J. Org. Chem. **1999,** *64,* 6815−6821

A Mechanistic Study of the Horner−Wadsworth−Emmons Reaction: Computational Investigation on the Reaction Pass and the Stereochemistry in the Reaction of Lithium Enolate Derived from Trimethyl Phosphonoacetate with Acetaldehyde

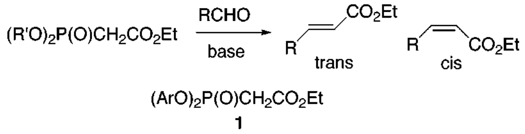
Kaori Ando*

College of Education, University of the Ryukyus, Nishihara-cho, Okinawa 903-0213, Japan

Received June 4, 1999

The mechanism of the Horner−Wadsworth−Emmons (HWE) reaction has been investigated using ab initio calculations (RHF/6-31+G*). This study revealed that the HWE reaction of the lithium enolate derived from trimethyl phosphonoacetate with acetaldehyde occurs with the addition of the lithium enolate to aldehyde, followed by oxaphosphetane formation, pseudorotation, P−C bond cleavage, and then O−C bond cleavage. The oxaphosphetane formation is the rate-determining step both in the gas phase and in the presence of one dimethyl ether molecule. The transition state leading to *trans*-olefin is more stable than the transition state leading to *cis*-olefin. Product selectivity is reproduced by these calculations.

The Horner−Wadsworth−Emmons (HWE) modification of the Wittig reaction is a widely employed method in organic synthesis for the preparation of α,β-unsaturated esters. The phosphonate anions are strongly nucleophilic and react readily with carbonyl compounds under mild conditions to form olefins and water-soluble phosphate esters in high yields. A characteristic feature of the general HWE reaction is the predominant formation of thermodynamically favored *trans*-olefins. Especially high trans selectivity was found in the presence of strongly coordinating counterions such as Li$^+$.[1] On the other hand, several attempts have been made to prepare *cis*-olefins by the choice of cation, temperature, solvent,[2] and special phosphonate reagents[3,4] including our ethyl (diarylphosphono)acetates **1**.[5,6] Although both experimental and computational efforts have been devoted to elucidate the reaction mechanism of the parent Wittig reaction,[7] those of the HWE reaction are scattered[8] and the mechanistic details of the HWE reaction still remain unclear. To define the factors which influence its stereochemistry, we have been studying the mechanism of the HWE reaction by ab initio calculations. We now report our computational results on the HWE reaction of lithium enolate[9] derived from trimethyl phosphonoacetate with acetaldehyde.



Results and Discussion

It is generally accepted that the stereoselectivity of the HWE reaction is a result of both kinetic and thermodynamic control upon the reversible formation of the *erythro* and *threo* adducts and their decomposition to olefins (Scheme 1).[1] That is, a combination of the stereoselectivity in the carbon−carbon bond-forming step and reversibility of the intermediate adducts determine the stereochemistry. The predominant formation of the *trans*-olefins in the case of usual HWE reagents [(dialkylphosphono)acetates] can be explained as a result of the

---

* E-mail: ando@edu.u-ryukyu.ac.jp.

(1) For reviews of the Horner−Wadsworth−Emmons reaction, see: (a) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863−927. (b) Boutagy, J.; Thomas, R. *Chem. Rev.* **1974**, *74*, 87−99.

(2) (a) Wadsworth, D. H.; Schupp, O. E.; Seus, E. J.; Ford, J. A., Jr. *J. Org. Chem.* **1965**, *30*, 680−685. (b) Kinstle, T. H.; Mandanas, B. Y. *J. Chem. Soc., Chem. Commun.* **1968**, 1699−1700. (c) Lefébvre, G.; Seyden-Penne, *J. Chem. Soc., Chem. Commun.* **1970**, 1308−1309. (d) Deschamps, B.; Lampin, J. P.; Mathey, F.; Seyden-Penne, J. *Tetrahedron Lett.* **1977**, 1137−1140. (e) Thompson, S. K.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 3386-3388.

(3) Nagaoka, H.; Kishi, Y. *Tetrahedron* **1981**, *37*, 3873−3888.

(4) (a) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405−4408. (b) Breuer, E. Bannet, D. M. *Tetrahedron Lett.* **1977**, 1141−1144. (c) Patois, C.; Savingnac, P. *Tetrahedron Lett.* **1991**, *32*, 1317−1320. (d) Kokin, K.; Motoyoshiya, J.; Hayashi, S.; Aoyama, H. *Synth. Commun.* **1997**, *27*, 2387−2392. (e) Zhang, T. Y.; O'Toole, J. C.; Dunigan, J. M. *Tetrahedron Lett.* **1998**, *39*, 1461−1464.

(5) (a) Ando, K. *Tetrahedron Lett.* **1995**, *36*, 4105−4108. (b) Ando, K. *J. Org. Chem.* **1997**, *62*, 1934−1939. (c) Ando, K. *J. Org. Chem.* **1998**, *63*, 8411−8416.

(6) For an application of our reagents, see: (a) Ishii, K.; Ohno, H.; Takemoto, Y.; Ibuka, T. *Synlett* **1999**, 228−230. (b) Zhang; T. Y.; O'Toole J. C.; Dunigan, J. M. *Tetrahedron Lett.* **1998**, *39*, 1461−1464. For asymmetric versions of the HWE reaction, see: (c) Abiko, A.; Masamune, S. *Tetrahedron Lett.* **1996**, *37*, 1077−1080. (d) Kreuder, R.; Rein, T.; Reiser, O. *Tetrahedron Lett.* **1997**, *38*, 9035−9038.

(7) (a) For a leading mechanistic review, see; Vedejs, E.; Peterson, M. J. *Top. Stereochem.* **1994**, *21*, 1. Also see ref 1a. (b) Yamataka, H.; Nagase, S. *J. Am. Chem. Soc.* **1998**, *120*, 7530−7536 and references therein. (c) Mari, F.; Lahti, P. M.; McEwen W. E. *J. Am. Chem. Soc.* **1992**, *114*, 813−821.

(8) (a) Brandt, P.; Norrby, P.-O.; Martin, I.; Rein, T. *J. Org. Chem.* **1998**, *63*, 1280−1289. (b) Armstrong, D. R.; Barr, D.; Davidson, M. G.; Hutton, G.; O'Brien, P.; Snaith, R.; Warren, S. *J. Organomet. Chem.* **1997**, *529*, 29−33. (c) Narasaka, K.; Hidai, E., Hayashi, Y.; Gras, J.-L. *J. Chem. Soc., Chem. Commun.* **1993**, 102−104. (d) Wolfgang, Z.; Maarsch, M.; Harms, K.; Haller, F.; Frenking, G.; Boche, G. *Chem. Ber.* **1991**, *124*, 861−866. For a theoretical study of phosphorus-stabilized carbanion, see: (e) Koch, R.; Anders, E. *J. Org. Chem.* **1995**, *60*, 5861−5866. (f) Kranz, M.; Denmark, S. E. *J. Org. Chem.* **1995**, *60*, 5867−5877. (g) Cramer, C. J.; Denmark, S. E.; Miller, P. C.; Dorow, R. L.; Swiss, K. A.; Wilson, S. R. *J. Am. Chem. Soc.* **1994**, *116*, 2437−2447.

(9) Brandt and Rein et al. studied the mechanism of the HWE reaction using the free anion system.[8a] However, we believe that the system containing countercation is very important. Even tertrabutylammonium enolates derived from malonates have a U-shaped structure, just like metal enolates of 1,3-dicarbonyl compounds: Reetz, M. T.; Hütte, S.; Goddard, R. *J. Am. Chem. Soc.* **1993**, *115*, 9339−9340.

10.1021/jo9909150 CCC: $18.00

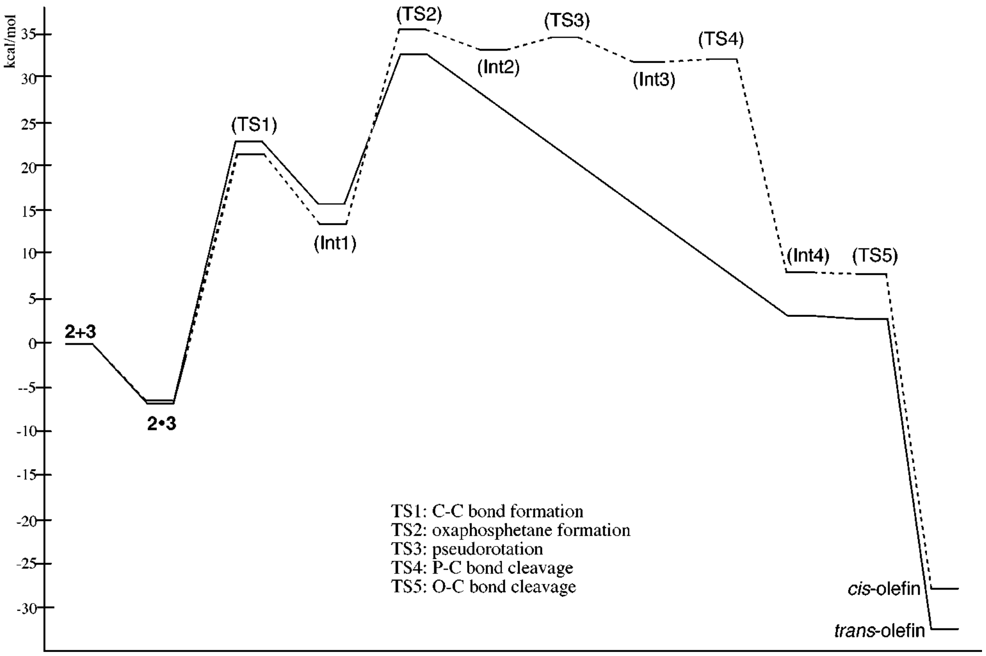
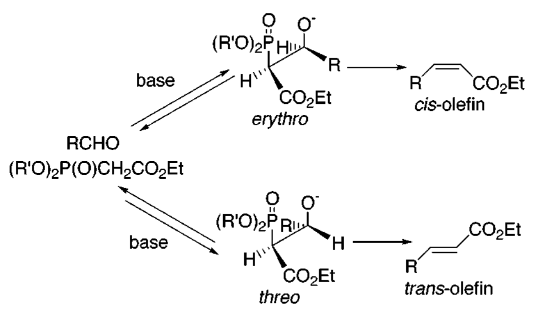


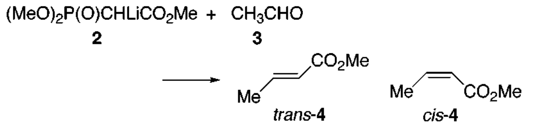
Figure 1. Gibbs free energy profiles of the Horner—Wadsworth—Emmons reaction of **2** and **3** leading to *cis*- and *trans*-olefins (RHF/6-31+G*).

Scheme 1



predominant formation of thermodynamically more stable *threo* adducts. Recently, we have developed new reagents, ethyl (diarylphosphono)acetates **1**, for highly cis selective HWE reaction.[5] We assumed that the electrophilicity of the phosphorus in the intermediate adducts derived from **1** is enhanced due to the electron-withdrawing character of the aryloxy group [Taft's σI value:[10] 0.27 for MeO, 0.38 for PhO]. Therefore, the initial addition of the phosphonate enolate to the aldehyde would be irreversible and determine the stereochemistry of olefins. With the above assumption derived from the experimental results in our mind, we started computational investigation about the reaction pass of usual (trans selective) HWE reaction.

The reaction of lithium enolate derived from trimethyl phosphonoacetate **2** with acetaldehyde (**3**) was chosen as a model system. Our main interest is the origin of the stereochemistry of the product olefin. The reaction pass was first followed using ab initio RHF (restricted Hartree—Fock) calculations with the 3-21+G basis set incorporated in the GAUSSIAN 94 program.[11] All the reaction intermediates and transition structures were reoptimized by RHF/6-31+G*,[12] and those energies were calculated by the B3LYP hybrid functional[13] together with the 6-31+G* basis set. Vibrational frequency calculations (RHF/6-31+G*) gave only one imaginary frequency for all transition structures and confirmed that those structures are authentic transition structures.



Gas-Phase Energy Surfaces. The reaction energy profiles (relative to the starting materials **2** + **3**) of the HWE reaction leading to *cis*- and *trans*-olefins are shown in Figure 1 (RHF/6-31+G*). The electronic energies and Gibbs free energies of all intermediates and all transition states are also tabulated in Table 1 along with the electronic energies at the B3LYP/6-31+G*//RHF/6-31+G* level. Gibbs free energies are the values at 298.15 K and 1.00 atm obtained from frequency calculations. Complexation between the lithium enolate **2** and aldehyde **3** occurs spontaneously to give **5a**—**5d** (Figure 2). A hydrogen of aldehyde forms a hydrogen bond to an oxygen of the phosphonate enolate in these four complexes. At the RHF/6-31+G* level, there is a small preference for the hydrogen bond containing the aldehyde hydrogen rather

---

[10] Brownlee, R. T.; Taft, R. W. *Prog. Phys. Org. Chem.* **1973**, *10*, 1.

[11] 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.; Binskley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. P.; Head-Gordon, M.; Gonzalez, C.; Pople. J. A. *GAUSSIAN 94*, Revision D.3; Gaussian, Inc.: Pittsburgh, PA, 1995.

[12] Diffuse functions allow orbitals to occupy a larger region of space. Basis sets with diffuse functions are important for systems where electrons are relatively far from the nucleus: anions, molecules with lone pairs, and so on.

[13] (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648—5652. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785—789. For reviews of density-functional methods see: (c) Ziegler, T. *Chem. Rev.* **1991**, *91*, 651. (d) *Density Functional Methods in Chemistry*; Labanowski, J., Andzelm, J., Eds.; Springer; Berlin, 1991. (e) Parr, R. G.; Yang, Y. *Density-Functional Theory of Atoms and Molecules*; Oxford University Press: New York, 1989.

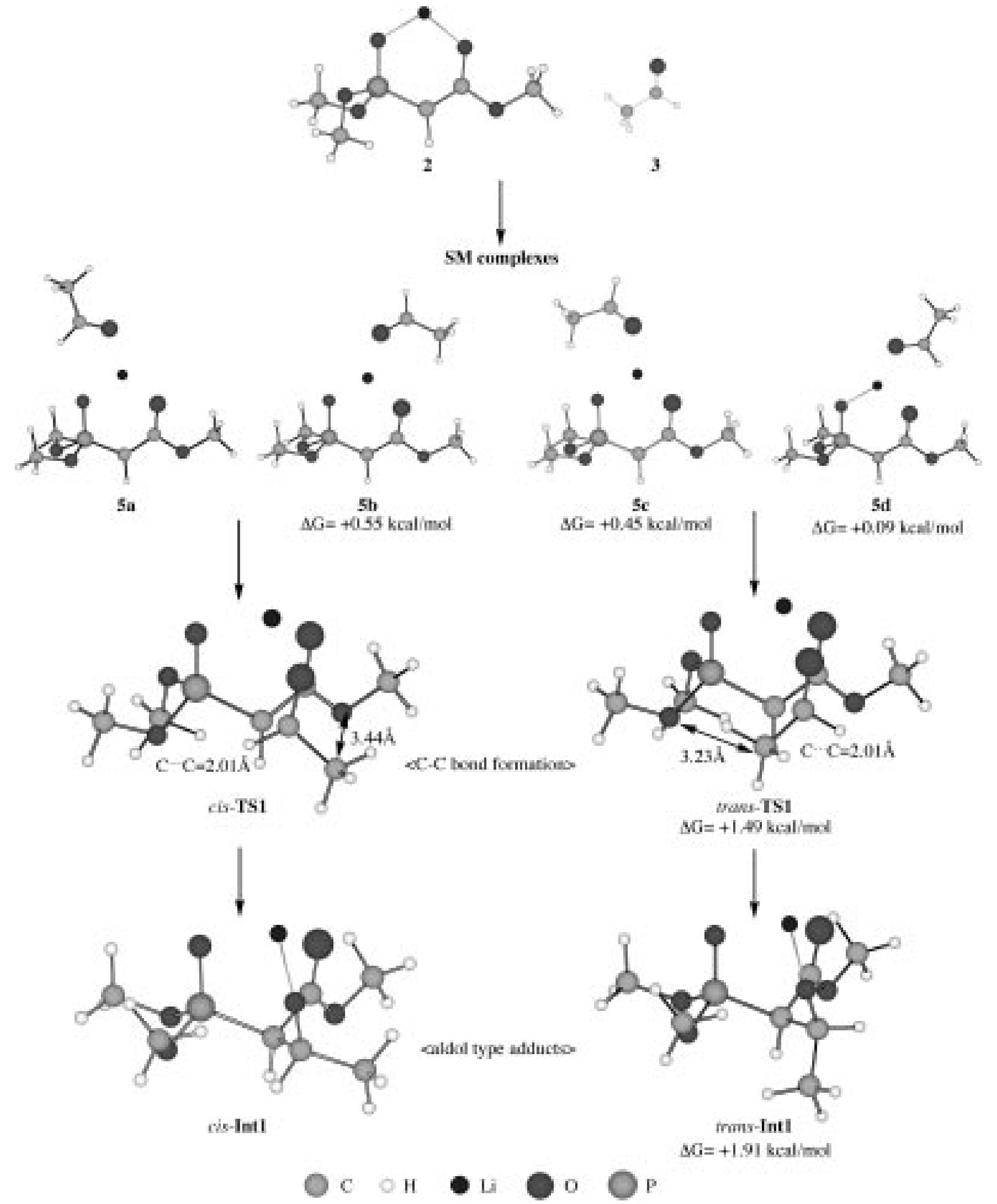


Figure 2. The reaction paths of the Horner−Wadsworth−Emmons reaction between the lithium phosphonate enolate **2** with acetaldehyde (RHF/6-31+G*): complexation and the C−C bond forming process.

Table 1. Relative Energies of All the Intermediates and Transition States in the Reaction of 2 and 3 (kcal/mol)

computational level	SM complex	**TS1**	**Int1**	**TS2**	**Int2**	**TS3**	**Int3**	**TS4**	**Int4**	**TS5**	**TM**
RHF/6-31+G*/cis	−18.01 −17.46	+6.30	−4.28	+16.66	+15.62	+15.67	+14.09	+14.18	-7.22	-6.90	-39.30
RHF/6-31+G*/trans	−17.93 −17.56	+7.79	−2.37	+14.46					−11.79	-11.28	-44.85
B3LYP/6-31+G*//6-31+G*/cis	−17.69 −17.34	−2.25	−7.87	+8.66	+7.90	+7.50	+5.98	+5.74	-7.98	-9.72	-36.71
B3LYP/6-31+G*//6-31+G*/trans	−17.39 −17.52	−0.78	−6.11	+6.43					−12.13	-14.01	-41.76
Gibbs Free Energies											
RHF/6-31+G*/cis	−7.28	+21.76	+13.56	+35.43	+33.51	+34.95	+32.29	+32.41	+7.90	+7.82	-27.98
RHF/6-31+G*/trans	−7.16	+23.12	+15.59	+33.27					+3.43	+3.33	-32.41

than the hydrogen of the methyl group. The complexes **5a** and **5b** give the *erythro* adduct (*cis*-**Int1**) via *cis*-**TS1**, and the complexes **5c** and **5d** give the *threo* adduct (*trans*-**Int1**) via *trans*-**TS1**. In the transition states of the nucleophilic addition to the carbonyl group of aldehyde with the phosphonate enolate, *cis*-**TS1** is more stable

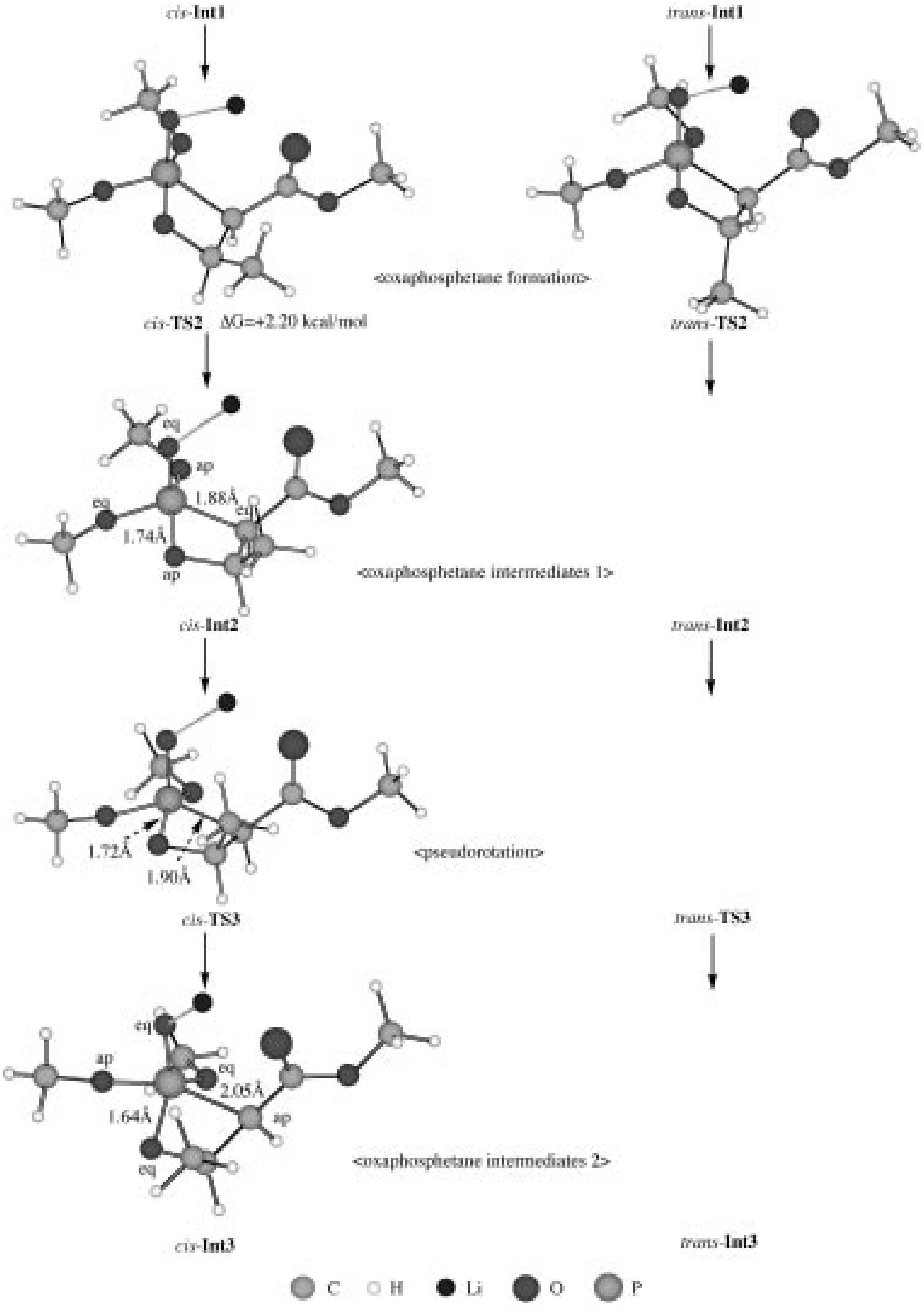


Figure 3. The reaction paths of the Horner–Wadsworth–Emmons reaction between the lithium phosphonate enolate **2** with acetaldehyde (RHF/6-31+G*): oxaphosphetane formation and pseudorotation processes.

than *trans*-**TS1** by 1.49 kcal/mol. In *trans*-**TS1**, there is a repulsive interaction between the phosphonate moiety and the methyl substituent of aldehyde. As shown in Figure 2, the distance between O and CH_3 is 3.23 Å, which is less than the sum of their van der Waals radii (3.4 Å). The distances of the forming bonds are both 2.01 Å in *cis*- and *trans*-**TS1**. Also the intermediate, *cis*-**Int1** is more stable than *trans*-**Int1** by 1.91 kcal/mol. Thus, the formation of *cis*-**Int1** is favored over the formation of *trans*-**Int1**.

The transition state for the oxaphosphetane formation favors *trans*-**TS2** over *cis*-**TS2** by 2.16 kcal/mol (Figure 3). This energy difference could be derived from the steric repulsion between the ester moiety and the alkyl substituent of aldehyde. As shown in Figure 1, the rate-determining transition state for the HWE reaction is **TS2**. Therefore, the *trans*-olefin is the product of choice, in accord with the experimental observations. The oxaphosphetane intermediates are not stable intermediates and easily undergo pseudorotation around the phosphorus atom. Pseudorotation of *cis*-**Int2**, which requires an activation free energy of only 1.44 kcal/mol, produces a slightly more stable oxaphosphetane intermediate, *cis*-**Int3**. During the pseudorotation, the P–C distance

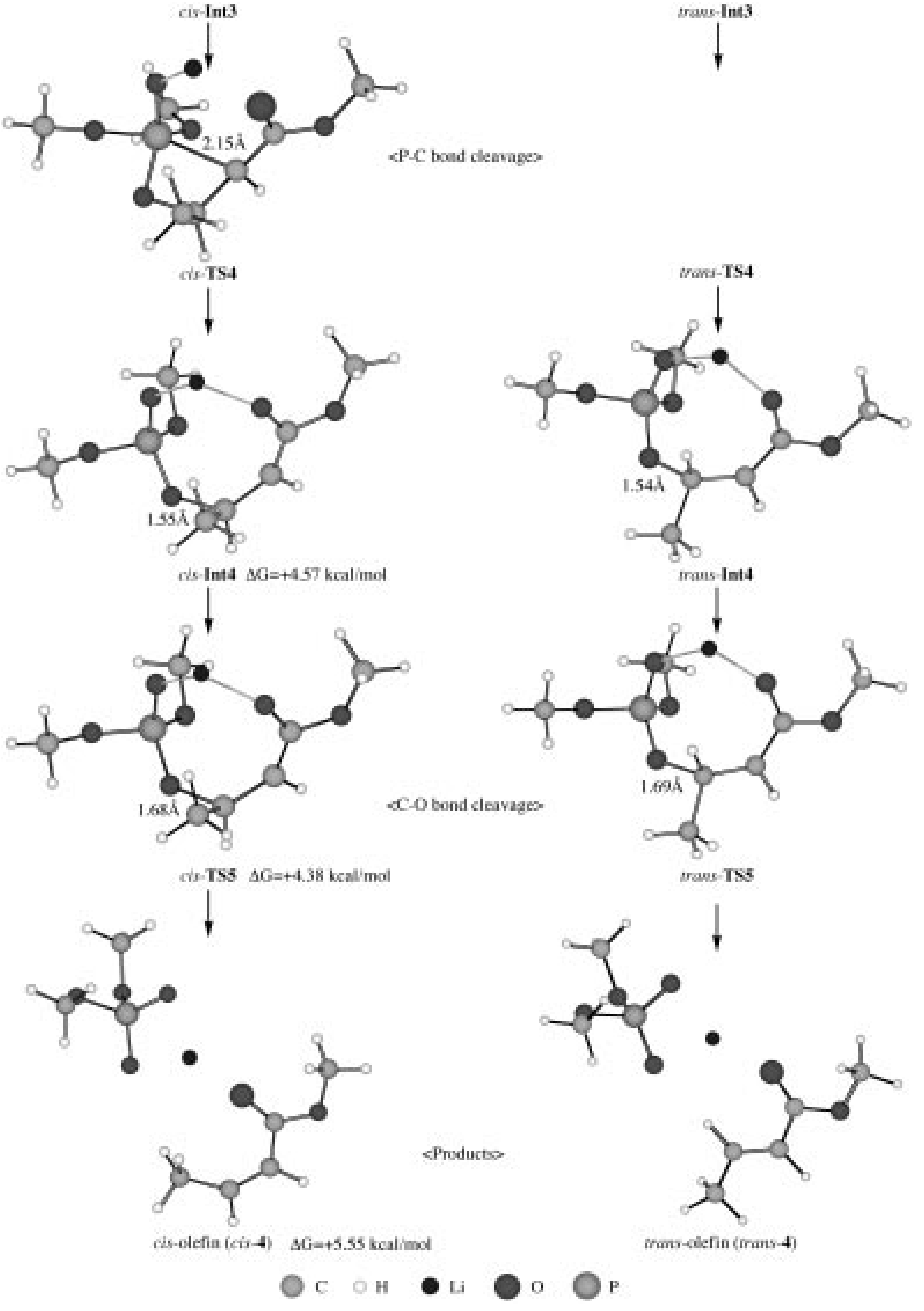


Figure 4. The reactions paths of the Horner−Wadsworth−Emmons reaction between the lithium phosphonate enolate **2** with acetaldehyde (RHF/6-31+G*): P−C bond cleavage and C−O bond cleaveage processes.

increases from 1.88 Å (*cis*-**Int2**) to 2.05 Å (*cis*-**Int3**), while the P−O (aldehyde oxygen) distance decreases from 1.74 Å (*cis*-**Int2**) to 1.64 Å (*cis*-**Int3**). The alkoxide ion of *cis*-**Int1** (aldehyde oxygen) attacks the phosphorus atom from the apical direction with the carbon group equatorial to yield *cis*-**Int2**. The pseudorotation of the latter gives *cis*-**Int3** with the carbon group in the apical position and the oxygen group (aldehyde oxygen) in the equatorial position. The intermediate *cis*-**Int3** undergoes cleavage of the P−C bond to yield *cis*-**Int4** (Figure 4). Cleavage of the P−C bond in *cis*-**Int3** is also quite an easy process, which requires an activation energy of only 0.12 kcal/mol. The involvement of P−C bond cleavage of the oxaphosphetane intermediate to form a "stable" enolate has been suggested before.[14] On the other hand, the trans series does not yield any stable oxaphosphetane intermediate, and the optimization starting from *trans*-**TS2**

---

[14] (a) Bestmann, H. J. *Pure Appl. Chem.* **1979**, *51*, 515−533. (b) Sturtz, G. *Bull. Soc. Chim. Fr.* **1964**, 2349−2357.

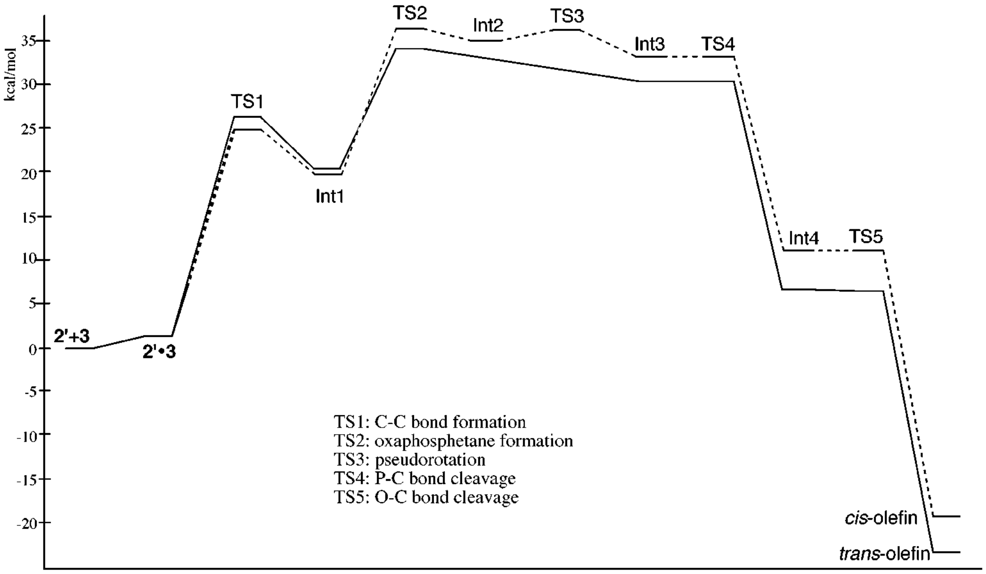


Figure 5. Gibbs free energy profiles of the Horner–Wadsworth–Emmons reaction of **2′** (**2**·MeOMe) and **3** leading to *cis*- and *trans*-olefins (RHF/6-31+G*).

Table 2. Relative Energies of All the Intermediates and Transition States in the Reaction of 2·MeOMe and 3 (kcal/mol)

computational level	SM complex	**TS1**	**Int1**	**TS2**	**Int2**	**TS3**	**Int3**	**TS4**	**Int4**	**TS5**	**TM**
RHF/6-31+G*/cis	−8.49	+10.04	+3.25	+17.49	+16.52	+16.65	+15.21	+15.50	-4.43	-4.03	-31.93
RHF/6-31+G*/trans	−8.49	+11.36	+3.46	+15.40			+12.05	+12.13	-8.87	-8.30	-36.43
B3LYP/6-31+G*//6-31+G*/cis	−7.74	+1.73	+0.89	+9.60	+8.76	+8.43	+7.16	+7.30	-5.01	-6.83	-28.83
B3LYP/6-31+G*//6-31+G*/trans	−7.74	+3.33	+0.99	+7.44			+4.21	+4.07	-9.12	-11.00	-32.99
Gibbs Free Energies											
RHF/6-31+G*/cis	+1.45	+25.00	+19.98	+36.47	+34.99	+36.39	+33.67	+33.64	+11.25	+11.27	-19.26
RHF/6-31+G*/trans	+1.45	+26.29	+20.39	+34.32			+30.17	+30.18	+6.84	+6.76	-23.43

Table 3. Relative Energies of TS1, Int1, and TS2 in the Reaction of 2·2MeOMe and 3 (kcal/mol)

computational level	**TS1**	**Int1**	**TS2**
RHF/6-31+G*/cis	+9.69	0.00	+11.62
RHF/6-31+G*/trans	+11.94	+0.38	+10.43
B3LYP/6-31+G*//6-31+G*/cis	+4.87	0.00	+6.92
B3LYP/6-31+G*//6-31+G*/trans	+7.15	+0.64	+4.87
Gibbs Free Energies			
RHF/6-31+G*/*cis*	+7.07	0.00	+14.54
RHF/6-31+G*/trans	+8.98	+0.05	+13.04

affords directly *trans*-**Int4** via oxaphosphetane formation, pseudorotation, and P–C bond cleavage. *trans*-**Int4** is more stable than *cis*-**Int4** by 4.47 kcal/mol.

Although the cleavage of the C–O bond of **Int4** (β-elimination of the enolate anions) has transition states (**TS5**) on the basis of electronic energies, it occurs spontaneously on the basis of Gibbs free energies to yield the olefin products, *cis*- and *trans*-**4**. The transition state, *trans*-**TS5**, and the product, *trans*-**4** are more stable than *cis*-**TS5** and *cis*-**4** by 4.38 and 5.55 kcal/mol, respectively.

These calculations indicate that the HWE reaction occurs with the addition of the phosphonate enolate to the aldehyde, followed by oxaphosphetane formation, pseudorotation, P–C bond cleavage, and then O–C bond cleavage. The oxaphosphetane formation is the rate-determining step, in which the transition state leading to *trans*-olefin is 2.16 kcal/mol lower in energy than that leading to *cis*-olefin (RHF/6-31+G*). The electronic energy differences between *cis*-**TS2** and *trans*-**TS2** are 2.20 and 2.23 kcal/mol at RHF/6-31+G* and B3LYP/6-31+G*//RHF/6-31+G*, respectively. The biggest difference between electronic energies at RHF/6-31+G* and at B3LYP/6-31+G*//RHF/6-31+G* levels is that **TS1**–**TS4**, **Int2**, and **Int3** have lower energies at B3LYP than at RHF by about 8 kcal/mol. General trend and energy differences between the trans and cis series are similar. Thus, the usual preference for *trans*-olefins in the HWE reaction of (dialkylphosphono)acetate reagents is reproduced by our calculations. Since the addition to aldehyde favors the formation of *cis*-**Int1** over *trans*-**Int1**, the observed predominance of *trans*-olefins in the HWE reaction is attributed to a reversible addition step followed by a slow oxaphosphetane formation reaction.

The Effects of Solvation to Lithium Cation. Generally, trans selective HWE reaction is performed in a mildly coordinating solvent such as tetrahydrofuran, diethyl ether, toluene, and acetonitrile. To simulate the reaction path properly, it is indispensable to consider the effect of solvated lithium cation. We chose dimethyl ether as a coordinating solvent.[15,16] The reaction energy profiles (relative to the starting materials **2**·MeOMe + **3**) of the HWE reaction leading to *cis*- and *trans*-olefins are shown in Figure 5. The electronic energies and Gibbs free energies are tabulated in Table 2. The obtained reaction energy profile is similar to the one in the gas phase. That is, *cis*-**TS1** is favored over *trans*-**TS1** by 1.29 kcal/mol, and *trans*-**TS2** is favored over *cis*-**TS2** by 2.15 kcal/mol.

---

(15) (a) More, M. B.; Glendening, E. D.; Ray, D.; Feller, D.; Armentrout, P. B. *J. Phys. Chem.* **1996**, *100*, 1605–1614. (b) Abbotto, A.; Streitwieser, A.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1997**, *119*, 11255–11268. (b) Ando, K.; Houk, K. N.; Busch, J.; Menassé, A.; Séquin, U. *J. Org. Chem.* **1998**, *63*, 1761–1766.

(16) Although the lithium enolates exist as aggregates in solution, a monomeric species is the reactive intermediate at least in some cases: Abbotto, A.; Streitwieser, A. *J. Am. Chem. Soc.* **1995**, *117*, 6358–6359.

Table 4. Gibbs Free Energies (hartrees) and the Solvation Energies (kcal/mol) by Dimethyl Ether Molecule (RHF/6-31+G*)

	TS1	TS1+MeOMe	TS1+2MeOMe	Int1	Int1+MeOMe	Int1+2MeOMe	TS2	TS2+MeOMe	TS2+2MeOMe
cis	−1070.534609	−1224.551603	−1378.548610	-1070.547668	-1224.559600	-1378.559881	-1070.512823	-1224.533335	-1378.541477
solvation		−5.55	+6.99		−2.38	+2.55		-7.76	+2.99
trans	-−1070.532440	−1224.549546	−1378.545574	-1070.544439	-1224.558959	-1378.559802	-1070.516265	-1224.536753	-1378.539106
solvation		−5.62	+7.60		−4.00	+4.58		-7.75	+3.63

[a] MeOMe: $G = -154.008142$ hartrees.

In addition, the general trends depending on the computational level are similar to the results in the gas phase. Since the rate-determining step is **TS2**, *trans*-olefin is obtained predominantly. In the presence of one dimethyl ether molecule, the energy difference between **TS1** and **TS2** is 11.47 and 8.03 kcal/mol for the cis and trans series, respectively. On the other hand, it is 13.67 and 10.15 kcal/mol in the gas phase for the cis and trans series, respectively. These data show that **TS2** is more stabilized by solvation than **TS1**. The lithium takes tricoordination in **TS2**, while it takes tetracoordination in **TS1** in the presence of one dimethyl ether molecule. Therefore, we further investigated the effect of an additional coordinating dimethyl ether molecule. The electronic energies and Gibbs free energies of **TS1**, **Int1**, and **TS2** are tabulated in Table 3. *cis*-**TS1** is favored over *trans*-**TS1** by 1.91 kcal/mol, and *trans*-**TS2** is favored over *cis*-**TS2** by 1.50 kcal/mol. Since the rate-determining step is **TS2**, *trans*-olefin is the product of choice. In the presence of two dimethyl ether molecules, the energy difference between **TS1** and **TS2** is 7.47 and 4.06 kcal/mol for the cis and trans series, respectively. The solvation energies of **TS1**, **Int1**, and **TS2** by one or two dimethyl ether molecule(s) are shown in Table 4. Although **TS2** is still more stabilized by solvation than **TS1**, the second solvation values are all positive. That is, the second molecule of solvent does not provide any net stabilization in Gibbs free energy. It is experimentally known that lithium sometimes does not reach tetracoordination with external ligands especially in the sterically crowded environment.[17]

Conclusions

The above calculations indicate that the HWE reaction occurs with the addition of the phosphonate enolate to the aldehyde, followed by oxaphosphetane formation, pseudorotation, P−C bond cleavage, and then O−C bond cleavage. The oxaphosphetane formation is the rate-determining step, in which the transition state leading to *trans*-olefin is 2.16 kcal/mol lower in energy than that leading to *cis*-olefin (RHF/6-31+G*) in the gas phase. This energy difference corresponds to a product ratio of 97.5:2.5 at 298.15 K (calculated from the equation $k_1/k_2 = e^{-\Delta G(\mathrm{calcd})/RT}$), which is of the same order of magnitude as the experimental results. In the presence of one dimethyl ether molecule, *cis*-**TS1** is favored over *trans*-**TS1** by 1.29 kcal/mol and *trans*-**TS2** is favored over *cis*-**TS2** by 2.15 kcal/mol. The second solvation also did not change general trend and energy differences between the trans and cis series. Thus, the usual preference for *trans*-olefins in the HWE reaction of (dialkylphosphono)acetate reagents is reproduced by our calculations.

Further efforts to elucidate the origin of the stereochemical variation (the trans/cis selectivity) depending on the phosphonate reagents are presently under active investigation in our laboratory.

Acknowledgment. This work was supported by the Research Foundation for Pharmaceutical Sciences and by the Grant-in-Aid from the Ministry of Education, Science, Sports and Culture, of the Japanese Government. We are grateful to the Computer Center of the Institute for Molecular Science, for the use of the NEC SX5 computer. We thank Professor Hiroshi Yamataka for helpful discussions.

JO9909150

---

(17) Jackman, L. M.; Lange, B. C. *Tetrahedron* **1977**, *33*, 2737−2769. Luch, B. L.; Collum, D. B. *J. Am. Chem. Soc.* **1994**, *116*, 6009−6010. Hitchcock, P. B.; Lappert, M. F.; Layh, M. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 501−504.