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An *ab initio* Molecular Orbital Study on the Lewis Acidity of TMS-Cl and TMS-CN Toward an α,β-Unsaturated Aldehyde: Are These Acid-Base Interactions Important in Organocuprate 1,4-Additions to Enones?

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Abstract: *High-level ab initio calculations were used to determine the effectiveness of commonly used silanes as Lewis acids toward acrolein as a model for Gilman cuprate conjugate addition reactions. The data suggest that complexation with an enone is by a weak dipole-dipole interaction and is* ***not*** *directly responsible for the rate accelerating effect of TMS-X.* Copyright © 1996 Elsevier Science Ltd

The remarkable effect of TMS-Cl as an additive in conjugate addition reactions of cuprates R_2CuLi has previously been attributed, in part, to its role as a Lewis acid.[1] Recently, TMS-CN has been shown to elicit the same type of response; that is, to increase both rates and yields of 1,4-additions to enals/enones.[2] While there is little argument regarding the potential for BF_3 to associate with a carbonyl oxygen lone pair, it is far less obvious that a related acid-base interaction exists to any significant extent with either TMS-Cl or TMS-CN. These two silanes are unique relative to other silyl derivatives, *e.g.*, TMS-Br, TMS-I, and TMS-OTf in that at low temperatures (between -50 and -78°C) they do not react rapidly with Gilman cuprates to form R-TMS and LiCl.[3] They do, however, based on recently disclosed multinuclear NMR spectral evidence, appear to associate to at least some extent with R_2CuLi, where the chlorine in TMS-Cl and the nitrile group in TMS-CN act as Lewis *basic* ligands toward lithium[2a,3] or copper within the cluster.[4] Such interactions, nonetheless, do not exclude the possibility that a purely Lewis acid interaction (between enone and TMS-X) could be operating as well. Although there is no physical data[5] (*e.g.*, IR or NMR) supporting the notion that either TMS-Cl or TMS-CN acts in this capacity toward an aldehyde or ketone carbonyl, high level *ab initio* calculations[6] were undertaken to assess the extent to which such interactions might exist. Considering the growing number of TMS-X influenced processes in synthetic chemistry,[7] and the postulation of Lewis acid complexation to explain the effects of TMS-X in these processes,[1,8] it was felt that such a study might have far broader implications than just those related to cuprate Michael additions. We now describe the preliminary results of our calculations.

Acrolein (**1**) was chosen as our model α,β-unsaturated carbonyl compound. The presumed Lewis acids chosen for study were chlorosilane ($Cl\text{-}SiH_3$, **2**), cyanosilane ($H_3Si\text{-}CN$, **3**), TMS-Cl (**4**), and TMS-CN (**5**). The geometries of all compounds and complexes were optimized at the HF/6-31G(d) level of theory. Frequency calculations were performed to ensure that a minimum had been found. The water complexes of **2** and **3** were also optimized at the MP2/6-31+G(d,p) level. To assess whether competing solvent complexation is important, the complex of **2** with dimethyl ether was modeled. All silyl compounds were constrained to the C_{3v} point group; acrolein and all complexes had C_s symmetry (except for the acrolein-DME complex which had C_1 symmetry). The calculated geometries of all of the complexes (Scheme 1) involve weak interaction between the oxygen and silane with Si-O bond distances of about 2.9 (R = H) and 3.8 (R = Me) Angstroms. Attempts to locate trigonal bipyramidal minima for the complexes were not successful.[9] The calculated free energies of complexation for each complex are summarized in Table 1.

Scheme 1

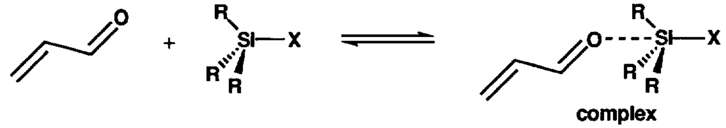


Table 1. Gas Phase Free Energies of Complexation (kcal/mol)[a]

Complex	HF/6-31g(d)		MP2/6-31+G(d,p)		CCSD(T)/6-311+G(2df,2pd)
	25°C	-78°C	25°C	-78°C	25°C
H_3SiCl-acrolein	4.08	1.82	3.26	1.00	
H_3SiCN-acrolein	3.57	1.36	2.73	0.52	
TMS-CN-acrolein	2.66	1.07			
TMS-Cl-acrolein	2.43	1.07			
H_3SiCl-Me_2O	3.37	1.40	2.14	0.17	2.4
H_3SiCl-H_2O	2.66	0.83	2.22	0.39	3.0
H_3SiCN-H_2O	2.03	0.31	1.54	-0.18	2.5

[a] Calculated values corrected for zero-point energies and thermal contributions.

The calculated potential energies of complexation were negative by only 2 to 4 kcal/mol reflecting the weak interaction suggested by the structures. Correction of these energies with calculated zero-point and thermal energy terms and entropy terms gave positive free energies of complexation (Table 1) at 25°C. Comparison of the MP2 energies with those from calculations at a much higher level of theory indicate that these energies have largely converged at this level with respect to further improvements in theoretical treatment. MP2 calculated energies for similar complexes correlate well with experimental energies[10] suggesting that the MP2 energies in Table 1 are likely to be reliable for the prediction of the positions of the complexation equilibria. The weakly positive free energies suggest that complexation would not be very favorable; however, at -78°C, the temperature at which cuprate 1,4-additions are routinely carried out, the entropy effects are diminished, and ΔG° becomes more favorable by 1.5-2.0 kcal/mol. Furthermore, the complexation energy for TMS-Cl (or TMS-CN) at the Hartree Fock level is more favorable than for H_3Si-Cl leading to a prediction that the free energies of complexation will approach zero at -78°C. Complexation of dimethyl ether solvent with TMS-Cl is predicted to be slightly weaker than for enones and should not significantly interfere with enone complexation. The MP2 complexation energy is much stronger for BF_3, where a tight complex is formed with a smaller (1.71Å) O-B bond distance. The TMS-Cl complex does not, in fact, appear to be unusually stable when compared to that formed with *t*-BuCl, which shows a similar O-C bond length (3.81Å for TMS-Cl *vs* 3.97Å for *t*-BuCl), somewhat weaker complexation energy, and comparable charge densities and LUMO energy. The Me_2O-acrolein complex is even weaker, but appears to result from a similar dipole-dipole interaction at the carbonyl oxygen.

Although the Lewis acid complexation of TMS-Cl (and TMS-CN) with acrolein is weak and may even be slightly endergonic, these complexes are at a low enough energy that they *could* play a role in the mechanism of cuprate addition to enones provided that the electronic structure of the enone in the complex is altered sufficiently to activate it toward cuprate addition. Charge densities and LUMO energies in the complex can give some indication of whether such activation appears feasible. The Mulliken charge densities of each complex at the HF/6-31G(d) level are shown in Table 2. As expected, there is an increase in positive character at carbon 3 relative to acrolein alone, which could serve to activate the complex toward cuprate addition. However, the change is quite small compared to that involving BF_3. Hence, *we conclude that interactions of a Lewis acid/Lewis base nature involving these silanes and α,β-unsaturated aldehydes and ketones are most unlikely to lead to the observed large increases in rates of 1,4-additions.* An analysis of LUMO orbital energies and coefficients leads to a similar conclusion for complexed acrolein (Table 2).

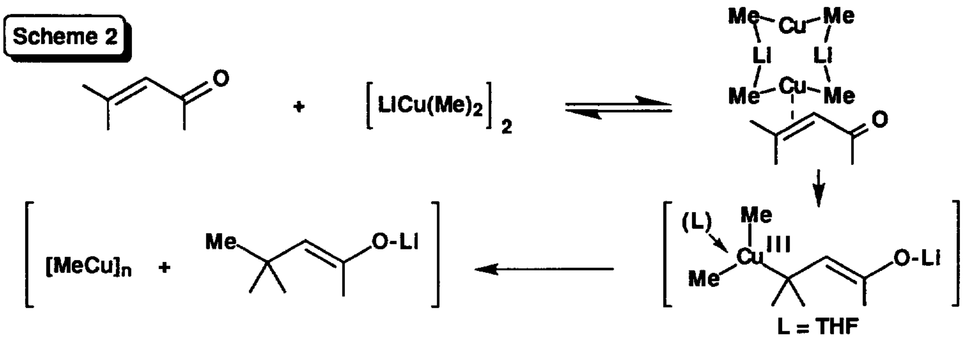
Table 2. Charge Distribution[a] / LUMO energies

Complex	C3	C2	C1	O	E_{LUMO} (eV)
acrolein	0.0317	-0.0076	0.4665	-0.4906	2.70
BF_3•acrolein	0.1126	0.0146	0.5793	-0.5516	1.08
H_3SiCl•acrolein	0.0511	-0.0026	0.4911	-0.5087	2.24
H_3SiCN•acrolein	0.0534	-0.0031	0.4920	-0.5111	2.16
TMSCl•acrolein	0.0469	-0.0094	0.4825	-0.5013	2.32
TMSCN•acrolein	0.0495	-0.0101	0.4843	-0.5040	2.24
t-BuCl•acrolein	0.0445	-0.0093	0.4801	-0.5015	2.37
Me_2O•acrolein	0.0378	-0.0085	0.4730	-0.4964	2.58

[a] Mulliken densities at the HF/6-31G(d)//HF/6-31G(d) level summed to heavy atoms.

A mechanism for cuprate addition consistent with Krauss and Smith's kinetic results[11] is shown below. The rate-limiting step involves rearrangement of a π-complex of the cuprate and enone to a Cu(III) σ-complex. They found that electron-withdrawing substituents on the aromatic ring of 1-phenyl-3-methyl-2-buten-1-ones led to substantial rate accelerations (rho = 1.58), that could be related to stabilization of negative charge in the Cu(III) σ-complex. Acceleration of this reaction could then be attributed to stabilization of this transient Cu(III) σ-complex by TMS-Cl. Preliminary calculations indicate that enolates are strongly stabilized by interaction with BF_3 or silyl chlorides (to form silyl enol ethers). Thus, a likely mechanism could involve TMS-X in a rate-determining rearrangement to the silylated Cu(III) σ-complex, as postulated by Corey to explain rate accelerations and stereochemical preferences in the presence of TMS-Cl.[12]

Scheme 2



The calculations presented here indicate that the TMS-Cl enone complex can participate in a reaction equilibrium with the enone. The TMS-Cl (and TMS-CN) enone complex, however, is weak, and not much different from that with *t*-BuCl, which in our hands does *not* accelerate cuprate additions. Since TMS-X complexation of enones is not likely to accelerate the addition reactions, these additions to the enone or the complexed enone are probably not the rate-determining steps in these processes. This conclusion might well have implications for the mechanisms of other reactions promoted by TMS-X additives. While TMS-Cl could interact with the π-complex between the cuprate and enone more strongly than the enone itself, what could make these silanes unique, relative to *t*-BuCl, might be their ability to stabilize the transition state leading from the π-complex to product, possibly with concommitant cleavage of the Si-X bond together with highly favorable salt (LiX) formation.

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