DFT Theoretical Study of the Chemioselectivity of the Crotonic Acid Dianion and its Trimethylsilyl Ester Silylation. Role of the Solvent

Gjergji Sini,* Moncef Bellassoued and Nancy Brodie

Université de Cergy-Pontoise, Bâtiment des Sciences de la matière, 5, Mail Gay Lussac, Neuville sur Oise 95031, Cergy-Pontoise Cedex, France

Abstract—The different chemioselectivity observed experimentally during the silylation of the title species was investigated by means of theoretical methods. The influence of the solvent on the optimized geometries and relative energies of different reaction intermediate species was studied by applying the continuum model at the DFT/6-31+G*//DFT/6-31+G* level. Two groups of neutral reaction intermediates were considered: dianion–bislithium intermediates in the case of crotonic acid and monoanion–lithium intermediates in the case of its silyl ester. It was found in both cases that in the gas phase the negative charge is better stabilized when delocalized over the entire molecular skeleton, while in solution the solute–solvent interactions are more important when the charge is localized over the oxygen atoms. For the dianion–bislithium intermediates, the intramolecular interactions are more important and the chain-delocalized charge intermediate remains the most stable one, even in solution. This is not the case for the monoanion–lithium intermediates because the solvent effect inverts the gas phase stability order. The differences observed experimentally in solution are thus explained by the differences in the stability order of these reaction intermediate species. © 2000 Elsevier Science Ltd. All rights reserved.

Introduction

Lithium dienolates derived from α,β-unsaturated carboxylic acids generally undergo alkylation reactions nearly exclusively at the α carbon.[1] However, γ-regioselectivity is significantly enhanced by using the cuprated species[2] (Scheme 1). Similar results were obtained with ester[3] and amide[4] enolates.

We have found[5] that trapping the dienolates of crotonic and senecioc acids (or the non conjugated isomers) with trimethylsilyl chloride (TMSCl) affords exclusively γ-silylated products (Scheme 2).
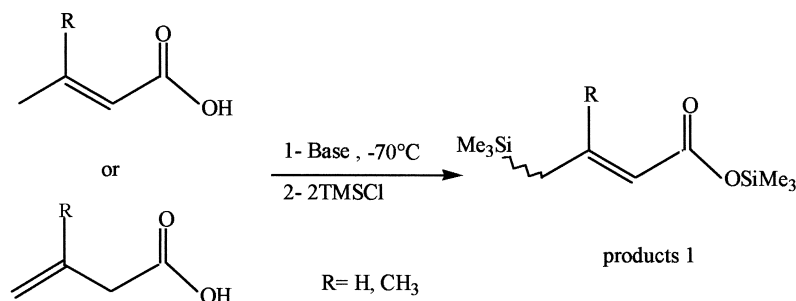
With crotonic (vinylic acetic) acid, one single *trans* compound is obtained whereas with senecioc (methylvinylic
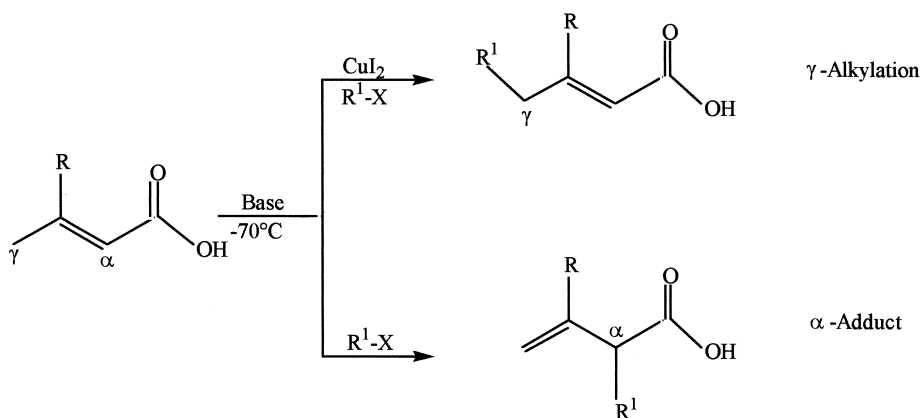
Scheme 1.

Scheme 2.

acetic) acid, a mixture of the two stereoisomers (*E/Z* approximately 80:20) is observed.

On the other hand, trapping the enolates of the corresponding trimethylsilyl ester produces only the O-silylated dienol ethers (Scheme 3).

The difference between these two results is surprising because the experimental methodology and reaction conditions for the two reactions (Schemes 2 and 3) are exactly the same. It is then reasonable to think that the difference observed in these two results should be due to the differences in the two reactions' paths. These intriguing observations prompted us to investigate this reaction by theoretical methods.
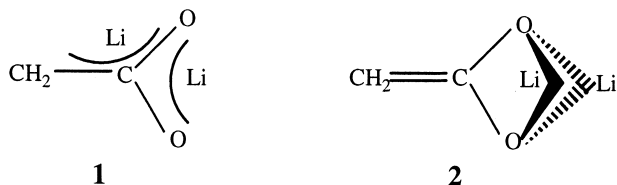

Theoretical studies concerning some aspects of these types of reactions have been carried out previously.[6,8,9] In the case of acetic acid, Schleyer et al.[6] have proposed the existence

of two possible bislithiated intermediates (**1** and **2**). It was shown by ab-initio calculations that **1** is 7.9 kcal mol^{-1} lower in energy than **2**, indicating that the terminal CH_2 group carries considerable electron density. This can explain why the carbon of this CH_2 group is a potential center for subsequent S_N2 reaction. The following experimental results[7] confirm this conclusion: after heating the bislithiated intermediates in the case of acetic acid, the bis-silylation (reaction with $ClSiMe_3$) afforded exclusively the O,C silylated product ($Me_3Si–CH_2–CO_2SiMe_3$) while without heating, a mixture of O,C and O,O ($CH_2=C(OSiMe_3)_2$) products was observed.

The reactions presented in Scheme 2 have also been the subject of some theoretical treatments.[8,9] Bongini et al.[8] have studied **3**, in which one Li atom is placed above the molecular plane. They found that this structure is more stable in the gas phase as well as in solution as compared to **4** that has the two Li atoms in the molecular plane. Domingo et al.[9] performing calculations at the PM3 level found that the *s-trans* structure **6** is less stable than the *s-cis* **5** in the gas phase. By considering three dimethyl ether solvent molecules per lithium atom, they showed that the previous stability order is inverted. This suggests that considering the implicit solvation[10a] is very important for the study of this type of species.
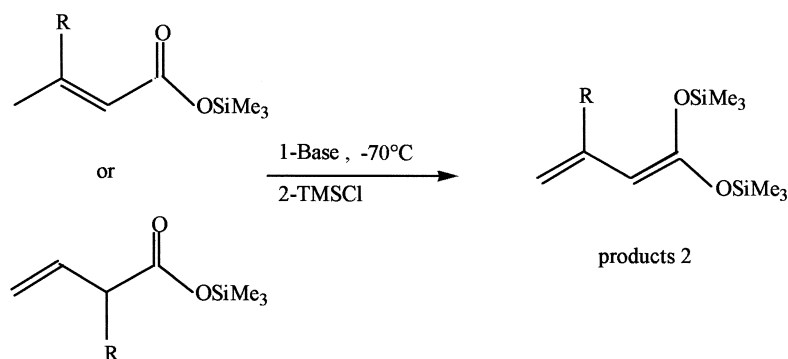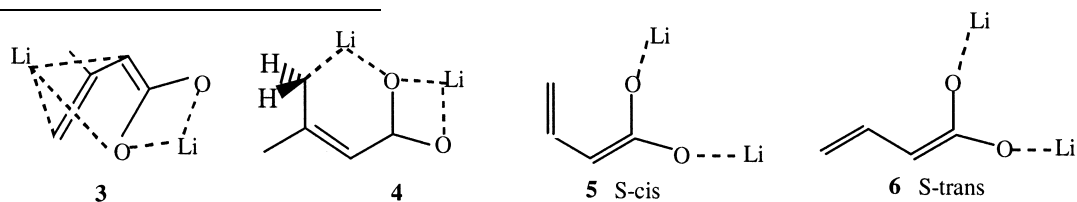
Scheme 3.
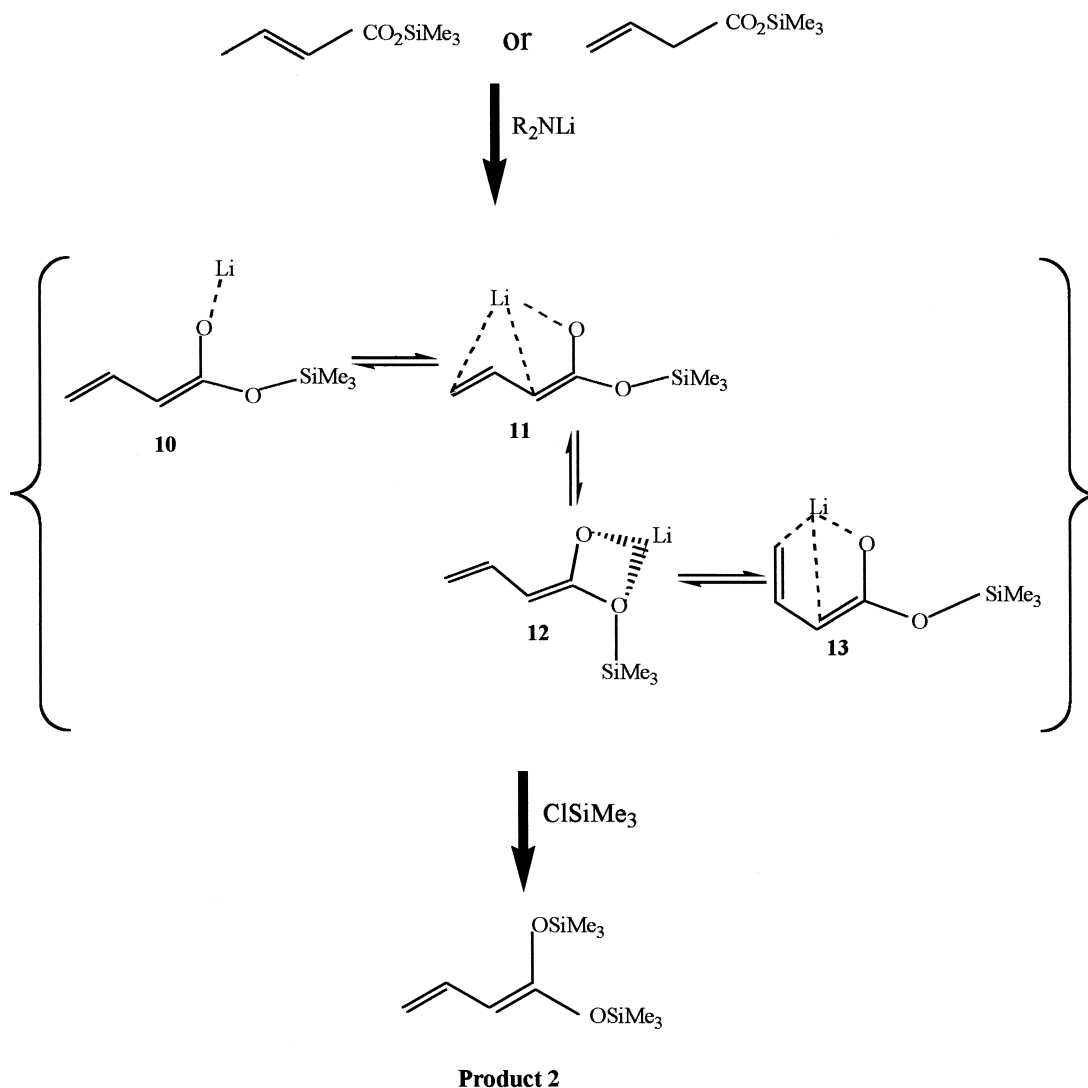
Scheme 4.

It is then reasonable to think that with respect to our reaction (Scheme 2), the double silylation of the crotonic acid should involve similar bislithiated dianion intermediates (**6**, **7**, **8** and **9** in Scheme 5). Moreover, for analogy with **1** and **2**, one can suppose that **9** would be probably the most stable between all the possible intermediates, which can explain the reaction result in Scheme 2. It is, however, interesting to investigate the influence of the longer carbon chain in **9** and to understand why there is only one of the oxygen atoms that can act as a nucleophilic center.

As for the reactions in Scheme 3, the experimental results are surprisingly different and it is very tempting to believe that the monoanion reaction intermediates do not present the same reactivity as their corresponding dianions. As no theoretical calculations have been reported, we lack structural and energy data for these species. It was necessary then to study these types of reaction intermediates so that experimental chemioselectivity could be understood.

In this paper, we propose an explanation for the formation of the C and O-silylated products with the use of ab-initio DFT

calculations by the study of the structure and the stability order of some reaction intermediates. Because of the important charge separation in these types of reaction intermediates, we have also considered the influence of the medium effects.

As is well known, there are two different approaches when taking into account the solvent effect: (i) the supermolecular model that considers the interaction between the solute and the real solvent molecules; (ii) the continuum model, where the solvent is replaced by a continuum of uniform dielectric constant ϵ. It is clear that the first approach, when properly carried out, gives a more realistic description of the solute–solvent interactions. The scope of this paper is to show that even within the limitations of the continuum model, we can obtain results in good agreement with experimental ones.

Computational methods

The geometries for all the considered species were optimized at the DFT-B3LYP/6-31+G* level, using the GAUSSIAN 94
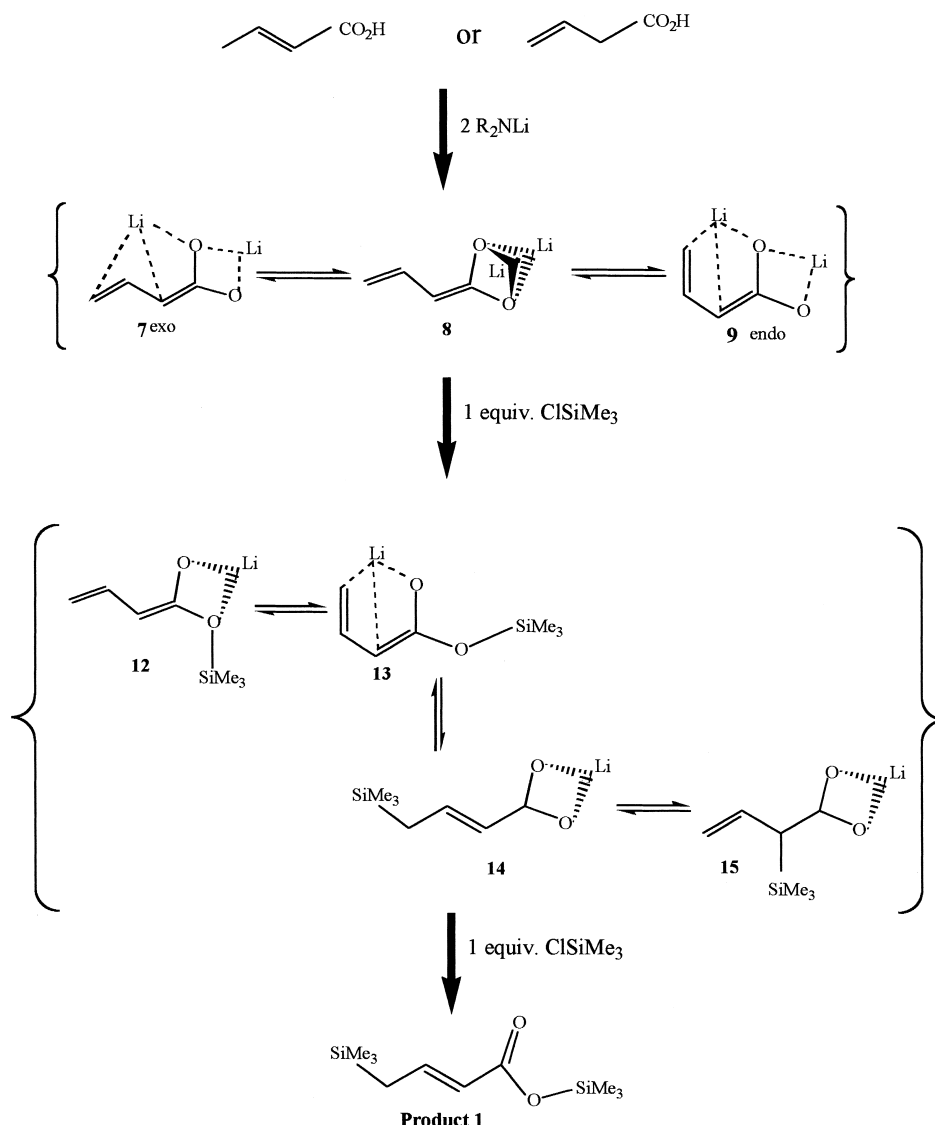
Scheme 5.

program.[10] One test calculation at the B3LYP/3-21G level was carried out to take into account the solvent effect on the geometry optimization. Generally, the solvent effect was considered by applying the continuum model (SCRF= SCIPCM, with a value of 0.0004[11e] for the isodensity)[11] incorporated in the GAUSSIAN 94 program system. A dielectric constant ϵ=7.6 was introduced into the calculations to account for the effect of the real solvent (THF).

Population analysis was carried out by using the Natural Population Analysis (NPA)[12] at the RHF and DFT levels. To check the stability of the charge analysis, two other basis sets (3-21G and 6-31G*) were considered.

Results and Discussion

The mechanism for the reaction in Scheme 3 is straightforward. In the first step, the lithium amide abstracts one proton from the reactant to produce a mixture of different possible intermediate species (**10–13** in Scheme 4). In the

following step, the ClSiMe₃ reacts with these intermediates to form a bond with one oxygen center (product **2**).

In Scheme 2, the same experimental procedure was used but the results are quite different (see Scheme 5). An important insight into the difference in reaction mechanism is given by the following experimental observations: in the presence of only one equivalent of ClSiMe₃ (second step in Scheme 2), the first silylation of crotonic acid occurs exclusively at the terminal carbon.[7] This suggests that the double silylation of the bislithium intermediate in Scheme 2 should proceed by two steps. Consequently, we have considered a three step mechanism for this reaction: (i) each equivalent of lithium amidure abstracts one proton from the reactant to produce a mixture of different bislithium–dianion intermediates (**7**, **8** and **9**, Scheme 5); (ii) one equivalent of ClSiMe₃ reacts with these intermediates to form a second group of possible reaction intermediates (**12–15**); (iii) a second equivalent of ClSiMe₃ reacts with the previous monosilylated intermediates to form the bissilylated product **1**.

When considering the reaction mechanisms involved in our

Table 1. Selected geometrical parameters for the optimized structures at the DFT/6-31+G*//DFT/6-31+G* level; 'dihed' is the $C_1-C_2-C_3-C_4$ dihedral angle; for **7**, **9** and **12**, Li_1 is the atom which is positioned over the molecular plane

	7	8	9	12	13	14	15
C1–C2	1.410	1.369	1.425	1.361	1.404	1.483	1.517
C2–C3	1.447	1.444	1.429	1.448	1.440	1.343	1.504
C3–C4	1.362	1.352	1.384	1.349	1.374	1.495	1.339
C1–O1	1.371	1.365	1.282	1.277	1.278	1.282	1.277
C1–O2	1.286	1.366	1.351	1.485	1.361	1.282	1.279
Li1–O1	1.808	1.874	1.837	1.773	1.843	1.852	1.856
Li2–O2	1.810	1.875	1.819	–	–	–	–
Li1–C4	3.103	–	2.145	–	2.217	–	–
dihed	−161.8	180.0	8.8	180.0	11.4	180.0	138.4

Table 2. Relative energy differences (kcal mol^{-1}) with respect to **8** for the dianions and with respect to **12** for the monoanions (DFT/6-31+G*//DFT/6-31+G* level)

	$\Delta E = E(i) - E(8)$				$\Delta E = E(i) - E(12)$			
	6	7	8	9	12	13	14	15
GP[a]	15.2	−12.3	0.0	−19.8	0.0	−6.8	−13.2	−7.9
GP(ZPE)[b]	14.7	−12.0	0.0	−19.1	0.0	−6.1	−12.5	−7.5
THF	−3.5	−2.7	0.0	−5.7	0.0	5.3	−11.1	−6.0

[a] Gas phase.
[b] Gas phase plus zero point energy correction.

study, one should also take into account the transition states for each of these steps. A brief review of the acetic acid results gives an idea about this. Actually, when the silylation of **1** and **2** was conducted without previous heating, a mixture of O,O and O,C-silylated products was obtained.[7] This means that between the two reaction intermediates **1** and **2**, there exists an important activation barrier. However, only the O,C-silylated compound (product **1**) was obtained

for the reaction at −70°C (Scheme 2). Under these experimental conditions, this suggests that there is no important activation barrier between the dianion reaction intermediates and probably between these two intermediate species only the most stable one is present in solution. It can then be concluded that some important aspects of the reaction mechanisms could be obtained by only examining the stable intermediate species.

All the reaction intermediates mentioned above (**6**–**15**) were optimized at the DFT theory level. Some of their geometrical parameters are presented in Table 1. Energy differences between these structures are presented in Table 2. The NPA charges are represented in Tables 3 and 4. The differences between the energies in the gas phase and in solution are reported as the solvent effect in Table 5.

Charge distribution

The charge distribution (NPA) is not very sensitive to the basis set level (see Table 3). In Table 4, it is shown that for

Table 3. Gas phase charges from Natural population analysis (NPA) (DFT-B3LYP level)

	7			8			9		
	3-21G	6-31G*	6-31+G*	3-21G	6-31G*	6-31+G*	3-21G	6-31G*	6-31+G*
C1	+0.56	+0.65	+0.62	+0.41	+.49	+0.46	+0.60	+0.69	+0.66
C2	−0.33	−0.33	−0.35	−0.21	−0.21	−0.22	−0.33	−0.33	−0.34
C3	−0.14	−0.13	−0.13	−0.01	−0.01	+0.01	−0.05	−0.04	−0.04
C4	−0.08	−0.08	−0.10	−0.08	−0.08	−0.09	−0.24	−0.25	−0.26

Table 4. NPA charges in the gas phase (GP) and in solution (THF), DFT/6-31+G*//DFT/6-31+G* level

	6		7		8		9		12		13		14		15	
	GP	THF	GP	THF	GP	THF	GP	THF	GP	THF	GP	THF	GP	THF	GP	THF
C_1	+0.70	+0.72	+0.64	+0.64	+0.46	+0.52	+0.67	+0.67	+0.64	+0.66	+0.69	+0.69	0.73	0.73	+0.73	+0.77
C_2	−0.30	−0.36	−0.37	−0.39	−0.22	−0.29	−0.35	−0.37	−0.26	−0.29	−0.21	−0.22	−0.11	−0.12	−0.50	−0.50
C_3	−0.01	−0.01	−0.12	−0.10	+0.01	+0.01	−0.02	−0.03	+0.01	+0.01	−0.03	−0.03	0.10	0.11	+0.01	+0.03
C_4	−0.17	−0.25	−0.10	−0.16	−0.10	−0.17	−0.29	−0.31	−0.08	−0.11	−0.20	−0.21	−0.39	−0.39	−0.02	−0.03

Table 5. Energy stabilization ΔE (kcal mol^{-1}) due to the solvent effect

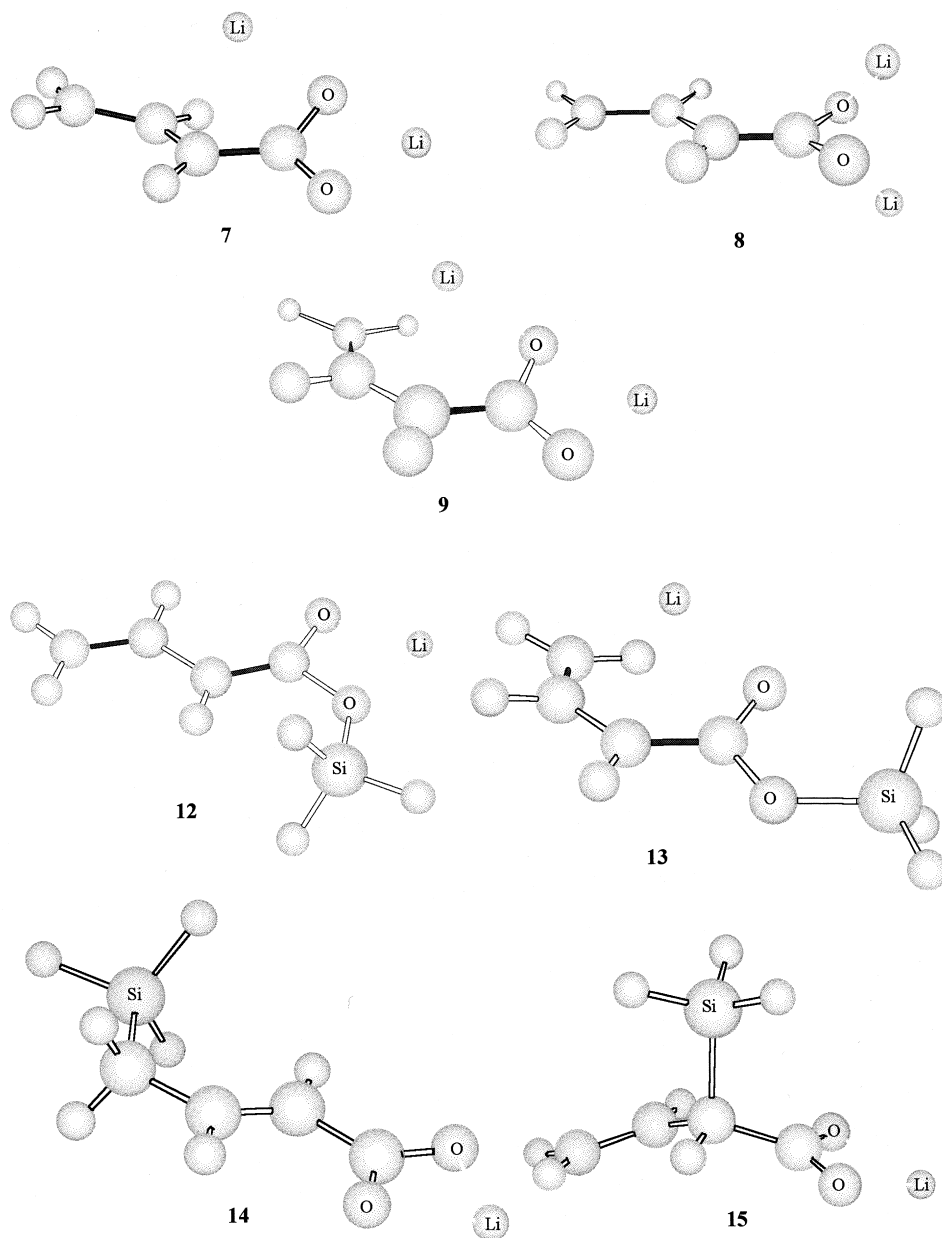| | Dianions | | | | Monoanions | | | |
| | | | | | O-silylated | | C-silylated | |
Structure	9	7	8	6	13	12	14	15
Dipolar moment (D)	5.4	6.4	7.7	11	3.7	7.4	2.7	3.8
ΔE	40	46	53	72	20	31	28	28

Figure 1. DFT/6-31+G* optimized geometries for the reaction intermediate structures.

all the structures considered, the negative charge is more important at the C_2 atom than at the C_4 atom. This is in good agreement with other calculations[9a,b] and experimental[9c] estimations carried out for these and similar species.[9]

Geometries

The geometrical parameters presented in Table 1 are not very different from those found in some previous works.[8,9] The differences are probably due to the influence of the theoretical method, basis set and correlation level used. In the structures where there is only one Li cation between the oxygen atoms, the Li center is roughly positioned in the O–C_1–O plane. On the other hand, if Li is placed between the oxygen and carbon atoms, only a bridging position over the molecular plane is preferred (see also the optimized structures for these intermediates, Fig. 1).

It is important to point out that our geometrical optimizations were carried out in the gas phase. However, the role of the solvent effect on the optimized geometries was also considered. Previously, it has been shown[6,8] that when some water molecules were included to account for the solvent effect, no qualitative change to the results was found. On the other hand, it has been shown in some other cases that the consideration of the medium effect changes dramatically the geometry optimized in the gas phase.[9,13] To be sure that no important structural modifications appear in solution, we carried out geometry optimizations for **8** and **9** in the presence of the solvent effect (3-21G, DFT level). The energy difference $\Delta E(9-8)$ calculated in THF, but with the geometries optimized in the gas phase, is -2.5 kcal mol^{-1}. The geometry optimizations were also carried out taking into account the solvent effect. In this case, the energy difference was found to be -3.1 kcal mol^{-1}. It appears
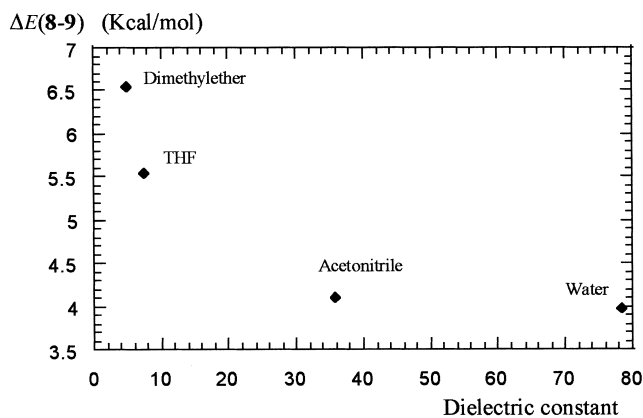
$\Delta E(\textbf{8-9})$ (Kcal/mol)

Figure 2. Influence of the solvent polarity on the $\Delta E(\textbf{8–9})$

then that when taking into account the solvent effect, the gas phase geometries are not qualitatively affected. Consequently, we estimated that for this type of species, the geometries optimized in the gas phase are sufficient for energy related comparisons.

It must not be forgotten that the continuum model does not account for the steric effect of the solvent. It is reasonable to expect then that the geometry optimizations here result in structures with, for example, two Li counterions bridging the two oxygen atoms (**8**) instead of two quasicovalent O–Li bonds (**6**). Actually, starting from the geometry of **6**, the optimization in the presence of the solvent effect results in a structure similar to **8**. One can then imagine that the geometry difference between **6** and **8** would affect their dipole moments. In fact, this is very important when considering the solute–solvent interactions. To take into account this effect, the optimization of **6** was carried out by freezing the Li–O–C_1 angles at 180°. The dipole moment of this structure was found to be considerably high ($\mu =$ 11 D) and the solvent effect is very much reinforced (Table 5). In any case, the structure **6** is always higher in energy than **9** by 2.2 kcal mol^{-1} but only 0.7 kcal mol^{-1} lower in energy than **7**. These results imply that in the case of the dianions, the preferred geometries are the ones where one of the Li atoms bridges the O–C_2–C_4 atoms (**7** and **9**).[14]

Energy aspects

The relative stabilities of different intermediate species are presented in the Table 2. All of these metastable intermediate species can be considered as being formed by two imaginary fragments: the first is the crotonic dianion (or silyl crotonic ester monoanion) and the second fragment being the Li$^+$ counterion system. With the charges on each fragment being very high, the stability trend between all of the considered intermediate species should be imposed by the charge–charge interactions between the two mentioned fragments.

It is shown in Table 2 that **9** is more stable than **8** by 19.8 kcal mol^{-1} in the gas phase. This is a reasonable result if one considers that the coulombic repulsion is less important for **9**. On the other hand, the interaction of Li$_1$ with the π delocalized system of the carbon chain is probably more important for **9** than for **7**. Actually, the NPA charges on the

Li centers show that the charge transfer from the dianion fragment to the Li one is higher for **9** than for **7** or **8** (0.14, 0.12, 0.11, respectively, in the gas phase).

The same energy trend is found in the case of the mono-anions as **13** is more stable than **12** by 6.8 kcal mol^{-1}. The charge transfer values for **13** and **12** (0.07 and 0.05, respectively) support this result and give the idea that the interaction of Li$^+$ with the O_1–C_1–C_2–C_3–C_4 π system in **13** is probably stronger than the interaction of Li$^+$ with the O_1–O_2 lone pair system.

When the solvent effect is considered, all the energy differences are reduced by approximately 8–12 kcal mol^{-1}. However, the most important result is that the stability order between the dianionic intermediate species in solution is the same as in the gas phase, while this trend is inverted for the monoanionic intermediate species in solution. Thus, in solution, **12** becomes more stable then **13** while **9** is always more stable than **7** or **8** (Table 2). It is then clear that it is the solvent effect which makes all the difference between the two reactions given in Schemes 2 and 3.

It is important to remember that the interaction of the solute with the polar solvent would become greater with the increase of the charge separation and the increase of the dipole moment in the molecule. Actually, the stabilization due to the solvent effect is roughly 20–30 kcal mol^{-1} for the monoanions and 40–50 kcal mol^{-1} for the dianions (72 kcal mol^{-1} for **6***, Table 5). It is obvious from Table 5 that the stabilization due to the solvent effect follows the same trend as the magnitude of the dipole moment, which means that this factor is very important for these species.

These results indicate that for the monoanions, the differences in the solute–solvent interactions are more important than the intrinsic ones. This is not the case for the dianions for which the intrinsic interactions remain the most important in the gas phase as well as in solution.

It is also well known that the medium effect is dependent on the solvent's polarity. In order to determine the influence of this factor, we have presented the energy difference between **8** and **9** as a function of the polarity of different (imaginary) solvents in Fig. 2.

This energy difference is reduced as the solvent polarity is increased which is in agreement with the differences between the dipole moments of **8** and **9**. Even for such a strong polar solvent as water, the electrostatic solvent effect is less important than the intrinsic molecular interactions. The intermediate species **9** remains the most stable one.

Mechanistic aspects

The relative stabilities in terms of energy of the various intermediate species in solution, determined using our simplified model of the reaction mechanism, are in agreement with the experimental results. We found that **12** is more stable than **13**. If we look more closely at **12**, the O_1 is the only nucleophilic center and consequently the only possible product should be the product **2** (Scheme 3). Similarly, the greater stability of **9** versus **8** is in agreement with

the experimental result that product **1** (Scheme 2) is obtained when the crotonic acid is used as reactant. Actually, one can imagine four possible nucleophilic centers (O_1, O_2, C_2 and C_4) owing to the localized negative charges on **9** (see Table 4). It follows that once the first S_N2 reaction between **9** and $ClSiMe_3$ has been achieved, there are four possible intermediates formed: **12**, **13**, **14** and **15**. Our calculations show that, in THF, **14** is the most stable of these four intermediates[15] as it is 11.1 kcal mol^{-1} lower in energy than **12** and 5.1 kcal mol^{-1} lower in energy than **15** (see Table 2). These results are in agreement with the previous observation[7] that **14** is obtained as intermediate when only one equivalent of $ClSiMe_3$ is used. We conclude then that in the case of the crotonic acid and its trimethylsilyl ester, theoretical results in good agreement with experimental results can be obtained by using the simple assumption that these reactions are under thermodynamic control.

The last point that seems to us to be important is to understand why the γ-silylated product is more stable than the α-silylated one. One could imagine that steric factors are responsible. However, replacement of SiH_3 by H in the calculations within the same theoretical level shows that the structure similar to **14** is always more stable by 6.1 kcal mol^{-1} in the gas phase and 5.4 kcal mol^{-1} in THF than the equivalent of **15**. We conclude that only the intramolecular electronic factors are responsible for the greater stability of the γ-silylated product in comparison to the α-silylated one. This result can also be explained by the delocalization of the $O-C_1-C_2-C_3$ π-system for **14** which should be absent for **15**. Actually, the geometrical parameters confirm this idea: **14** has a planar geometry (Fig. 1) and a C_1-C_2 distance of 1.486 Å which, as expected, is shorter than the C_1-C_2 distance of 1.517 Å in **15**.

Conclusion

This study shows that for many highly polar species, the consideration of solvent effects is crucial for the reliability of theoretical results. Therefore, the different experimental results presented in Schemes 2 and 3 can be understood by considering the competitivity between two important factors: intramolecular interactions and the solute–solvent interactions in the metastable intermediate species. These two types of interactions are found to support two different intermediate structures. The intramolecular interactions prefer intermediate structures with the Li counterion above the molecular plane, bridging one oxygen and two carbon atoms, C_2 and C_4 (**7**, **9** and **13**). Owing to the high dipole moments, the solute–solvent interactions support another type of intermediate structure where one (or two) Li counterion(s) bridge the two oxygen atoms (**8**, **12**).

With respect to the dianions, the charge separation within the intermediate species is very important and the intrinsic interactions change considerably for different geometrical structures. The solute–solvent interactions tend to diminish these energy differences, but they are not strong enough to invert the stability order found in the gas phase. For this reason, the carbon-chain silylated product is thus observed. In the case of the monoanion species, the intramolecular interactions are not very different going from one geometrical

structure to another, and the priority in the stability order is imposed by the solute–solvent interactions via the differences in the dipole moments. Thus, the O–Li–O bridging structures are predominant and the bis-oxygen silylated products are obtained.

More precise information concerning this reaction could certainly be obtained by considering the supermolecular model, but we hope to have shown here that the continuum model can be applied to give results in good agreement with experimental data.

References

1. (a) Cainelli, G.; Cardillo, G.; Contento, M.; Umani-Ronchi, A. *Gazz. Chim. Ital.* **1974**, *104*, 625. (b) Katzenellenbogen, J. A.; Crumrine, A. L. *J. Am. Chem. Soc.* **1976**, *98*, 4925.

2. Katzenellenbogen, J. A.; Savu, P. M. *J. Org. Chem.* **1981**, *46*, 239.

3. (a) Katzenellenbogen, J. A.; Crumrine, A. L. *J. Am. Chem. Soc.* **1974**, *96*, 5662. (b) Gesson, J. P.; Jacquet, J. C.; Mondon, M. *Tetrahedron Lett.* **1980**, *21*, 2509.

4. Oakleaf, J. A.; Thomas, M. T.; Snieckus, V. *Tetrahedron Lett.* **1978**, 1645.

5. (a) Bellassoued, M.; Ennigrou, R.; Gaudemer, M. *J. Organomet. Chem.* **1988**, *338*, 149. (b) Bellassoued, M.; Ennigrou, R.; Gaudemer M. *J. Organomet. Chem.* **1990**, *393*, 19.

6. Kaneti, J.; Schleyer, P. v. R.; Kos, A. J. *J. Chem. Soc., Chem. Commun.* **1985**, 1014.

7. (a) Bellassoued, M.; Dubois, J. E.; Bertounesque, E. *Synth. Commun.* **1987**, 1181. (b) Bellassoued, M.; Dubois, J. E.; Bertounesque, E. *Bull. Soc. Chim. Belg.* **1988**, *97* (4), 263.

8. Bongini, A.; Orena, M.; Sandri, S. *J. Chem. Soc., Chem. Commun.* **1986**, 50.

9. (a) Domingo, L. R.; Gil, S.; Mestres, R.; Picher, M. T. *Tetrahedron* **1995**, *51* (26), 7207. (b) Domingo, L. R.; Gil, S.; Mestres, R.; Picher, M. T. *Tetrahedron* **1996**, *52* (33), 11105. (c) Aurell, MaJosé; Gil, S.; Mestres, R.; Parra, M.; Tortajada, A. *Tetrahedron* **1994**, *50* (17), 5109.

10. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Cioslowski, J.; Stefanov, B. B.; Nanayakkara, A.; Challacombe, M.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Replogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. P.; Head-Gordon, M.; Gonzalez, C.; Pople, J. A. GAUSSIAN 94, Revision D.2, Gaussian: Pittsburgh PA, 1995.

11. (a) Foresman, J. B.; Keith, T. A.; Wiberg, K. B.; Snoonian, J.; Frisch, M. J. *J. Phys. Chem.* **1996**, *100* (40), 16098. (b) Wiberg, K. B.; Castejon, H.; Keith, T. A. *J. Comp. Chem.* **1996**, *17* (92), 185–190. (c) Wiberg, K. B.; Keith, T. A.; Frisch, M. J.; Murcko, M. *J. Phys. Chem.* **1995**, *99* (22), 9072. (d) Wiberg, K. B.; Rablen, P. R.; Rush, D. J.; Keith, T. A. *J. Am. Chem. Soc.* **1995**, *117* (15), 4261. (d) Wiberg, K. B. *J. Org. Chem.* **1999**, *64*, 6387. (e) It is true that the choice of the isodensity value is important for determining the volume of the solute cavity. A good choice should be made by comparing the calculated liquid molecular volume with the experimental ones. We did not have this information for our intermediate species so no test calculations were possible. However, we tried to correlate the NPA charges at the carbon atoms C2 and C4 of **9** with

different isodensity values (0.0004, 0.0005, 0.0006, 0.0008, 0.001) but no variation was found. Meanwhile, it has been shown[11a,c,d] that a value of 0.0004 for the isodensity more closely reproduces the liquid molar volumes. We have then chosen this value.

12. Glendening, E. D.; Reed, A. E.; Weinhold, F. NBO version 3.1.

13. Papalardo, R. R.; Markos, E. S.; Ruiz-Lopez, M. F. M.; Rinaldi, D.; Rivail, J. L. *J. Am. Chem. Soc.* **1993**, *115*, 3722.

14. It should be noted that this geometry constraint gives rise to energy values which must be considered very carefully. In our case, we have estimated that the energy error introduced by this constraint is largely compensated by the exaggeration of the solvent effect due to the overestimation of the dipole moment. Actually, when using the local geometrical parameters found by Domingo et al.[9a] (supermolecular model, PM3 level) for the two Li atoms in **6**, the dipole moment decreases by approximately 3D. This in turn should be accompanied by a decrease in the solvent effect of roughly 15–20 kcal mol^{-1} (Table 5). We reaffirm that this argumentation is purely speculative but estimate that the value of 2.2 kcal mol^{-1} for the relative stability between **6** and **9** could be considered as a lower limit.

15. This is probably due to the differences in the distribution of the remaining negative charge after the first silylation: the electron density is much more stabilized when localized over the two oxygen atoms than elsewhere.