Computational Insight into the Chemistry of β-(Phosphatoxy)alkyl Radicals: [3,2]- and [1,2]-Phosphatoxy Rearrangements and a New Pathway for *syn*-Elimination of Phosphate

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Abstract: The [3,2]- and the [1,2]-phosphatoxy rearrangements have been studied in the 2-(phosphatoxy)ethyl radical, the 2-(dimethylphosphatoxy)ethyl radical, and the 2-(phosphatoxy)propyl radical with the Becke3LYP/6-31G(d) density functional method. Barriers have also been calculated through single-point energy calculations at the B3LYP/6-311+G(d,p), PMP2/6-31+G(d,p), and, in part, QCISD/6-31G(d) levels of theory. In contrast to acyloxy rearrangements in otherwise identical systems, the [1,2]-shift pathway is slightly preferred in phosphatoxy rearrangements. The degree of charge separation is much more significant in the [3,2]- than the [1,2]-shift pathway. Barriers for phosphatoxy and dimethylphosphatoxy shifts are rather similar for both pathways. Introduction of a methyl group adjacent to the radical center lowers the barrier quite significantly. The effect is larger for the [1,2]- than for the [3,2]-shift. Inspection of the charge and spin density distributions indicates that this effect is composed of steric as well as polar contributions. On the basis of these results, the experimentally found ratio of [1,2]- to [3,2]-phosphatoxy rearrangements should be strongly dependent on solvent polarity as well as substrate substitution pattern. The *syn*-1,3-elimination of phosphate has been described as a novel reaction type. The barrier for this process is significantly lower than for *syn*-1,2-elimination of phosphate from closed shell substrates, but somewhat above the barriers for 1,2-phosphatoxy rearrangements.

Introduction

The chemistry of β-(phosphatoxy)alkyl radicals is of significant interest, mainly due to the occurrence of such species in degradation processes of DNA and other biologically relevant reactions.[1] Under biological conditions, the fate of these reactive intermediates depends on the presence of trapping agents such as oxygen. In the absence of oxygen, elimination of phosphate through heterolytic cleavage of the carbon−oxygen bond leads to formation of alkene radical cations (pathway A, Scheme 1), which are subsequently trapped by solvent.[1−3] In the presence of oxygen, this heterolytic fragmentation pathway competes with trapping of DNA radicals by oxygen.[3] Metal-mediated DNA damage appears to involve yet another pathway for phosphate elimination through rapid oxidation of the initially formed radical, trapping with solvent, and subsequent base-induced phosphate elimination.[1] Reactions of substituted β-(phosphatoxy)alkyl radicals in apolar solvents such as benzene, however, show a distinctly different reactivity pattern, which has been thought to result from the combination of 1,2-phosphatoxy migration, trapping of the rearranged radicals, and (in some cases) subsequent elimination.[3b,4] Two different pathways (B and C, Scheme 1) have been proposed for the 1,2-migration of phosphate groups, and pathway C has been found to be preferred in many cases.[4b] Also, phosphatoxy rearrangements appear to be faster than the closely related acyloxy rearrangments by 2−4 orders of magnitude.[3c,d,4b] Yet another mechanism has been invoked for the overall *trans*-1,4-elimination of phosphate in the chorismate synthase reaction.[5,6] One general conclusion that can be derived from the listing above is that the chemistry of β-(phosphatoxy)alkyl radicals appears to be remarkably sensitive to the reaction medium, the structure of the model system, and especially the choice of phosphate protecting groups. We focus here on various unimolecular reactions occurring in β-(phosphatoxy)alkyl radicals including the [3,2]- and the [1,2]-phosphatoxy rearrangement, and a novel pathway for phosphate elimination (pathway D, Scheme 1) which has not been considered before.

Theoretical Methods

Calculations were performed with the hybrid Becke3LYP density functional method[7] as implemented in Gaussian 92dft and Gaussian

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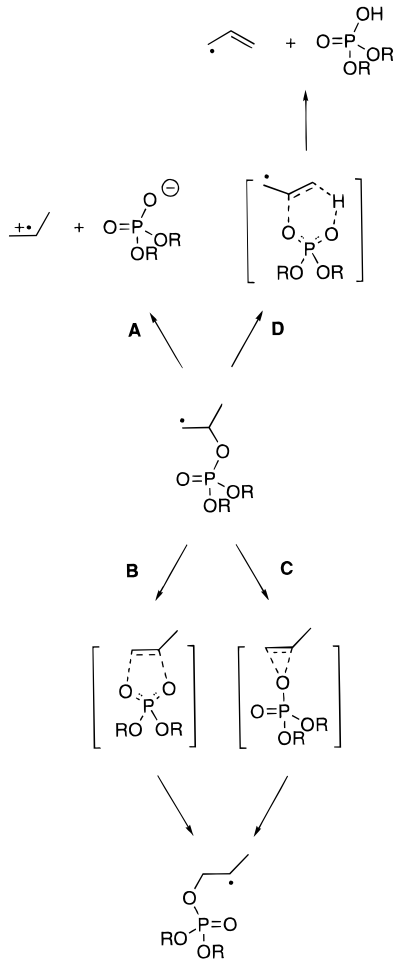
Scheme 1



94.[8] The split valence 6-31G basis set augmented with polarization functions on all non-hydrogen atoms was used throughout.[9] This level of theory has given good results in studies of the Cope and Claisen rearrangements[10] as well as acyloxy rearrangements in open and closed shell molecules.[11,12] Conformational space of all ground states was first explored at the lower UHF/3-21G(*) level. The three most favorable conformers for each ground state were then reoptimized at the higher Becke3LYP/6-31G(d) level. Analytical second derivatives were used to calculate vibrational frequencies for all stationary points at this level. If not noted otherwise, relative energies are reported without zero point energy corrections. Single-point energies have also been calculated at the Becke3LYP/6-311+G(d,p), PMP2/6-31+G(d,p), PMP3/6-31G(d), and QCISD(6-31G(d) levels of theory. Charges have been derived from the Mulliken population analysis of the Becke3LYP/6-31G(d) Kohn−Sham orbitals. The trends observed with these charges have also been reproduced with charges fitted to the molecular electrostatic potential.[13] The three model systems considered here are

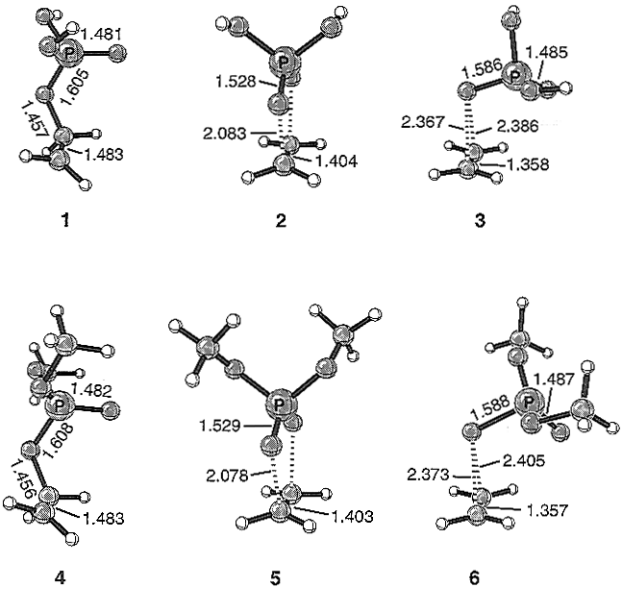
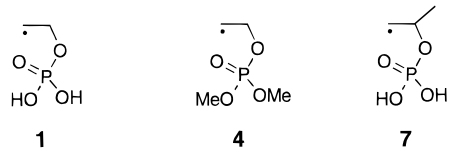


Figure 1. Ground and transition states in the rearrangement of the 2-(phosphatoxy)ethyl radical (**1**) and the 2-(dimethylphosphatoxy)ethyl radical (**4**) optimized at the Becke3LYP/6-31G(d) level of theory.

the 2-(phosphatoxy)ethyl radical (**1**), the 2-(dimethylphosphatoxy)ethyl radical (**4**), and the 2-(phosphatoxy)propyl radical (**7**).



2-(Phosphatoxy)ethyl Radical (1)

This small model system is well suited to study the relative barriers for the [3,2]-phosphatoxy rearrangement leading through a five-membered transition structure (Scheme 1, pathway B) and the [1,2]-phosphatoxy rearrangement leading through a three-membered transition structure (pathway C). Structures for all stationary points are shown in Figure 1 together with selected structural data. Relative energies are collected in Table 1. For all stationary points in this and the other model systems, a large number of conformers exist for rotation around the O−P bonds. In general, only the most favorable conformer is shown. Structural and energetic data for all conformers are included in the Supporting Information. The transition structure **2** for the [3,2]-shift shows a strong similarity to the corresponding transition state for acyloxy rearrangement in that the phosphate group is positioned upright on top of the ethylene moiety, orienting the oxygen lone pairs downward.[11,12] The unpaired spin density is to a major part located at the ethylene carbon atoms with coefficients of 0.32 and to a minor part at the phosphate oxygen atoms with coefficients of 0.16. The phosphate group carries an overall negative charge of −0.41e in **2**, which is 0.09e more negative than in **1** at −0.32e. Both the charge and the spin density distribution support the classification of **2** as the transition structure for an intramolecular nucleophilic substitution reaction, in which the oxygen lone pair of **1** functions as the nucleophile attacking the radical center, displacing the neighboring C−O bond as the leaving group.[14] In contrast to all the acyloxy rearrangements investigated at the same theoretical level (including the (trifluoroacetyl)oxy shift),[11] the phosphatoxy shift appears to include a higher degree of charge separation. This should result in a higher sensitivity of

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Table 1. Relative Energies and Differences in Zero Point Vibrational Energy (in kcal/mol) for Stationary Points in the Rearrangement of the 2-(Dimethylphosphatoxy)ethyl Radical (**4**), the 2-(Phosphatoxy)ethyl Radical (**1**), and the 2-(Phosphatoxy)propyl Radical (**7**)

structure	Δ*E*(B3LYP/ 6-31G(d)// B3LYP/6-31G(d))	ΔZPE(B3LYP/ 6-31G(d))	Δ*E*(B3LYP/ 6-311+G(d,p)// B3LYP/6-31G(d))	Δ*E*(PMP2/ 6-31+G(d,p)// B3LYP/6-31G(d))	Δ*E*(PMP3/ 6-31G(d)// B3LYP/6-31G(d))	Δ*E*(QCISD/ 6-31G(d)// B3LYP/6-31G(d))
1	0.0	0.0	0.0	0.0	0.0	0.0
2	−19.6	0.0	+18.0	+25.8	+31.7	+28.1
3	+19.6	−0.5	+17.6	+29.8	+29.9	+27.9
4	0.0	0.0	0.0	0.0		
5	+20.1	+0.1	+18.9	+26.1		
6	+19.6	−0.7	+17.7	+30.7		
7	0.0	0.0	0.0	0.0		
8	−1.8	+0.5	−1.4	+0.8		
9	+17.4	−0.1	+15.6	+25.1		
10	+16.2	−0.5	+14.2	+26.6		
11	+22.7	−3.5	+18.0	+33.9		
8 → **12** + **13**	+6.3	−2.8	−2.1	+13.0		
8 → **17** + **18**	+158.2	−3.7	+144.8	+153.7		
14	0.0	0.0	0.0	0.0		
15	+41.9	−4.8	+37.2	+46.8		
16 + **13**	+23.0	−3.5	+14.6	+22.2		
17 + **19**	+173.4	−5.3	+159.0	+171.0		

this reaction to the polarity of the medium and to substituent effects. The phosphate group in **3** on the other hand, carries an overall charge of −0.32e and has the spin density located on the shifting oxygen atom (+0.59) and at the two ethylene carbon atoms with coefficients of +0.22 and +0.20, respectively. This suggests that **3** has much more the characteristics of a phosphatoxy radical shifting from one ethylene carbon atom to the other. This classification is also supported by the much shorter C−C bond length in **3** as compared to that in **2**. By coincidence, both pathways face identical barriers at the Becke3LYP level of theory. Improving the basis set to 6-311+G(d,p) gives somewhat lower barriers for both the [3,2]- and the [1,2]-pathways with a slight preference for the [1,2]-shift. A small preference for the [1,2]-shift is also found at the PMP3/6-31G(d)//B3LYP/6-31G(d) and QCISD/6-31G(d)//B3LYP/6-31G(d) levels of theory. The *absolute* barrier height is, however, significantly larger for the latter two methods.

The barriers derived from PMP2/6-31+G(d,p) single-point calculations are also much larger than the B3LYP values, but in contrast to all other theoretical methods studied here and also in contrast to most experimental evidence the [3,2]-pathway is now strongly preferred over the [1,2]-pathway. It therefore appears that the PMP2/6-31+G(d,p)//B3LYP/6-31G(d) level of theory is not well suited to study unimolecular rearrangements in (phosphatoxy)alkyl radicals. One more result from this small model system becomes apparent only after comparison with results for acyloxy rearrangements in simple model systems. Whatever level of theory is chosen, the barriers for acyloxy rearrangements are predicted to be lower than those for phosphatoxy rearrangements. This contrasts with the experimental finding that phosphatoxy rearrangements usually occur with a higher rate than acyloxy rearrangements in otherwise comparable systems. Assuming equal preexponential factors, this translates into lower barriers for phosphatoxy rearrangements than for acyloxy rearrangements.

2-(Dimethylphosphatoxy)ethyl Radical (4)

In order to establish whether the deviation from experiment noted for **1** is due to the substituents present in the phosphate groups, the [3,2]- and the [1,2]-shift pathways were also studied for **4**. This larger model system carries the additional benefit of excluding possible side effects introduced through varying degrees of hydrogen bonding between the hydroxy groups present in **1**. The structures found for ground state **4** and transition states **5** and **6** are all rather similar to those found for the corresponding stationary points in the smaller model system. The barrier for the [3,2]-rearrangement amounts to +20.1 kcal/mol at the B3LYP/6-31G(d) level of theory, which is 0.5 kcal/mol more than for the same process in **1**. Virtually no increase in reaction barrier is found for the [1,2]-pathway, which faces the same barrier in **4** and in **1** as calculated with both density functional levels. The phosphate group carries an overall negative charge of −0.40e in **5** and −0.31e in **6**. For both structures this is 0.01e less than in the corresponding transition states **2** and **3** of the small model system. Overall this indicates no major difference between calculations using hydroxy- or methoxy-substituted phosphate groups for the processes studied here. The cause for the deviating experimental and theoretical characteristics must therefore be located either in the substitution pattern of the substrate or in medium effects.

2-(Phosphatoxy)propyl Radical (7)

To evaluate the possibility of substituent effects on the substrate side, barriers for the phosphatoxy rearrangement pathways were also studied in radical **7** (Figure 2). In contrast to the two smaller model systems, the rearrangments are not degenerate anymore in **7**. Through either the [3,2]- or the [1,2]-phosphatoxy shift, the secondary radical **8** is obtained starting from the primary radical **7**. The [3,2]-phosphatoxy rearrangement through transition structure **9** faces a barrier of 17.4 kcal/mol, which is 2.2 kcal/mol less than in **1**. This more facile rearrangement is accompanied by a somewhat larger distance between the phosphate and the alkene moiety in **9** as compared to **2**. Other structural parameters are, however, unchanged. The negative charge of the phosphate group in **9** is −0.45e, which is 0.11e more negative than in ground state **7**. From all the systems studied here, this represents the structure with the highest degree of absolute and relative (to **7**) degree of charge separation. The difference from the charge development in **2** is, however, only minor. The spin density is mainly located at the propene C1 and C2 carbon atoms in **9** with coefficients of 0.41 and 0.31, respectively. The spin density coefficients at the two phosphate oxygen atoms pointing toward the propene carbon atoms are 0.16 in both cases. Considering all the details in charge and spin density distributions as well as structural changes, the lower barrier found in **7** for the [3,2]-phosphatoxy

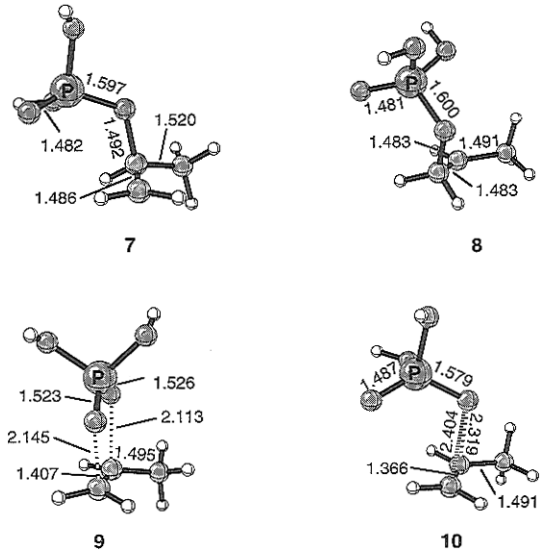


Figure 2. Ground and transition states in the rearrangement of the 2-(phosphatoxy)propyl radical (**7**) optimized at the Becke3LYP/6-31G(d) level of theory.

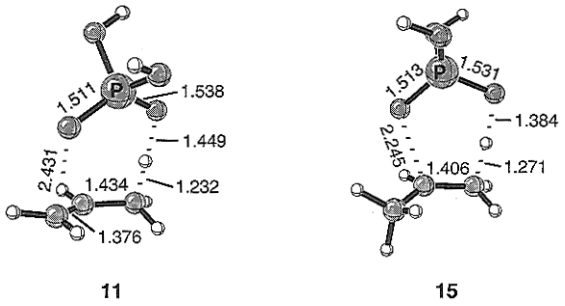


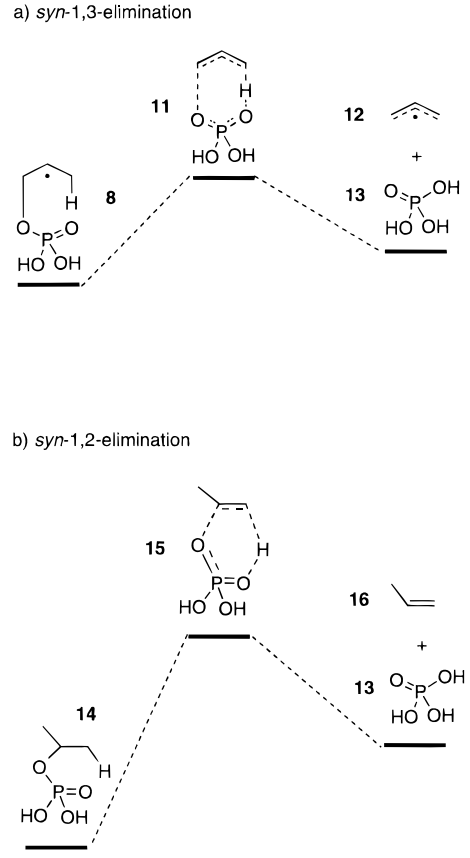
Figure 3. Transition states for phosphate elimination from the 2-(phosphatoxy)propyl radical (**8**) and from isopropyl phosphate (**14**) optimized at the Becke3LYP/6-31G(d) level of theory.

rearrangement appears to result from stabilization of the partial positive charge in the alkyl moiety through the methyl group but also through relief of some steric strain through planarization of the central carbon atom of the propene fragment, which is strongly pyramidalized in **7**, but almost planar in **9**. An even more significant lowering is found for the [1,2]-phosphatoxy rearrangement in **7** as compared to **1**. The transition structure **10** for this process is located only +16.2 kcal/mol above the ground state, 3.4 kcal/mol less than in **1**. This makes the [1,2]-shift the preferred mode of action in model system **7** at either of the two B3LYP levels of theory. The spin density in **10** is mainly located on the phosphate oxygen atom closest to the propene moiety with coefficient 0.53 and on the propene C1 and C2 carbon atoms with coefficients of 0.32 and 0.16, respectively. The phosphate group charge is −0.38e in **10**, slightly more negative than in ground state **7**. The C1−C2 bond distance is slightly larger in **10** than in **3**. Overall, the added methyl group appears to add only slightly more polar character to the transition state for [1,2]-acyloxy rearrangement. The major effect leading to a lower barrier, however, appears to be relief of steric strain through planarization of the central propene carbon atom.

Elimination of Phosphate

Radical **7** is also well suited to study the effects a radical center has on the *syn*-elimination pathway (Scheme 2a). In order to put the results obtained for the open shell system into proper perspective, the same process was also investigated for the corresponding closed shell system **14** (Scheme 2b). All attempts to locate a transition structure for *syn*-1,2-elimination starting from ground state **7** failed, and transition structure **11** was obtained instead. Following the intrinsic reaction coordinate (IRC) leads to radical **8** on one side and to a weak complex of allyl radical (**12**) and phosphate **13** on the other side. The latter complex proved hard to optimize completely, and energies for the separate products are given instead. On the basis of the IRC results, one must conclude that structure **11** is the transition state for *syn*-1,3-elimination of phosphate from radical **8**. The barrier for this process is +22.7 kcal/mol, significantly more than for either the [3,2]- or the [1,2]-phosphatoxy shift in the same system. This is also the case when B3LYP/6-311+G-(d,p) energies are used. In contrast to all other processes investigated before, however, a rather large zero point energy correction must be taken into account for the elimination process. Including this correction, the elimination barrier falls well into the range of rearrangement barriers, especially at the B3LYP/6-311+G(d,p) level of theory. Transition structure **11** is characterized through a very long C−O bond of over 2.4 Å (Figure 3) and an in-flight proton, which is somewhat closer to the donating carbon atom (1.232 Å) than the accepting oxygen atom (1.449 Å). The cumulative charge of the phosphate group is −0.14e including and −0.48e excluding the traveling proton. The spin density is mainly located at the former propene C1 and C3 atoms with coefficients of 0.40 and 0.17, at the hydrogen-accepting oxygen atom (0.17), and the other participating oxygen atom (0.16). Putting all these details into one picture, the *syn*-1,3-elimination transition structure involves an essentially free phosphate group engaged in pulling a proton away from the propene moiety. The overall elimination reaction is endothermic by 6.3 kcal/mol at the B3LYP/6-31G(d) level. Including a significant zero point energy correction and using

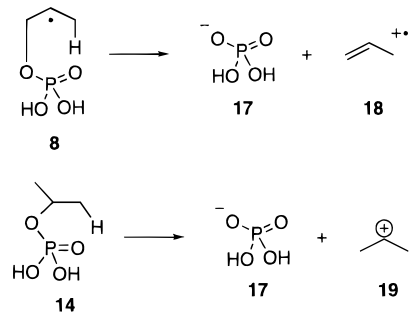
Scheme 2



single-point B3LYP/6-311+G(d,p) energies, the reaction becomes slightly exothermic.

syn-1,2-Elimination of phosphate was studied at the same level of theory for the closed shell substrate **14** (Scheme 2b). This reaction yields phosphate **13** and propene (**16**) as reaction products. As a first major difference from the open shell system, we have to note that the reaction is much less favorable thermochemically than the open shell elimination reaction, being endothermic by +23.0 kcal/mol at the B3LYP/6-31G(d) level of theory. Also, the elimination barrier is significantly higher now at +41.9 kcal/mol, more than 19 kcal/mol higher than for the open shell system. Including the large zero point energy correction of 4.8 kcal/mol, a barrier of +32.4 kcal/mol is obtained using the Becke3LYP/6-311+G(d,p) single-point energy. No experimental data appear to be available for this system. However, the "apparent" barrier for phosphate release from tri-*n*-butyl phosphate has been measured as +40 kcal/mol.[15] Despite the significant differences in reaction energetics between the open and closed shell system, no drastic differences can be found between transition structures **11** and **15** (Figure 3). The cumulative charge of the phosphate group in **15** is −0.55e without and −0.18e including the shifting hydrogen atom. As in **11**, breaking of the C−O bond is well advanced in **15** and the hydrogen atom is just in the process of moving from carbon to oxygen. In agreement with recent theoretical investigations of *syn*-1,2-eliminations[16] in related substrates, carbon oxygen bond breaking is therefore far more advanced than the proton transfer process. Two main conclusions can be derived from the comparison of phosphate elimination from radical **8** and from isopropyl phosphate (**14**). First, the *syn*-1,3-elimination mechanism appears to be another example for the possibility to expand reaction systems not only by vinyl groups (vinylology principle) but also by a radical center ("methylenology principle").[12] As has been found in earlier examples concerned with nucleophilic substitution reactions,[14,17] the basic characteristics of the reaction type are preserved in the open shell system. Second, despite all the similarities in transition state charge distribution and structure, the barrier for the 1,3-elimination is substantially lower than for the 1,2-elimination at all theoretical levels studied here. In the current case, this appears to be connected to considerably different reaction energies. Given the fact that C−O bond cleavage is far more advanced than hydrogen transfer in both cases, the main effort appears to consist in setting up the proper electrostatic environment for proton transfer. If this assumption is correct, one should assume to see some correlation between the reaction barrier and the energy required for C−O bond heterolysis in **8** and **14** (Scheme 3). In absolute terms, gas phase heterolysis is, of course, very unfavorable for both systems. In relative terms, however, the formation of dihydrophosphate **17** and propene radical cation **18** from **8** is 15 kcal/mol more favorable than formation of **17** and **19** from **14** (Table 1). Thus, most of the 17 kcal/mol difference in overall reaction energy for phosphate elimination appears to be due to differences in C−O bond heterolysis, the subsequent proton transfer being only of minor importance. The same conclusion is reached when single-point energies at the B3LYP/6-311+G(d,p) level of theory are used with or without zero point energy corrections. The considerably lower barrier for 1,3- as compared to 1,2-phosphate elimination therefore appears to be based on the radical-induced stabilization of the positive charge, which develops in intermediate stages of phosphate elimination.

Scheme 3



Conclusions

At the Becke3LYP/6-31G* level of theory, the [3,2]- and [1,2]-phosphatoxy rearrangements show similar barriers for shifts involving the phosphate and the dimethyl phosphate group. In contrast to 1,2-acyloxy rearrangements, the [1,2]-shift is much more competitive now and is usually slightly preferred over the [3,2]-shift. A significantly lower barrier is found upon introduction of alkyl substituents adjacent to the radical center. The effect is larger for the [1,2]- than for the [3,2]-shift, making the former the preferred pathway in the more highly substituted systems. As a consequence, barriers for both processes will be strongly dependent on the substituent pattern at hand. The degree of charge separation is much more significant in transition structures for the [3,2]- than for the [1,2]-rearrangement. The ratio of both processes observed in experiment should therefore also be strongly dependent on solvent polarity. The *syn*-1,3-elimination of phsophate has been described as a new type of elimination reaction. The barrier for this process is somewhat higher than for the 1,2-rearrangements but is significantly lower than for closed shell *syn*-1,2-elimination reactions.

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Supporting Information Available: Structures of all stationary points in Gaussian archive format and a table listing the absolute energies of all optimized structures (9 pages). See any current masthead page for ordering and Internet access instructions.

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