 3 h at room temperature. There was obtained 6.68 g (97%) of fine white needles.

General Procedure for Isomerization of Silyl Ketene Acetals. (It is essential that reactants and solvents be scrupulously anhydrous. Water does not interfere with isomerization, but hydrolysis, competitive with equilibration, is observed when water is present.) Under an atmosphere of nitrogen, a solution of 0.6 mmol of the (*E*)-*tert*-butyldimethylsilyl ketene acetal[7] in 0.5 mL of deuteriochloroform was prepared in a dry 5-mm NMR sample tube. After recording the spectrum, 0.12 mL (0.06 mmol) of a 0.5 M solution of the diisopropylethylammonium perchlorate in $CDCl_3$ was added to the sample. Spectra were recorded periodically until the ratio of isomers reached a constant value. Stable product mixtures were isolated by dilution of the sample with 50 mL of *n*-pentane, extraction with two 30-mL portions of 0.1 N NaOH, and drying with $MgSO_4$. Ratios of isomers were

(11) This preference for *s*-cis conformers may be understood in terms of the concept of aromaticity as applied to "non-bonded" 6-π electron systems. See: Hoffman, R.; Olofson, R. A. *J. Am. Chem. Soc.* **1966**, *88*, 943–946. A more quantitative analysis of these effects is to be found: Bernardi, F.; Epiotis, N. D.; Yates, R. L.; Schlegel, H. B. *Ibid.* **1976**, *98*, 2385–2390.

(12) It is neither implied nor expected that these conformers lie at conformational energy minima. The figure is presented to aid in discussing factors influencing the stability of these conformers. These factors include "non-bonded" interactions and steric effects. Clearly, the smaller of the oxygen substituents is more likely to occupy the position syn-periplanar with respect to the olefin.

determined by NMR and by capillary VPC analysis (80 °C). Ratios and characteristic NMR data are presented in Table II.

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Registry No. (*E*)-Dimethyl(1,1-dimethylethyl)[(1-methoxy-1-propenyl)oxy]silane, 84784-58-7; (*Z*)-dimethyl(1,1-dimethylethyl)[(1-methoxy-1-propenyl)oxy]silane, 84784-64-5; (*E*)-dimethyl(1,1-dimethylethyl)[(1-ethoxy-1-propenyl)oxy]silane, 89043-55-0; (*Z*)-dimethyl(1,1-dimethylethyl)[(1-ethoxy-1-propenyl)oxy]silane, 73967-98-3; (*E*)-dimethyl(1,1-dimethylethyl)[[1-(1-methylethoxy)-1-propenyl]oxy]silane, 89043-56-1; (*Z*)-dimethyl(1,1-dimethylethyl)[[1-(1-methylethoxy)-1-propenyl]oxy]silane, 89043-57-2; (*E*)-dimethyl[[1-(1,1-dimethylethoxy)-1-propenyl]oxy](1,1-dimethylethyl)silane, 89043-58-3; (*Z*)-dimethyl[[1-(1,1-dimethylethoxy)-1-propenyl]oxy](1,1-dimethylethyl)silane, 89043-59-4; (*E*)-dimethyl(1,1-dimethylethyl)[[3-methyl-1-(1-methylethoxy)-1-buten-1-yl]oxy]silane, 89043-60-7; (*Z*)-dimethyl(1,1-dimethylethyl)[[3-methyl-1-(1-methylethoxy)-1-buten-1-yl]oxy]silane, 89043-61-8; (*E*)-(1,1-dimethylethyl)diphenyl[[1-(1-methylethoxy)-1-propenyl]oxy]silane, 89043-62-9; (*Z*)-(1,1-dimethylethyl)diphenyl[[1-(1-methylethoxy)-1-propenyl]oxy]silane, 89043-63-0; (*E*)-[[1-(1-methylethoxy)-1-propenyl]oxy]triethylsilane, 89043-64-1; (*Z*)-[[1-(1-methylethoxy)-1-propenyl]oxy]triethylsilane, 89043-65-2; diisopropylethylammonium perchlorate, 16473-89-5; perchloric acid, 7601-90-3; diisopropylethylamine, 7087-68-5.

Reaction of Formaldehyde with Nucleosides: Addition to 2′,3′,5′-Triacetyl 9-β-D-Arabinofuranosyladenine

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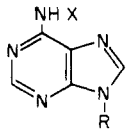
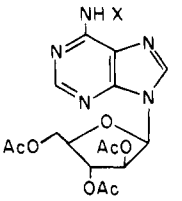
The reactions between nucleosides and formaldehyde have been extensively investigated.[1-3] Since the initial discovery that this reaction occurs with amino groups in both RNA and DNA, it has been used as a probe for undisrupted secondary structure in nucleic acids, as these regions are resistant to attack by formaldehyde.[4] Controversy exists regarding the nature of the reaction products and the functional group(s) that react with formaldehyde. These reactions have been generally carried out in aqueous solution, and since the products are labile and difficult to purify, they have not been well characterized. Such diverse products as Schiff bases,[5] monomethylol[6] and dimethylol[7] derivatives, and dimeric methylene compounds[8] have been suggested. Spectral[9] and kinetic[9a,10] evidence has been presented for the product from adenosine, the most studied nucleoside, suggestive of the N^6-hydroxymethyl structure **1**. It is generally agreed[2] that



1, X = CH_2OH
2, X = CH_2OEt



3, X = H
4, X = CH_2OCH_2OH
5, X = CH_2OCH_2OAc
6, X = CH_2OCH_2OCO-*t*-Bu

this product would be favored at equilibrium over the stronger bases that result from reaction at the N-1, N-3, or N-7 positions. It was shown more recently[11] that 2′,3′-*O*-isoprolylideneadenosine when reacted with formaldehyde in refluxing ethanol gave the *N*-ethoxymethyl derivative **2**. In connection with our interest in low-melting and lipophilic derivatives of adenosinearabinoside (ara-A) which may have increased skin permeability,[12] we studied the reaction of ara-A derivatives with formaldehyde. In this paper we present spectral evidence for the structure of a product isolated for the first time, in a reaction of an adenine pentose derivative with formaldehyde in aqueous solution.

2′,3′,5′-Triacetyl ara-A[13] (**3**) chosen for its solubility in nonaqueous solvents was readily prepared without significant formation of N^6-acetylated product by reacting ara-A in excess acetic anhydride and pyridine at 0 °C. Initial experiments showed the formation of a mixture of several compounds when **3** reacted with formaldehyde. However, it was possible to obtain one major product if the reaction was carried out in 5 M aqueous formaldehyde at 0 °C. This product could be extracted into dichloromethane. A ^1H NMR spectrum of this unstable adduct **4** in deuteriochloroform showed two new peaks, one at δ 5.5, which overlapped with the multiplet due to 2′-H and 3′-H (at δ 5.3–5.65) and the other at δ 5.15. The integrated area of the complex accounted for six protons, suggesting that the product may not be a monomethylol adduct.[9a] Other changes in the spectrum compared to that of **3** were the downfield shift of the anomeric doublet from δ 6.56 to 6.63 and of C_2-H and C_8-H each downfield by 0.13 ppm.

To determine the number and position of the methylene units, the adduct was acetylated with acetic anhydride and pyridine at 0 °C. The NMR spectrum[14] of the thin-layer chromatographically purified product showed only one additional acetate group. The methylene resonance at δ 5.15 in the ^1H NMR spectrum of **4** moved downfield and merged with the other methylene among the 2′-H and 3′-H multiplet on acetylation. The only other additional feature observed in the ^1H NMR spectrum of **5** was a broad triplet for one proton (exchangeable with D_2O) at δ 7.7 assigned to $NHCH_2$. Two methylene carbons at δ 72.23 and 88.03 assigned[14] to $NHCH_2O$ and OCH_2O, respectively, were present in the ^{13}C NMR, consistent with structure **5** for

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