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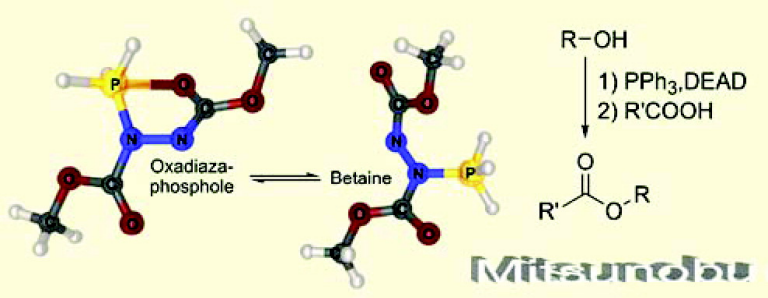

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Density Functional Investigation of the Mitsunobu Reaction

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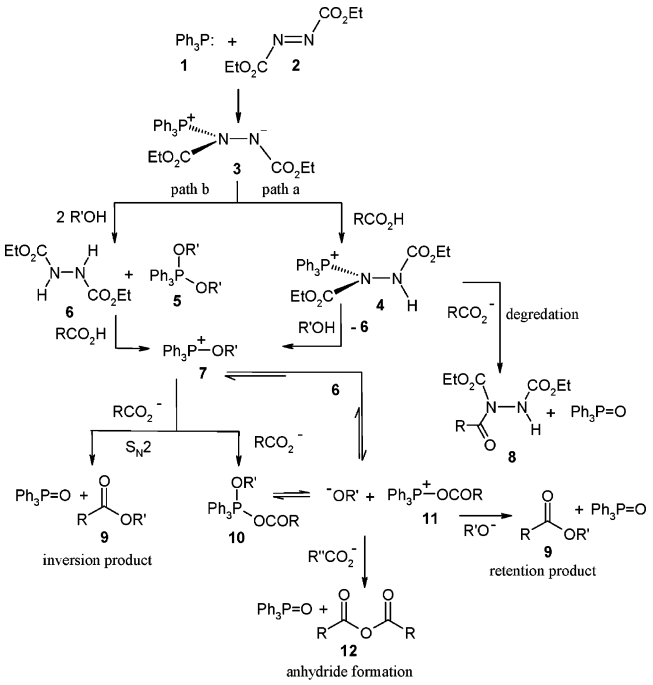
Abstract: In this article we performed an extensive density functional [BP86/6-311++G(3df,3pd) level] investigation of the hypersurface of the Mitsunobu reaction. Reaction of a phosphine with a dialkyl azodicarboxylate (first step in the Mitsunobu conversion) leads to either a five-membered oxadiazaphosphole ring (more stable) or a betaine. The subsequent formation of two stable intermediates, a dialkoxyphosphorane and an acyloxyalkoxyphosphorane, constitutes the second step in the mechanism. These intermediates are in equilibrium with each other (under exchange of alkoxy and acyloxy ligands), and both can undergo an acid-induced decomposition to yield the alkoxy- and/or acyloxyphosphonium salts. The alkoxyphosphonium salt generates the desired ester via a S_N2 mechanism (inversion product). Alternatively, the phosphorus atom in a mixed acyloxyalkoxyphosphorane species can easily undergo Berry pseudorotation. A subsequent intramolecular substitution leads to the final ester via a retention mechanism. The hypersurface is much more complicated than previously assumed, and the Mitsunobu reaction is fundamentally capable of running under either inversion or retention. The possibility of selective stereocontrol is discussed. Side reactions include the formation of a degradation product and an anhydride.

Introduction

The Mitsunobu reaction,[1,2] an efficient esterification method using very mild reaction conditions (usually Ph_3P, $EtO_2CN{=}NCO_2Et$, RCO_2H, and an alcohol R′OH), allows the stereoselective modification of an alcohol moiety in functionally complex and/or highly thermosensitive compounds and, as such, has been quite successfully employed in the total synthesis and modification of numerous natural compounds. Generally, the reaction is highly stereoselective under inversion of the configuration at the carbon bearing the alcohol functionality. This procedure has thus become quite popular for refunctionalizing and inverting the configuration of optically active alcohols.

Scheme 1 shows the mechanism of the Mitsunobu reaction to the extent it is understood at present and is exclusively based upon experimental evidence.[3−28] The reaction begins with the nucleophilic attack of a phosphine **1** (most often Ph_3P) on the N=N double bond of an azodicarboxylate **2** (usually $EtO_2CN{=}NCO_2Et$).[3] This first step has been shown to be irreversible[4]

Scheme 1. Postulated Mechanisms of the Mitsunobu Reaction



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and results in a relatively stable betaine intermediate **3**.[4] In a few cases a low concentration of a persistent radical cation accompanying the formation of **3** has been reported which does not seem to be directly involved in the reaction.[5] A modification of the Mitsunobu procedure at this point by simply adding a dialkyl phosphite and alcohol to the betaine **3** allows the convenient synthesis of $(RO)_3P$.[6]

The mechanism of the second step is still partially unclear and a topic of controversy in the literature.[7] It is evident that the betaine **3** can react via at least two different competing pathways.[7−10] In path a the betaine **3** is protonated to form **4**.[8] Experimental evidence for such a protonated betaine has recently been provided by Swamy et al., who managed to crystallize a compound whose structure is very similar to **4**.[9]

Compound **4** decomposes upon addition of an equivalent of alcohol to generate a hydrazine **6** and an alkoxyphosphonium salt **7**.[10] These alkoxyphosphonium salts can be independently synthesized,[11,12] are sometimes stable enough to isolate, and can be employed as alkylating reagents.[12] It is even possible to completely bypass the use of PPh_3 and **2** in the Mitsunobu procedure by employing the Hendrickson reagent[13] [$(Ph_3P^+)_2O$, $2OTf^-$] which directly generates **7**.[14]

In the competing path b the betaine **3** first reacts with two equivalents of alcohol to generate a dialkoxyphosphorane **5** and a hydrazine **6.**[7,8] An acid-induced decomposition of **5** then yields the oxyphosphonium salt **7** under regeneration of one equivalent of alcohol. Regardless of the pathway followed, a hydrazine **6** is a byproduct of the reaction. Quite some work indicates that the reaction conditions, especially the order in which the follow-up reagents (alcohol and acid) are added, help determine which pathway dominates.[8,15] Other studies indicate that both pathways are in equilibrium with each other regardless of the order of reagent addition.[7,16]

The nature (especially the pK_a value) of the carboxylic acid employed in the last step of the Mitsunobu reaction has a profound influence on the product yield.[17] This has been traced to a competition between the carboxylate anion and the alcohol for **4**. With acids stronger than acetic acid, such as 4-nitrobenzoic acid, this degradation side reaction can be suppressed.[18] Unfortunately, this also slows down the last step in the Mitsunobu reaction since the carboxylate must remain nucleophilic enough to react with **7,** thus placing an upper limit on the pK_a of acids that can be employed.

In the final step of the Mitsunobu reaction the alkoxyphosphonium salt **7** undergoes a substitution reaction with a carboxylate ion to form phosphine oxide and the desired ester **9**. To explain the second-order kinetics observed for this reaction step as well as the large excess of *inversion* product obtained, a S_N2 attack by the carboxylate ion on the C−O bond of the activated alcohol has been postulated.[1]

If the alcohol is sterically hindered and a very weak organic acid is employed, the Mitsunobu procedure can be diverted into an anhydride channel at this point.[19] The carboxylate anion present in the reaction medium competes with the alcohol for **7,** and an acyloxyalkoxyphosphorane **10** is generated. Species **10** is in equilibrium with yet another acyloxyphosphonium salt **11** as evidenced by ^{31}P NMR experiments.[16b,20] Such salts **11** can be independently generated and trapped.[21,22] A nucleophilic attack by a carboxylate anion on **11** then leads to the anhydride **12**.[19]

Retention of configuration in the Mitsunobu procedure has been rarely reported and almost always been attributed to large mechanistic deviations. Allylic alcohols sometimes undergo S_N2' or S_N1 processes leading to racemization of the alcohol or partial retention.[23] Intramolecular neighboring group participation can also lead in certain cases to retention of configuration.[24] However, more recently, several independent studies have reported the isolation of retention products from sterically hindered chiral secondary alcohols.[25,26] In the lactonization of a series of hindered alcohols, an equilibrium between **7** and **11** occurs and, due to steric congestion, **11** is favored over **7**.[26] Interestingly enough, this led to *retention* of the configuration of the alcohol, which is thought to originate from attack of the alcohol on the carbonyl carbon of the acyloxyphosphonium salt **11**.[16b,20,22,26,27]

Quite recently McNulty et al. succeeded in synthesizing a series of trialkylphosphoranes which, when applied in a Mitsunobu-like procedure with careful control of the reaction conditions, allows the acyloxyphosphonium salts **11** to be stabilized. They confirmed that this results in a preference for the retention product with chiral secondary alcohols.[22,28] Fur-

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thermore, they discovered that addition of a base to **11** triggers a base-mediated crossover to **7**.[22] Under normal Mitsunobu conditions the hydrazine **6** is usually basic enough to induce this crossover.

Despite the widespread application of the Mitsunobu procedure for solving problems in organic synthesis, computational studies dealing with the mechanism of this reaction have, to the best of our knowledge, not yet been reported in the literature. Using the mechanism depicted in Scheme 1 as a starting point we therefore carried out an extensive density functional investigation in order to contribute to a better understanding of the Mitsunobu reaction.

Computational Details

The hypersurface of the Mitsunobu reaction was investigated at the BP86/6-311+G(d,p) level, and all stationary points found were reoptimized at the higher BP86/6-311++G(3df, 3pd)[29] level. Triphenylphosphine was approximated with PH_3. The ethyl groups in $EtO_2CN{=}NCO_2Et$ were replaced with methyl. Methanol and acetic acid were used as the alcoholic and acidic components, respectively. Full geometry optimizations, i.e., without constraints, as well as frequency calculations on the stationary points thus obtained were performed for all species on the (Mitsunobu) hypersurface in the gas phase as well as in the presence of a dielectric field as described by the C-PCM (COSMO) model.[30] In this model the species of interest are embedded in a cavity of molecular shape surrounded by a polarizable continuum whose field modifies the energy and physical properties of the solute. The solvent reaction field is described by polarization charges distributed on the cavity surface. This procedure is known to reproduce experimental hydration energies quite well.[30] We chose $\epsilon = 36.64$ for the dielectric field [corresponds to acetonitrile, which is halfway between the gas phase ($\epsilon = 1$) and water ($\epsilon = 78.39$)]. Many Mitsunobu reactions are carried out in solvents of middle polarity due to insolubility problems in water itself.

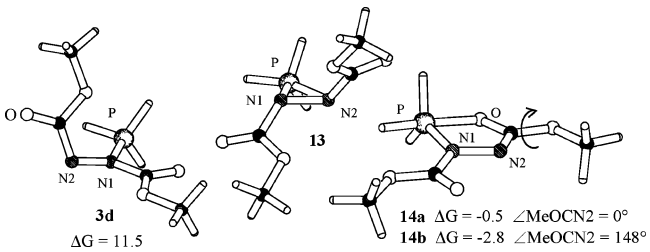
To roughly estimate the electronic effect of the substituents on phosphorus, we reoptimized the transition states for inversion and retention under variation of the substituents at phosphorus: H_2MeP, HMe_2P, and Me_3P [BP86/6-311++G(3df,3pd) level of theory] as well as Ph_3P (BP86/6-311+G(d,p) basis except for the phenyl substituents for which the 6-31G(d) basis was employed]). These calculations were also performed in an acetonitrile solvent field and compared to the results obtained for H_3P.

All optimizations and frequency calculations reported in this article were performed using either the Gaussian98[31] or the Gaussian03[32] program package. Atomic charges and hyperconjugative interaction energies were obtained using version 5.0 of the natural bond orbital (NBO) analysis of Weinhold et al.[33] as patched into Gaussian98.[31] Default convergence criteria were used for all calculations. All energies reported are Gibb's free energies (ΔG values) and thus contain zero-point, thermal, and entropy effects at 298 K and 1 atm pressure.

Results and Discussion

Reaction of the Diazene with Phosphine. Interested readers are referred at this point to the Supporting Information in which the energetic and structural properties of carbonyl-substituted diazenes in general are investigated and discussed. Addition of PH_3 to the double bond of a diazene (modeled in this study by $MeO_2CN{=}NCO_2Me$, **2d**) readily occurs. The hypersurface is extremely flat, and when PH_3 "sees" the N=N double bond (electrostatic contact), it spontaneously adds. We did not succeed in cleanly locating transition structures for this attack in either the gas phase or solution. In any case, the barrier to addition is less than 3 kcal/mol, which corresponds quite well with the observed experimental irreversibility[4] of this step. Depending on the initial orientation of PH_3 to **2d**, one of three possible intermediates was formed—the expected betaine **3d**, a diazaphosphoridine **13,** or an oxadiazaphosphole **14** (Chart 1).

Chart 1. Possible Intermediates for the First Step in the Mitsunobu Reaction[a]



[a] ΔG(acetonitrile) values (kcal/mol) are given relative to the educts (**2d** and PH_3). Intermediate **13** is unstable in solution.

The most stable structure is the five-membered heterocycle **14** for which two conformations exist (**a**/**b**) which differ only in the MeOCN dihedral angle. In solution, **14b** is slightly more stable ($\Delta G = -2.8$ kcal/mol) than **14a** (−0.5 kcal/mol). The rotational barrier about the central C−O bond is quite small (<4 kcal/mol). In accord with Westheimer's rules,[34] the ring oxygen in **14** occupies an apical position and the nitrogen an equatorial position. Oxadiazaphospholes **14** are known compounds that can be independently synthesized and, in the absence of heat and acids, isolated.[35,36] Recent work by Swamy et al. has shown that oxygen does not necessarily always occupy an apical position; solid-state structures of oxadiazaphospholes and related compounds have been obtained with an apical nitrogen and equatorial oxygen.[9,36] They postulate that this "reversed apicophilicity" may be relevant for stable intermediates in Mitsunobu-type reactions.[36] In addition, some spirophosphoranes also contain an equatorial oxygen and an apical carbon bond (*anti*-Westheimer conformation).[37]

In the following discussion of the Mitsunobu hypersurface we explicitly considered both possibilities; in each case we discuss the most stable intermediate as being relevant since the activation energy of Berry pseudorotation[38] for trigonal bipyramidal phosphorus is extremely low and does not present a significant barrier for further reaction.[39] In the case of **14**, the

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conformation with "reversed apicophilicity" (apical N; not illustrated) corresponds to a transition structure for pseudorotation.

The three-membered ring **13** is only stable in the gas phase. In solution, this conformer is a transition structure for the transfer of the phosphorus substituent from one nitrogen to the other and spontaneously opens to the betaine **3d** upon optimization in the moderately polar acetonitrile. This is in accord with ^{31}P NMR experiments, which have postulated a three-membered ring to be a transient species at low temperatures.[40]

As compared to the formation of **14** (slightly exothermic in solution), reaction of PH_3 and **2d** to form **3d** is an endothermic reaction which costs 11.5 kcal/mol. These computational results are in direct contrast with the fact that the betaine **3d** is usually observed in solution.[4,7] The reason for the thermodynamic preference of **14** seems to be the presence of the additional P−O contact; all other structural and electronic properties in the betainic form, although slightly less polarized, are very similar to those calculated for **14**. This could be a consequence of employing PH_3 as a model for PPh_3. As pointed out by one of the referees, three phenyl ligands on phosphorus can be expected to stabilize the betaine form **3d** relative to the five-membered ring **14**. Although the five-membered ring is clearly thermodynamically more stable than the betaine, the calculations on the simple model system show that **14** is kinetically unstable toward protonation as we will discuss below. This is not unusual since heat and acid sensitivity of similar five-membered heterocycles **14** is well documented in the chemical literature.[35,36,41] Under experimental conditions the intermediate formed (betaine or ring) can be expected to be strongly dependent on the identity of the ligands attached to phosphorus and/or the substitution pattern on the diazene.

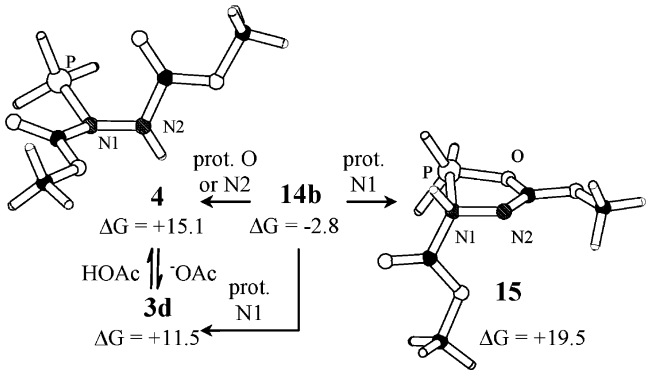
Regardless of which intermediate (**3d**/**14**) is generated, the addition of PH_3 to **2d** has several very large electronic consequences (Table S3 in the Supporting Information provides numerical data)—the neutral phosphorus atom in PH_3 has become positively charged, thus enabling it to easily undergo subsequent nucleophilic attack, e.g., by alcohols. At the same time the N−N functionality has been differentially polarized and both nitrogen atoms now bear a considerably higher negative charge than in **2d**. In addition, the lone pair orbitals on nitrogen (needed to abstract a proton from an organic acid) have been destabilized in both **3d** and **14b**. This is especially evident for the lone pair orbital on N1 in **14b**. As a consequence, the basicity of the N−N functionality is increased and one would expect the N1 atom in **14b** and the N2 atom in **3d** (in this case, the lone pair on N1 is involved in an imine-type mesomeric stabilization) to be easily protonated by an organic acid. Both compounds are also capable of protonation at oxygen as reaction of the diazene with the phosphine also results in destabilization of the p-type lone pair orbital at the ring oxygen in **14b** and the carbonyl oxygen of the ester group bound to N2 in **3d**. This functional duality opens up two fundamentally different pathways for further reaction—an acid−base interaction with an organic acid (both N- and O-protonation is theoretically possible)

Table 1. Gibb's Free Enthalpies of Formation (ΔG) for All Stationary Points Found on the Mitsunobu Hypersurface[a]

	ΔG_{gas}	ΔG_{MeCN}[b]		ΔG_{gas}	ΔG_{MeCN}[a]
2d + PH_3	0.0	0.0	**14b**	12.4	−2.8
3d	20.3	11.5	**15**	137.6	19.5
$\mathbf{E_{3d-17}}$	*c*	4.0	$\mathbf{E_{15-7}}$	140.0	25.3
$\mathbf{T_{3d-17}}$	*c*	6.4	$\mathbf{T_{15-7}}$	154.8	42.8
4	114.6	15.1	**16**	17.5	−2.0
$\mathbf{T_{4-7}}$	141.1	45.9	$\mathbf{T_{16-8}}$	27.6	10.2
5	−18.6	−20.6	**17**	−1.3	−0.4
$\mathbf{T_{5-20}}$	−5.6	−7.3	$\mathbf{T_{17-5}}$	13.0	21.2
7	116.9	9.1	**18**	22.3	6.7
$\mathbf{T_{7-9Inv}}$	29.1	19.2	**19**	13.1	12.7
$\mathbf{T_{7-9Ret}}$	41.2	29.8	**20**	−13.9	4.8
8	−13.6	−14.9	$\mathbf{T_{20-10}}$	*c*	3.5
9	−28.7	−30.2	**21**	−8.3	−17.3
10	−17.5	−19.2	$\mathbf{T_{21-9Ret}}$	16.9	5.2
11	154.9	40.2	**22**	33.9	16.4
12	19.4	7.5	$\mathbf{T_{22-23}}$	41.2	24.3
13	20.0	*d*	**23**	40.0	22.5
14a	0.2	−0.5	$\mathbf{T_{23-12}}$	46.3	25.8

[a] Calculated at the BP86/6-311++G(3df,3pd) level of theory and given in kcal/mol relative to the educts (PH_3 + **2d**). [b] Calculated with the C−PCM solvation model ($\epsilon = 36.64$; acetonitrile). [c] Does not exist in the gas phase. [d] The three-membered ring opens upon optimization in solution to yield the betaine.

Scheme 2. Reactions of **3d** and **14b** with Acetic Acid



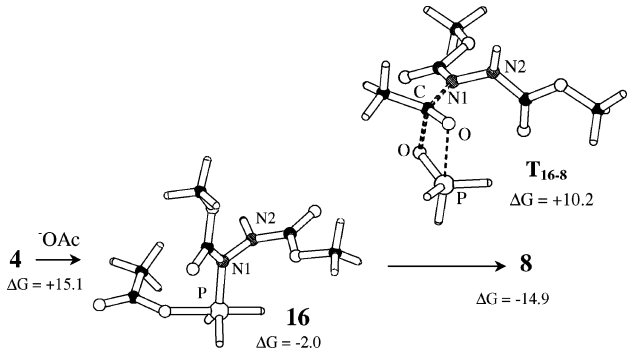
or a nucleophilic addition of an equivalent of alcohol to generate hypervalent phosphorus compounds.

Reaction of 3d and 14b with Organic Acids. Due to charge separation (especially in the acid−base steps involved), the Mitsunobu reaction cannot effectively take place in the gas phase. As an example, the protonation reaction **3d** + AcOH → AcO^- + **4** costs 94 kcal/mol to separate the charges in the gas phase. Reoptimization of the species involved in the explicit presence of the acetonitrile dielectric field (see computational details) reduced this value to a very comfortable 3.6 kcal/mol (Table 1). We therefore restricted our discussion in the entire article to the solvated hypersurface as obtained with the C−PCM model. For interested readers, Table 1 contains the gas-phase values as well. Graphical and chemical illustrations of the entire calculated hypersurface can be found in Figure 2 and Scheme 11.

If a molecule of acetic acid is placed within ca. 4 Å (electrostatic contact) of heterocycle **14b** and allowed to freely optimize, the ring heteroatom (N1, N2, or O) closest to the acid spontaneously deprotonates it (Scheme 2). When oxygen is protonated, the ring spontaneously opens to yield an unstable "iminol", which promptly tautomerizes to **4** (Scheme 2). This reaction coordinate contains several reactive modes belonging to pseudorotation at phosphorus, ring-opening, as well as

(39) (a) Chang, N.; Lim, C. *J. Phys. Chem. A* **1997**, *101*, 8706−8713. (b) Uchimaru, T.; Uebayasi, M.; Hirose, T.; Tsuzuki, S.; Yliniemelä, A.; Tanabe, K.; Taira, K. *J. Org. Chem.* **1996**, *61*, 1599−1608. (c) Cameron, D. R.; Thatcher, G. R. J. *J. Org. Chem.* **1996**, *61*, 5986−5997. (d) Moc, J.; Morokuma, K. *J. Am. Chem. Soc.* **1995**, *117*, 11790−11797.
(40) Navech, J.; Revel, M. *Tetrahedron Lett.* **1986**, *27*, 2863−2866.

Scheme 3. Degradation Pathway on the Mitsunobu Hypersurface



hydrogen-transfer processes. These reactive modes are strongly coupled with each other, and the extremely complex hypersurface of this process could not be further characterized at the C-PCM[BP86/6-311++G(3df,3pd)] level of theory. In any case, the barrier is less than 2−3 kcal/mol. Similar reaction coordinates containing several highly coupled reactive modes have been reported for ring-opening reactions of related oxathiaphospholanes.[42] These calculations were performed at the MP2(fc)/6-31+G(d) level of theory both in the gas phase and using the Onsager solvation model.[42]

If the imine nitrogen (N2) removes the proton from HOAc, intermediate **4** is directly generated (under spontaneous ring opening) and AcO^- starts to depart. As long as the newly formed AcO^- remains in the neighborhood of **4**, it can further react via two completely different pathways. The conjugate base of the organic acid can deprotonate **4** (a quasi-barrierless process at the level of theory considered) to generate the thermodynamically slightly more stable ($\delta\Delta G = -3.6$ kcal/mol) betaine **3d**. A dynamic equilibrium between **3d** and **4** then sets up. This explains quite satisfactorily the experimentally observed kinetic instability of oxadiazaphospholes in the presence of acids.[35,36,41] Alternatively, if the conjugate base is nucleophilic enough, it can attack the phosphorus functionality in **4,** which can prematurely "dead-end" the Mitsunobu procedure in a degradation pathway (discussed below).

Protonation at N1 leads to an energetically stable protonated ring structure **15** whose subsequent reaction with MeOH eventually leads to **7** [over a very high barrier ($\mathbf{T_{15-7}}$; +42.8 kcal/mol) and is therefore probably not an essential pathway on the Mitsunobu hypersurface].

Degradation Pathway. The success of the Mitsunobu procedure has been shown to be critically dependent upon the pK_a of the acidic component employed.[17,18] A systematic evaluation showed that the yield of expected ester **9** for a test reaction (Mitsunobu inversion of menthol) decreased from 77% to 20% and finally 0% when the pK_a of the acid was increased from 3.41 (*p*-nitrobenzoic acid) to 4.19 (benzoic acid) to 4.76 (acetic acid).[17] This has been attributed to a competition between the carboxylate anion and the alcohol for **4**, a fact which our calculations have now confirmed. AcO^- is nucleophilic enough that if it comes within electrostatic contact with the positively charged phosphorus in **4** it spontaneously attacks (this acid−base interaction is without a significant barrier in solution) to form a pentavalent intermediate **16** (Scheme 3) which is thermodynamically considerably more stable than **4** (−2.0 kcal/mol as compared to +15.1 kcal/mol).

The lone electron pair on N1 in the hydrazine ligand is then capable of attacking the acyl carbon in an intramolecular nucleophilic fashion over $\mathbf{T_{16-8}}$ ($\Delta G = +10.2$ kcal/mol), a process which is accompanied by extrusion of $H_3P{=}O$. The P−N1 contact is broken very early on the reaction coordinate. Rehybridization of the phosphorus group causes it to swing down and out, where it stabilizes a build up of negative charge on the carbonyl oxygen and weakens the $C-O_P$ bond in the late transition structure for this intramolecular nucleophilic substitution. The now negatively charged N1 promptly attacks the carbonyl bond under severance of the $C-O_P$ bond. As evident from Figure 2, this degradation step has the lowest overall barrier for the entire hypersurface of our model calculations. In complete accord with experiments,[17,18] use of acetic acid results in a premature dead end (formation of the degradation product **8** and $H_3P{=}O$).

Acid and then Alcohol. If the conjugate base of the acid is not reactive enough to attack **4** (degradation pathway), an equilibrium between **3d** and **4** occurs. In addition, small amounts of **15** can be expected to be present in the reaction mixture. All three of these compounds are capable of reacting with alcohols.

If methanol comes close enough to the betaine **3d**, it promptly stabilizes the negative charge on N2 by forming an encounter complex $\mathbf{E_{3d-17}}$ (ΔG of **3d** is +11.5 as compared to +4.0 kcal/mol for $\mathbf{E_{3d-17}}$; Scheme 4). $\mathbf{E_{3d-17}}$ is characterized by a strong hydrogen bond between N2 and the methanolic hydrogen. This hydrogen can thus be quite easily transferred to the N−N functionality over the transition structure $\mathbf{T_{3d-17}}$ (+6.4 kcal/mol). The phosphorus group intercepts the methanolate being formed to generate the *N*,*O*-phosphorane **17**. Intermediate **17** was proposed over 20 years ago but has never been observed.[4b,15e] It exhibits "reversed apicophilicity" (equatorial oxygen and apical nitrogen) and is approximately as stable as the original educts **2d** and PH_3.

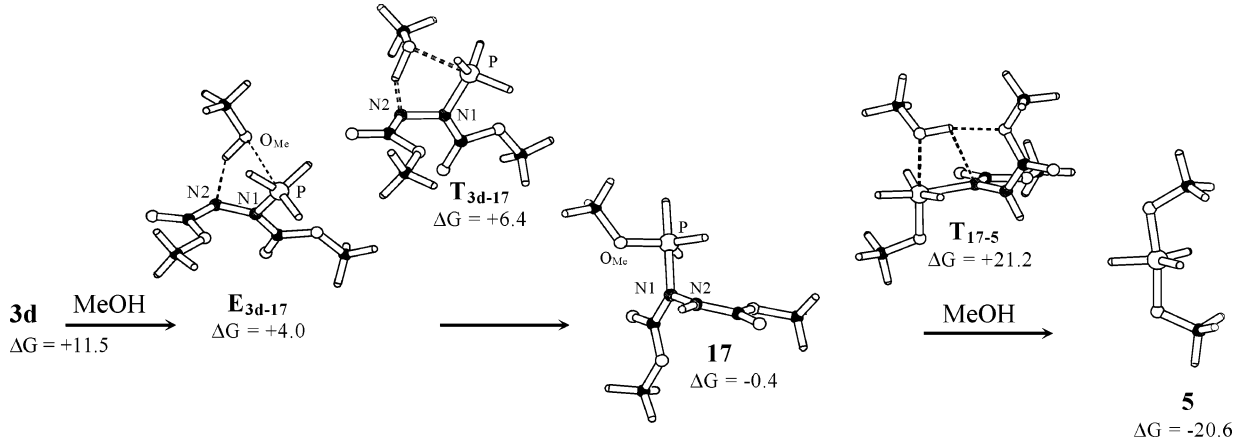
When a second equivalent of MeOH comes within electrostatic contact of **17**, a spontaneous pseudorotation at phosphorus occurs. This enables the final approach of the methanol via the preferred apical position. The hydrazine being generated in the course of this reaction departs from an equatorial position. The cyclic transition structure $\mathbf{T_{17-5}}$ (+21.2 kcal/mol) is stabilized by one of the ester groups in the hydrazine that is being generated in this step. The methanolic hydrogen is transferred quite late in the course of this nucleophilic attack; as the hydrazine **6** diffuses away from the product **5**, it takes the proton with it. This step is quite exothermic, and intermediate **5** ($\Delta G = -20.6$ kcal/mol) represents an important "thermodynamic hole" on the hypersurface of the Mitsunobu reaction. It is consistent with early ^{31}P NMR experiments demonstrating the formation of dialkoxyphosphoranes.[15e,f]

Methanol is also capable of attacking intermediate **4** (the equilibrium **3d** ⇌ **4** guarantees that both species are present). In this case, the methanolic oxygen directly attacks the phosphorus group (Scheme 5). Due to the poor electrophilicity of the PH_3 group, the barrier $\mathbf{T_{4-7}}$ is prohibitively high (+ 45.9 kcal/mol), even though an ester oxygen in the hydrazine ligand helps to stabilize the hypervalent transition structure.

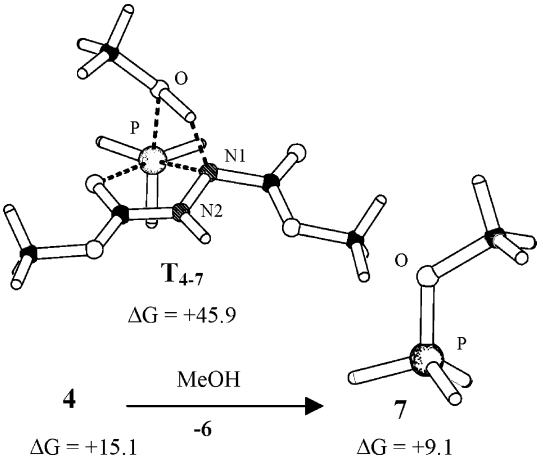
The final possibility that needs to be considered is that the protonated heterocycle **15** could react with methanol. It is unlikely, however, that large amounts of **15** are present since tautomerization and subsequent ring opening to form **4** is highly

(41) Chang, N.; Lim, C. *J. Am. Chem. Soc.* **1998**, *120*, 2156−2167.
(42) Uchimaru, T.; Stec, W. J.; Taira, K. *J. Org. Chem.* **1997**, *62*, 5793−5800.

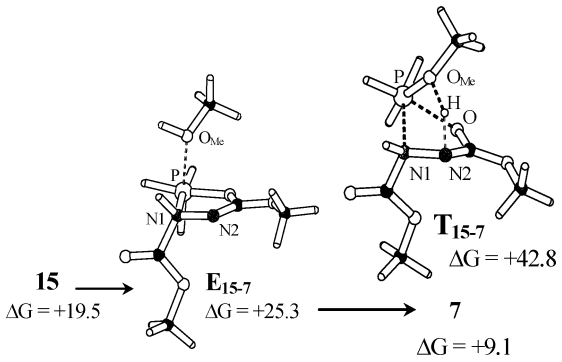
Scheme 4. Reaction of the Betaine **3d** with 2 Equiv of Alcohol



Scheme 5. Reaction of **4** with Methanol over $\mathbf{T_{4-7}}$ To Yield **7**



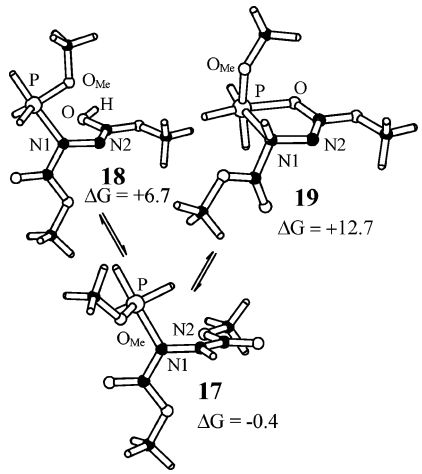
Scheme 6. Reaction of **15** with Methanol over $\mathbf{T_{15-7}}$ To Yield **7**



probable. Nevertheless, this process is theoretically possible (Scheme 6). Approach of a methanol results in the formation of an encounter complex $\mathbf{E_{15-7}}$ with a hypervalent interaction between the phosphorus group and the alcohol. A complex reaction coordinate involving pseudorotation at phosphorus with simultaneous transfer of the methanolic hydrogen to N2 results in the extrusion of **7** over the transition structure $\mathbf{T_{15-7}}$. This process is extremely energetically demanding (+42.8 kcal/mol) and almost certainly does not represent an essential pathway on the hypersurface of the Mitsunobu reaction.

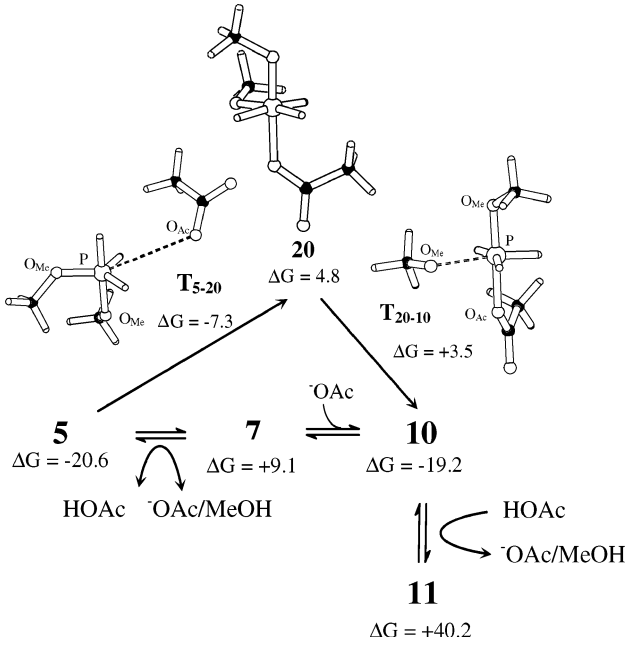
Alcohol and then Acid. In the absence of acid the calculations predict the five-membered heterocycle **14b** to be the initially formed intermediate on the hypersurface. When an equivalent of MeOH comes within electrostatic contact of the phosphorus atom in **14b,** they spontaneously interact to form an initial encounter complex which is not a stable intermediate on the hypersurface. As this complex is being formed, a complex vibrational mode swings the oxygen toward the phosphorus which automatically expands its coordination sphere to accept it. At the same time the methanolic hydrogen is transferred to the ring oxygen. In the course of this complex reactive mode (which has an estimated total barrier of less than 6 kcal/mol) the "iminol" **18** (Scheme 7) is generated. Intermediate **18** is in equilibrium with two other tautomers (**17** and **19**). We did not attempt to find transition structures for this process since tautomerism generally does not possess a significant barrier in solution (and is a little understood and extremely difficult to calculate process because solvent molecules are often explicitly involved in the hydrogen transfer). The thermodynamic equilibrium positions of these three intermediates guarantee that **17** is the preferred form [$\Delta G = -0.4$ kcal/mol as compared to +6.7 (**18**) and +12.7 (**19**) kcal/mol].

Scheme 7. Tautomers Formed upon Addition of an Equivalent of Methanol to **14b**



Intermediate **17** is then capable of adding a second alcohol to generate **5** (which has already been discussed; Scheme 4). When a molecule of acid comes into electrostatic contact with **5**, a smooth decomposition takes place (a quasi-barrierless acid−base interaction at the level of theory considered) to yield **7,** which is traditionally considered as being the "activated" species in the Mitsunobu procedure (Scheme 8). The equilibrium position, however, disfavors this decomposition. Compound **5** represents a thermodynamic hole (−20.6 kcal/mol) on the

Scheme 8. Interconversions between Intermediates **5, 7, 10,** and **11**



hypersurface. Intermediate **7** lies 29.7 kcal/mol above **5** and is probably only present in very low concentrations since it can readily add another alcohol (goes back to **5**). As discussed below, the conjugate base of the acid can also compete with the alcohol for **7**.

Competition between Alkoxy- and Acyloxyphosphoranes. As already discussed, the dialkoxyphosphorane **5** can undergo an acid-induced decomposition (elimination of MeOH) to yield **7** (Scheme 8). If it is basic enough, the conjugate base of the acid (AcO^-) can then react with **7** via a quasi-barrierless acid−base interaction to yield the mixed ligand intermediate **10**.

An equally valid alternative for further reaction is an addition−elimination mechanism. AcO^- can add to **5** to generate the metastable hypervalent species **20**. As the AcO^- approaches **5**, the phosphorus undergoes a spontaneous pseudorotation so that the incoming species can approach from an apical position ($\mathbf{T_{5-20}}$). This is in agreement with earlier calculations on the mechanism of alkaline (OH^-) hydrolysis of methyl aminoethylenephosphonate (a cyclic five-membered phosphate with an apical O−P and an equatorial N−P bond) which clearly showed that oxygen nucleophiles prefer to attack from an apical direction.[43] Due to the coupling of the active modes for pseudorotation and nucleophilic attack, the transition structure $\mathbf{T_{5-20}}$ lies below the hypervalent species **20** (A higher level of theory would be necessary to cleanly separate these two processes). Intermediate **20** can then eject the equatorial (more weakly bound) MeO^- ligand over $\mathbf{T_{20-10}}$ to generate the mixed species **10**. This active mode is again coupled with pseudorotation on phosphorus, and because of this, the transition structure lies slightly below **20** on the hypersurface.

In the course of our computational studies we realized that the critical step in the Mitsunobu inversion is the ability of **5** to eliminate MeOH (with the help of an equivalent of AcOH) to generate **7**. Otherwise, the reaction would end with an equilibrium mixture of **5** and **10**. Intermediate **10** is quite similar to **5,** and one would therefore expect a similar type of elimination to occur. This is indeed possible, and analogous to **7**, the corresponding acylphosphonium salt **11** is a stable intermediate on the hypersurface. It lies considerably higher in energy than **7** (40.2 vs 9.1 kcal/mol) because the AcO^- ligand is not capable of stabilizing the positively charged PH_3 group as well as MeO^-. Intermediate **11** thus represents an insurmountable barrier for this simple model system.

Anhydride Pathway. Despite its very high energy (+40.2 kcal/mol), intermediate **11** is extremely interesting from a mechanistic point of view because it can react with a second equivalent of AcO^- which opens a new reaction channel (anhydride generation) on the hypersurface (Scheme 9). As soon as AcO^- comes within electrostatic contact, it promptly adds to **11** (a nearly barrierless acid−base interaction in solution). Instead of generating a quasi-linear apical/apical pentavalent species such as **5** or **10**, intermediate **11** preferably adds the second acyl ligand in a bidentate equatorial manner to generate the hypervalent species **22** (+16.4 kcal/mol). The prealignment of the apical acyl group in **22** allows its carbonyl oxygen to easily attack the carbon atom in the bidentately bound equatorial ligand over the six-membered cyclic transition structure $\mathbf{T_{22-23}}$ (+24.3 kcal/mol). A relatively unstable (+22.5 kcal/mol) hypervalent intermediate **23** is generated which can easily expel $H_3P{=}O$ over $\mathbf{T_{23-12}}$ (+25.8 kcal/mol). The driving force for this step is the formation of the anhydride **12** (+7.5 kcal/mol) together with $H_3P{=}O$.

It has been experimentally observed that if the alcohol is sterically hindered and a very weak organic acid is employed, the Mitsunobu procedure can be diverted into this anhydride channel.[19] This step has been postulated to occur in a S_N2-type manner by nucleophilic attack on the oxygen in the P−O bond in **11**. Our calculations predict, however, that hypervalent phosphorus species are involved instead. In this manner, the phosphorus functionality succeeds in stabilizing an intramolecular addition−elimination mechanism by selective polarization of both acyl groups.

Mitsunobu Inversion. The last stage in the traditional mechanism for the Mitsunobu reaction is a nucleophilic substitution at carbon in the alkoxyphosphonium salt **7** (Scheme 1). Due to the second-order kinetics and inversion experimentally observed, a S_N2 mechanism has been postulated for this step.[1] In support of this, we easily located a nearly classical S_N2 transition structure ($\mathbf{T_{7-9Inv}}$) on the hypersurface (Chart 2). $\mathbf{T_{7-9Inv}}$ can be classified as "early" since bond formation has not progressed very far. This is in accord with kinetic investigations[7b] and not unexpected since carboxylate anions are weak nucleophiles and $H_3P{=}O$ an extremely good leaving group. The activation barrier for this step is only 19.2 kcal/mol as compared to the educts **2d** and PH_3. One of the reasons for this relatively low barrier is that $\mathbf{T_{7-9Inv}}$ is stabilized by a strong hydrogen bond between the carbonyl oxygen and a methyl hydrogen.

Retention Pathway. Although the preferred orientation of the oxygen ligands in the mixed acyloxyalkoxyphosphorane **10** is apical/apical, a facile Berry pseudorotation can easily generate the slightly more unstable apical/equatorial conformation **21** (Scheme 10). This brings the methanolate ligand in a position where it can undergo an electrostatic interaction with the acyl

(43) Tole, P.; Lim, C. *J. Am. Chem. Soc.* **1994**, *116*, 3922−3931.

Scheme 9. Anhydride Pathway on the Mitsunobu Hypersurface

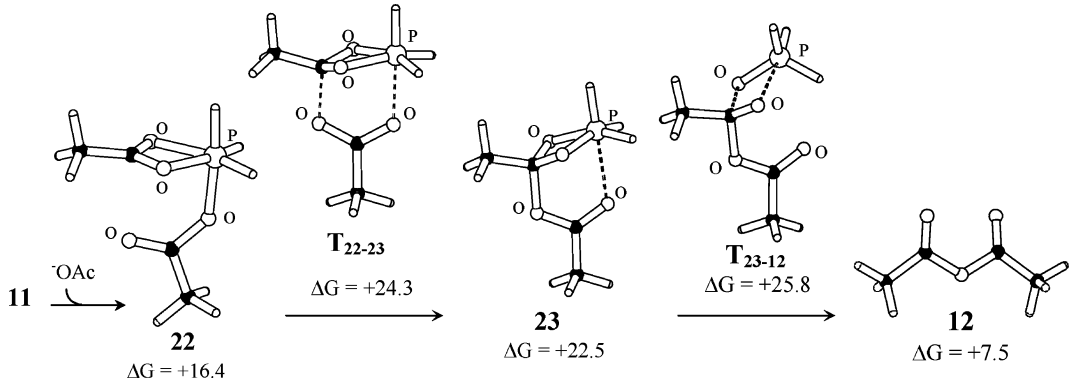


Chart 2. S_N2 Transition Structure $\mathbf{T_{7\text{-}9Inv}}$ for Mitsunobu Inversion

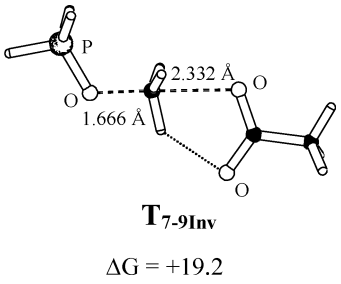
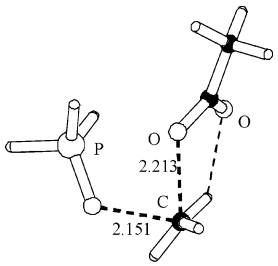
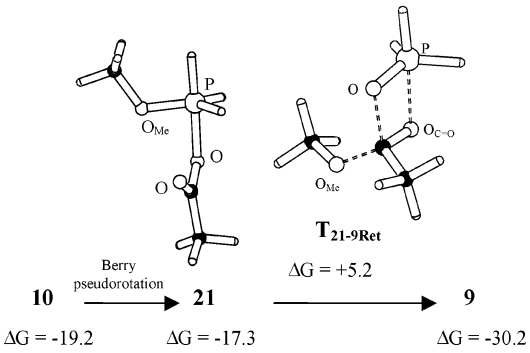


Chart 3. Alternative Transition State for Retention $\mathbf{T_{7-9Ret}}$ on the Mitsunobu Hypersurface



Scheme 10. Retention Pathway on the Mitsunobu Hypersurface



ligand, thus paving the way for an easy intramolecular addition of the methanolate to the carbonyl group ($\mathbf{T_{21-9Ret}}$; +5.2 kcal/mol) under extrusion of $H_3P{=}O$. Product **9** is the ester expected from the Mitsunobu procedure in all but one important aspect: If an optically active alcohol is employed, retention of configuration will occur. The Mitsunobu reaction is thus quite capable of running under retention as well as the normally observed inversion. Indeed, for this simple model system retention should be the sole stereochemical outcome, if the degradation side reaction has been successfully repressed.

In support of our calculations, both early[20] and more recent[25−27] experimental investigations have reported that certain sterically hindered chiral alcohols do indeed retain their configuration when subjected to Mitsunobu reaction conditions. The authors of these studies rationalized this by claiming that their conditions allowed **11** to be stabilized over **7**.[25−27] They then postulated that nucleophilic attack by the alcohol on the carbonyl carbon in **11** leads to the retention product observed.[25−27] Our calculations, however, indicate that **11** is probably not directly involved in the retention pathway. Even if **11** is independently synthesized, subsequent addition of the alcohol needed to generate the desired ester would lead to the formation of the addition product (**10** or **21**) due to the rather high oxophilicity of phosphorus rather than to the product expected from nucleophilic attack on the acyl carbon.

It is theoretically possible, even under base-catalyzed crossover conditions where the "traditional" alkoxyphosphonium salt **7** is overwhelmingly generated, that retention can still occur via a trantision structure $\mathbf{T_{7-9Ret}}$ in which the $H_3P{=}O$ being generated departs in an axial fashion from a nonclassical carbon center that is stabilized by an additional hydrogen bond to the second oxygen in the carboxylate group (Chart 3). The relative energy of this transition structure is, with +29.8 kcal/mol, quite high as compared to +19.2 kcal/mol for the classical S_N2 inversion ($\mathbf{T_{7-9Inv}}$). The calculations thus support the experimental findings in that if the alkoxyphosphonium salt **7** is preferably generated, the inversion product will be overwhelmingly obtained.

Possibility of Stereochemical Control. A glance at Figure 2 shows that there are two intermediates, **5** and **10** (thermodynamic "holes" on the hypersurface), and two critical transition structures, $\mathbf{T_{7-9Inv}}$ (inversion) and $\mathbf{T_{21-9Ret}}$ (retention), that determine the stereochemical outcome of the Mitsunobu reaction. If the retention product is desired, one would need to first ensure that the equilibrium between **5** and **10** favors the formation of the mixed acyloxyalkoxyphosphorane **10** and then one would have to stabilize the transition state for retention ($\mathbf{T_{21-9Ret}}$) over that for inversion ($\mathbf{T_{7-9Inv}}$).

The presence of hydrazine **6** (general base) under normal Mitsunobu conditions usually guarantees that the equilibrium favors **5** instead of **10** since **10** readily undergoes a base-assisted crossover to generate the alkoxyphosphonium salt **7**.[22] According to our calculations, **7** either adds an equivalent of alcohol to generate **5** or lands directly in the inversion pathway since most

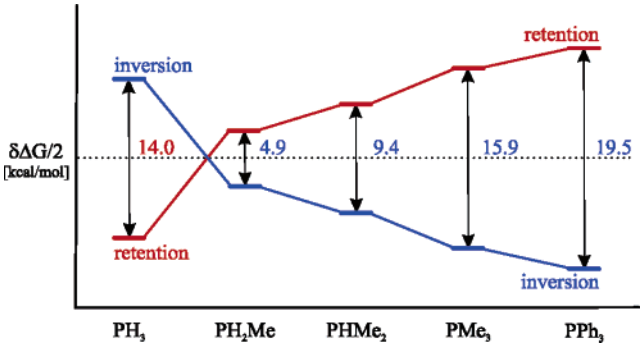


Figure 1. Substituent effect on the relative energy of the transition structures for inversion and retention ($\mathbf{T}_{7-9\mathrm{Inv}}$ and $\mathbf{T}_{21-9\mathrm{Ret}}$) on the Mitsunobu hypersurface. Calculated at the BP86/6-311++G(3df,3pd) level of theory except for PPh_3 [BP86/6-311+G(d,p) level with the 6-31G(d) basis set for the phenyl substituents themselves].

of the reaction barrier for inversion has been overcome with the generation of **7**. However, we feel that controlling this equilibrium should not present a fundamental problem since it is possible to selectively prepare **5** or **10** by independent methods.[15e−f,21,22]

Much more problematic is controlling the relative energies of the transition structures. According to our model system, retention should have been reported much more often in the chemical literature than it has been. Since this could be a result of employing H_3P to model Ph_3P, we investigated the effect of substitution at phosphorus by successively substituting hydrogen by methyl. Finally, we calculated the two transition structures for the Ph_3P system at a lower level of theory [BP86/6-311+G(d,p) level with the 6-31G(d) basis set being used for the phenyl substituents themselves]. The results are illustrated in Figure 1 and demonstrate that the identity of the substituent at phosphorus has a significant influence on the relative stabilities of the transition structures. By careful substituent tuning, it should be fundamentally possible to find conditions under which the transition structure for retention has been stabilized over inversion.

That this can be experimentally realized has already been demonstrated by several independent research groups.[22,25−28] DeShong et al. managed to obtain retention not by varying the substituents on phosphorus (they used Ph_3P) but by employing a series of hindered alcohols for which the S_N2 pathway is sterically congested.[26] McNulty et al. modified the phosphine used (n-Bu_3P instead of Ph_3P) which, according to our calculations, has already helped to reduce the energy difference between inversion and retention. They then managed to inhibit the production of **5**/**7** by avoiding base-induced crossover reactions, which according to our calculations basically guarantees an overwhelming excess of the acyloxyalkoxyphosphorane **10** in solution, and as a result observed retention for a series of chiral alcohols.[22,28] In contrast to DeShong et al., the alcohols employed by McNulty et al. were not especially sterically hindered (menthol or even 2-hexanol, for example).

We suggest that computer modeling of both transition structures at a moderate density functional level may be quite helpful in finding appropriate substituents. We would, however, recommend employment of at the very least a triple-ζ-valence basis set with diffuse and polarization functions for the phosphorus as well as all atoms directly involved in bond breaking/making in the transition structure for retention since the hypervalent interactions involved are extremely badly represented at a lower level of theory. A smaller basis set could be used for the rest.

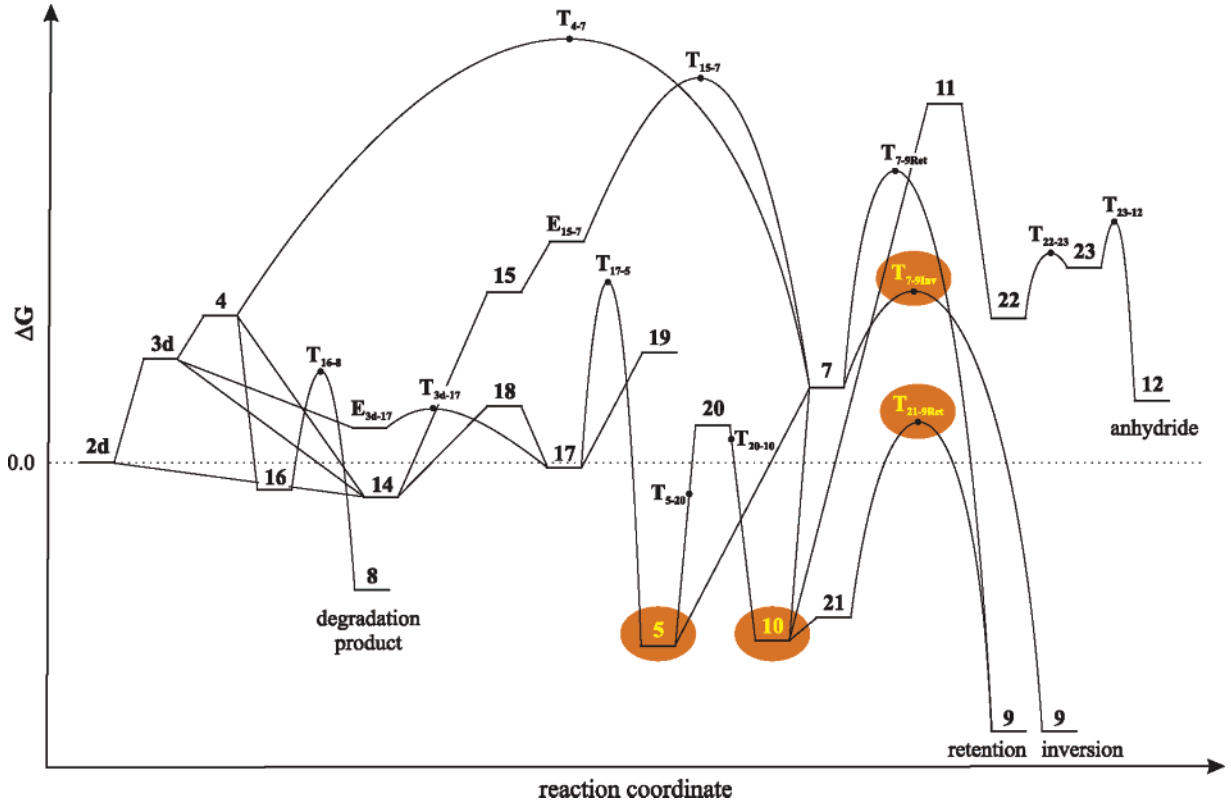
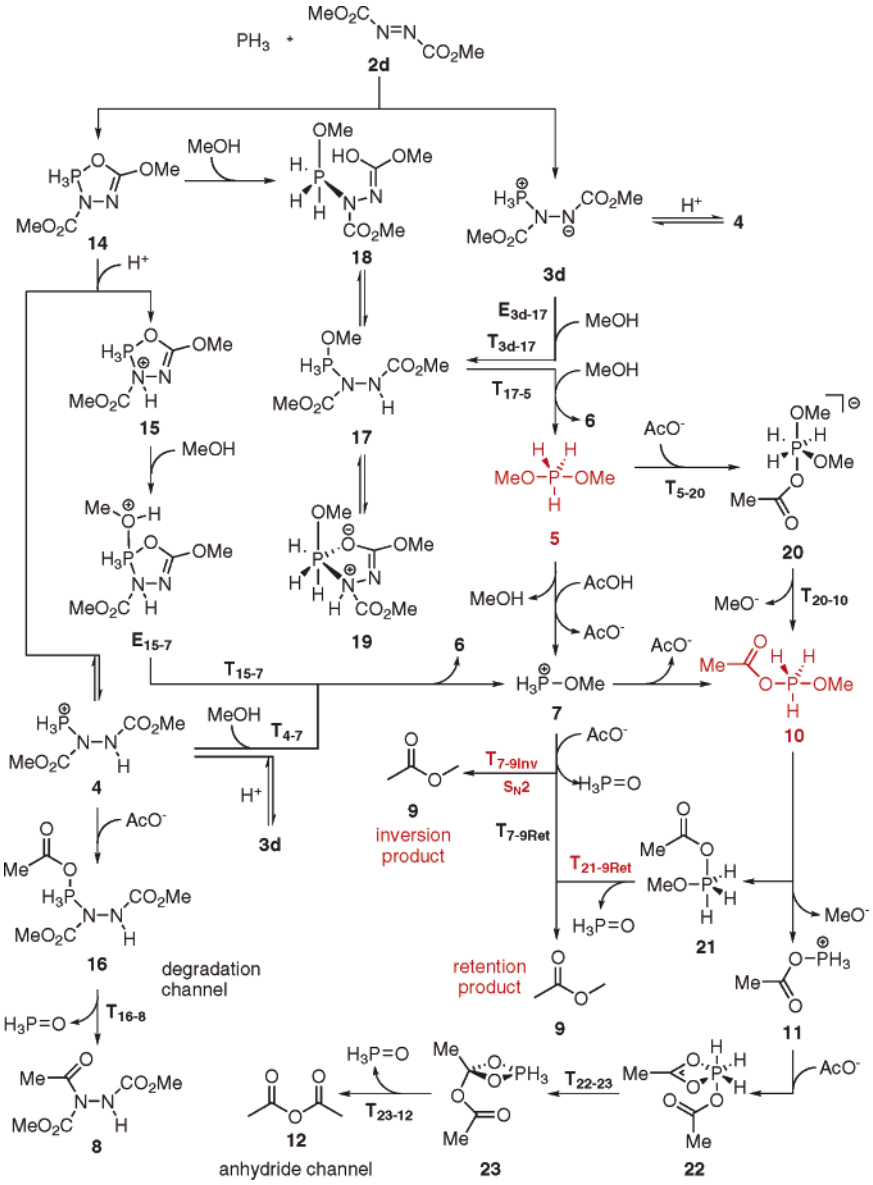


Figure 2. Energy diagram of the Mitsunobu hypersurface as calculated at the BP86/6-311++G(3df,3pd) level of theory (relative to the educts; **2d** + PH_3)

Scheme 11. Chemical Diagram of the Mitsunobu Hypersurface As Calculated at the BP86/6-311++G(3df,3pd) Level of Theory



Conclusion

As can be seen in Figure 2 and Scheme 11, the hypersurface of the Mitsunobu reaction is far more complex than is generally assumed, even for the simplest possible system which we considered in this theoretical study (PH_3, $MeO_2CN{=}NCO_2Me$, MeOH, and CH_3CO_2H). In contrast to the traditional mechanism (Scheme 1) usually discussed, the reaction of a phosphine with a dialkyl azodicarboxylate preferably leads to the formation of a five-membered ring (**14**). This could be a consequence of using PH_3 as a model for PPh_3. In any case, the preferred form will be determined to a great extent by the identity of the ligands on the phosphine and/or diazene employed. One should not forget that many oxadiazaphospholes (**14**) exhibit enhanced kinetic instability in the presence of trace amounts of organic acids.[35,36,41] Independent of the initial intermediate, an equilibrium between the betaine (**3d**) and its protonated form (**4**) can thus be expected to readily occur.

Depending on the sequence of reagent addition (acid first and then alcohol or alcohol first and then acid), a plethora of intermediates, many of which are in equilibrium with each other, become possible. Our computational results concur completely with experimental experience[17,18] in that it is necessary to select an acid that is stronger than CH_3CO_2H because its corresponding carboxylate anion ($CH_3CO_2^-$ is more of a nucleophile than a base under Mitsunobu conditions) can compete with the alcohol very early on the hypersurface for the protonated betaine (intermediate **4**) which will prematurely dead end the Mitsunobu reaction (degradation product **8**).

All pathways involving the many intermediates on the hypersurface ultimately end in the production of two extremely stable intermediates—a dialkoxyphosphorane **5** and an acyloxyalkoxyphosphorane **10**. Again, the computational results are in complete agreement with experimental observations.[15e,f,16b] Intermediates **5** and **10** represent important thermodynamic "holes" on the hypersurface and are furthermore in equilibrium with each other (exchange of the alkoxy and acyloxy ligands either over a metavalent phosphorus intermediate **20** or via an acid/methanol-induced decomposition over the alkoxy- (**7**) or acyloxyphosphonium salt (**11**). Experimental results have indicated that if the salt **11** is stabilized (sterically hindered

alcohol), an anhydride pathway becomes possible when a very nucleophilic carboxylate anion is employed.[19] Our calculations confirm that subsequent reaction of **11** with a carboxylate anion can indeed lead to an anhydride; however, stabilization of **11** is not achieved in such a simple model system.

In accord with the traditional mechanism, a nucleophilic attack on **7** by an alcohol via a S_N2-type transition structure is responsible for generating the ester end product under inversion of the original alcohol configuration. Quite surprisingly, our calculations also reveal that *retention of configuration is fundamentally* possible in the Mitsunobu procedure. However, this is only to be expected in the case of PH_3 and phosphines with very similar electronic properties. Retention is very rare, having been reported only in a few cases, and has been attributed to nucleophilic attack by the alcohol on the carbonyl carbon in **11**.[25−27] According to our calculations, it is not necessary to generate the (usually fairly unstable) acyloxyphosphonium salt **11**. The stable mixed alkoxyacyloxyphosphorane **10** (in which both oxygen ligands occupy apical positions) can undergo a facile Berry pseudorotation to generate the slightly more unstable apical/equatorial conformation (intermediate **21**). An intramolecular nucleophilic attack of the methanolate ligand on the carbonyl group of the acyl ligand becomes possible and is greatly facilitated by the presence of the central phosphorus atom which polarizes both ligands in an appropriate manner. This intramolecular process *retains* the original configuration of the alcohol. The identity of the substituent at phosphorus has a significant influence on the relative stabilities of the transition structures. Our calculations predict that use of PH_3 will lead to the retention product, whereas the inversion product will be obtained upon use of PPh_3. As a general rule, employing PPh_3 or closely related phosphines in the Mitsunobu procedure will lead, as reported countless times in the chemical literature, to the inversion product. With very careful selection of the experimental conditions, especially in the choice of substituent at phosphorus, it should, however, be possible to divert the Mitsunobu procedure into the retention channel for far more substrates than have been reported to date in the chemical literature.

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Supporting Information Available: Full literature citations, a discussion on substituted diazenes, a table of electronic properties for the intermediates involved in the first step of the Mitsunobu procedure as well as tables of absolute energies and Cartesian coordinates for all stationary points found on the hypersurface—calculated both in solution (C−PCM solvation model; acetonitrile) and the gas phase. This material is available free of charge via the Internet at http://pubs.acs.org.

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