The Methylenology Principle: How Radicals Influence the Course of Ionic Reactions

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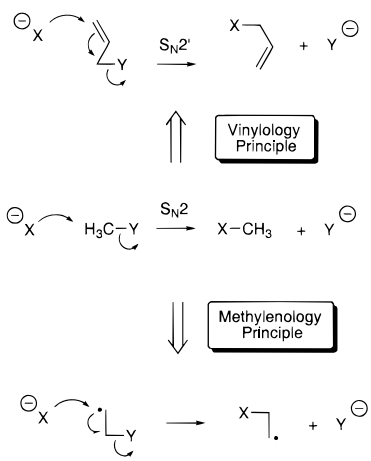
New ways to extend the scope of known reaction mechanisms are important as a source of solving reactivity and selectivity problems in organic chemistry. One well-known method is the "vinylology principle" [1] as demonstrated for the nucleophilic substitution reaction in alkyl halides in Scheme 1, which has a vinylogic counterpart in the S_N2' reaction of allylic substrates. Numerous examples for the vinylology principle suggest that the functional groups involved in a reaction can be coupled efficiently through the π-system of a C−C double bond such that the essential characteristics of the reaction type are conserved. The question arises whether this type of coupling can also be achieved through a simple methylene group, that is, half a double bond.[2,3] Is there a "methylenology principle" which allows extension of, for example, the S_N2 reaction to a novel type of nucleophilic substitution reaction with concomitant 1,2-transposition of the radical center as shown in Scheme 1? It should be emphasized at this point that we are not interested here in the homolytic reactivity of open shell substrates, but are looking for S_N2-type reactivity in appropriately substituted radicals using the radical center as a bridge between reaction centers. To test whether the methylenology principle is broadly applicable, we will also take a look at [3,3]-sigmatropic rearrangements and *syn*-elimination reactions. Besides finding new ways for understanding the chemistry of radicals in general, the methylenology principle also opens up the possibility of introducing reaction types known from closed shell compounds to the arena of radical chemistry. In the following we will analyze results from theoretical studies on small model systems and inspect a variety of experimental results documented in the literature to explore the scope and the limitations of the methylenology principle.

Scheme 1



An α-Radical Center Enhances Nucleophilic Substitution Reactions

Theoretical Studies. To study the influence of radical centers on nucleophilic substitution reactions, three small model systems have been investigated: the reaction of chloride anion with methyl and allyl chloride (Figure 1) and with the β-chloroethyl radical (Figure 2). The reaction type in the open shell case will be designated here as "$S_{RN}2^c$" to describe a bimolecular nucleophilic substitution reaction in a radical, which occurs with overall "cine" regiochemistry.[4,5] Even though our main interest is in the

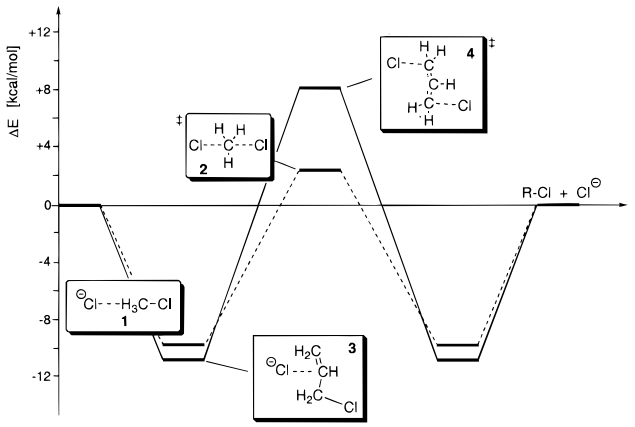


FIGURE 1. Potential energy surface for the S_N2 and S_N2' reactions as calculated at the BHLYP/6-31+G(d,p) + ΔZPE level of theory (drawn to scale).

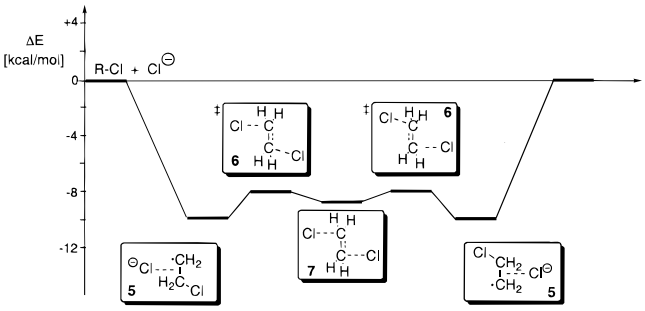


FIGURE 2. Potential energy surface for the $S_{RN}2^c$ reaction at the BHLYP/6-31+G(d,p) + ΔZPE level of theory (drawn to scale).

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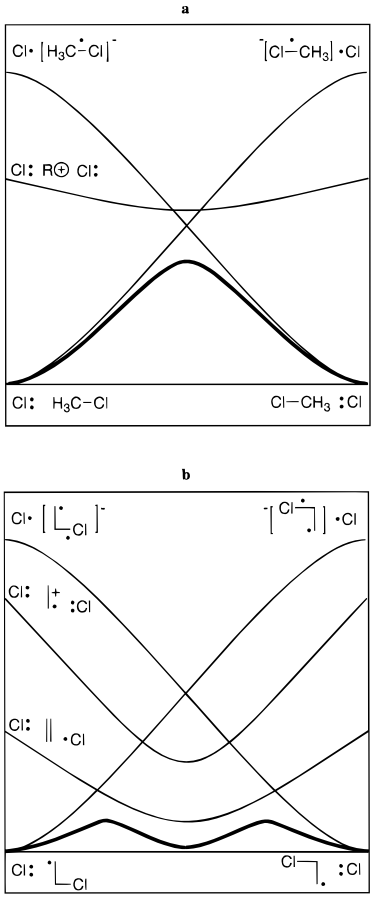
reaction of the open shell system, we will first calibrate our expectations on the known closed shell analogues. In agreement with experimental results a double-well-shaped potential energy surface is predicted for the gas-phase S_N2 reaction of methyl chloride with chloride by essentially all theoretical methods (Figure 1).[4,6−8] The binding energy of the ion−diole complex ranges around 9 kcal/mol, while the intrinsic barrier between ground-state complex **1** and transition state **2** is about 12 kcal/mol high.[6,8] A similar potential energy surface is predicted for the S_N2' reaction with allyl chloride, but the reaction barrier amounts to ΔE_A = 18.2 kcal/mol in this case.[9] The $S_{RN}2^c$ reaction (Figure 2) also starts out forming an ion−dipole complex. The subsequent course of the $S_{RN}2^c$ reaction then deviates strongly from the two closed shell cases in that the reaction barrier is a mere 2 kcal/mol and in that structure **7** corresponds to a minimum and not a transition state.[10,11] Minimum **7** is located just 1.1 kcal/mol below the true transition state **6**, yielding a potential energy surface characterized through three minima. In conclusion theoretical model studies predict that the introduction of a methylene group between the reaction centers of the S_N2 reaction leads to a strong reduction of the reaction barrier, while insertion of a double bond results in a significant barrier increase in the gas phase. The reduction of the barrier in the $S_{RN}2^c$ case studied here creates a potential energy surface including a symmetric intermediate in place of the S_N2 transition state.

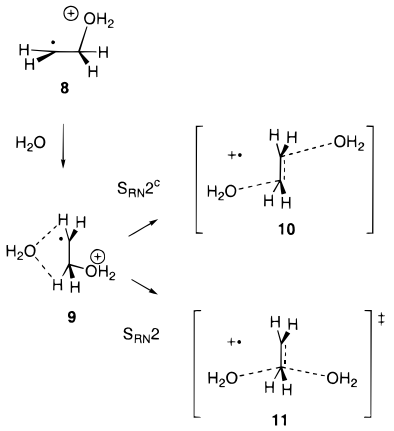
A consistent interpretation of the reaction barriers for all three reactions is possible in the framework of the valence bond curve crossing model (VBCM) by Shaik and Pross, which has been used quite successfully in the analysis of nucleophilic substitution reactions.[12,13] In this model the reaction barrier is the result of the crossing of valence bond curves describing the reactant and the product electronic configuration as well as the mixing of the reactant and product curves with intermediate electronic configurations. For the parent S_N2 reaction investigated here, the VBCM diagram includes three VB curves (Scheme 2a). The reactant curve designated "Cl^- CH_3−Cl" involves a nonpolar covalent bond between the methyl group and one chlorine atom as well as a negatively charged chloride anion. The energy of this curve is low in the reactant region but becomes less and less favorable on approaching the product region. The reverse is true for the product configuration "Cl−CH_3 Cl^-". Reactant and product configurations mix along the reaction coordinate to form the electronic ground state (shown in bold in Scheme 2). A third VB configuration designated "triple ion configuration" (Cl^- CH_3^+ Cl^-) must also be considered for the S_N2 reaction. This configuration becomes significant in the transition-state region, enhancing the ionic character of the transition state relative to the ground state. The S_N2 and S_N2' reactions can very well be discussed in the VBCM picture portrayed in Scheme 2a. The higher barrier computed for the S_N2' reaction is due to the additional electronic excitation necessary to promote the electrons in the allyl system from the reactant to the product electronic state.

Scheme 2

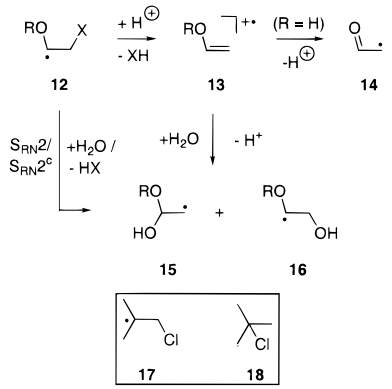


In the discussion of the $S_{RN}2^c$ reaction we again have to consider the reactant, product, and triple ion VB curves (Scheme 2b). However, the transition-state region now appears to be dominated by the low-lying "double bond" configuration, which can be described as "Cl^- CH_2=CH_2 $Cl^•$". That it is the double bond configuration which plays the key role here is clearly seen in the charge and spin density distribution of symmetric intermediate **7**. The spin density is more or less identical on all chlorine and carbon atoms of the system.[4] While spin density is positioned on the carbon atoms through the reactant, product, and triple ion configurations, it is only through the double bond configuration that spin density is brought to the chlorine atoms. A comparably low weight of the triple ion configuration would also imply the charge separation to be rather small in the open shell system. Indeed, the ab initio results show this prediction to be true.[4] We thus have to recognize that it is the interplay of typical S_N2-type reactivity with a *homolytic* bond cleavage process that creates a new type of reaction! One has to keep in mind, of course, that also in open shell systems the effects of solvent and substituents can stabilize the triple ion configuration to such a degree as to render the C−X bond cleavage essentially heterolytic. An $S_{RN}1$-type reaction involving a radical cation intermediate would then result. Not in all polar reactions will the double bond configuration be favorable enough as to force formation of a reaction intermediate. In other cases, in which the double

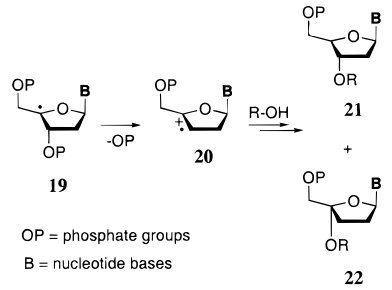
Scheme 3



Scheme 4



Scheme 5



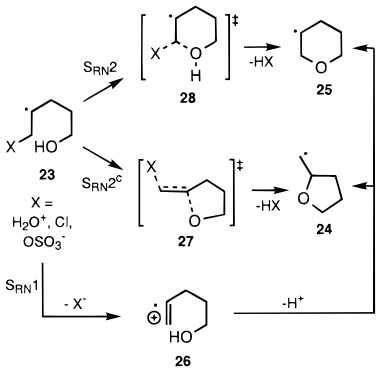
bond configuration is only modestly favorable, it will mix into the transition state of the concerted process and thereby lower the barrier.

In conclusion there is ample evidence from theoretical studies that nucleophilic substitution processes in radicals will face much lower barriers than in closed shell systems. This barrier lowering is the consequence of the mixed homolytic/heterolytic character of the dissociation process in open shell systems.

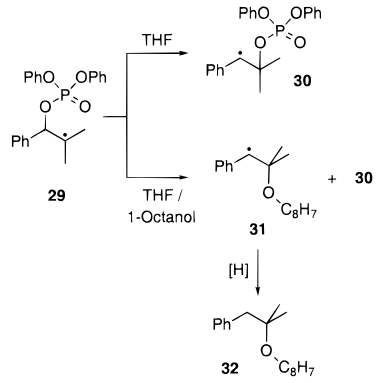
Experimental Examples. Numerous examples exist for the gas-phase reaction of nucleophiles with β-distonic radical cations such as **8** (Scheme 3).[14] Experimental gas-phase studies have shown that reaction of **8** with water or acetonitrile molecules leads to rapid displacement of the water molecule bound in **8**. The displacement process is much more efficient than proton transfer, which dominates the gas-phase chemistry of protonated ethanol, the corresponding closed shell counterpart. How competitive proton transfer is relative to the substitution process through transition states such as **10** or **11** depends, among others, on the attacking nucleophile as well as the leaving group.[15] Many more examples, in which nucleophilic substitution dominates, are known. Unfortunately, it is not possible from the presently available results to clearly identify the substitution reactions as being of the $S_{RN}1$, $S_{RN}2$, or $S_{RN}2^c$ type.

Radical-induced polar substitution and elimination reactions in polar media such as water have long been known[16−18] for radicals bearing α-alkoxy substituents such as hydroxy or methoxy and with leaving groups X = halide, phosphate, or sulfate. The proposed mechanism for these reactions (Scheme 4) starts out with radical **12** and involves proton-catalyzed loss of the anionic leaving group under formation of alkene radical cation **13**. In the presence of α-hydroxy substituents, rapid deprotonation occurs to give radical **14**. In competition with this process, water addition to radical cation **13** yields the radicals **15** and **16**. Formation of **15** and **16** through a concerted $S_{RN}2$ or $S_{RN}2^c$ process seems less likely, but cannot be rigorously excluded since **13** is usually not detected. An estimate for the increase in speed of the C−X bond heterolysis caused by the neighboring radical center can be obtained by comparing the activation energy for hydrolysis of **17** (+9 ± 1 kcal/mol) with that for **18** (+22 kcal/mol).[16c] The difference of 13 kcal/mol found here favoring the open shell system is accidentally very close to the theoretically derived difference in activation energies of ca. 12 kcal/mol for substitution in systems **1** and **5**. The high rate of solvolysis observed for β-phosphatoxy alkyl radicals[16,17] has important consequences for the interpretation of the chemistry of DNA radicals. One major pathway that has been identified for radicals located at the C4′ position of DNA or oligonucleotides such as **19** involves substitution of the 3′-phosphate group (Scheme 5).[17,18] Heterolytic fragmentation of the C3′−O bond leads to formation of alkene radical cation **20**, which is subsequently trapped by solvent and reduced to form the isolable products **21** and **22**. This $S_{RN}1$-type mechanism is supported by photocurrent measurements, by trapping of intermediate **20** with allylic alcohols, by the large influence of the 3′-phosphate protecting groups on the fragmentation rate, and, most recently, by CIDNP measurements.[19] Somewhat surprising is the face selectivity for trapping of intermediate **20**, which occurs exclusively anti to the nucleotide base **B** in the case of methanol.[16b] This result would be much more in line with active involvement of the nucleotide base in the sense that C−O bond cleavage is associated with bond formation between the radical cation and the base. Reaction with solvent would then lead to products **21** and **22** through $S_{RN}2$ and $S_{RN}2^c$ processes. Another example for radical-enhanced nucleophilic substitution is the intramolecular cyclization of radical cation **23**, which yields mainly radical **24** and only a small amount of radical **25** (Scheme 6).[20] Conceivable reaction pathways include a stepwise $S_{RN}1$-type mechanism through radical cation **26** as well as the concerted $S_{RN}2^c/S_{RN}2$ alternatives through

Scheme 6



Scheme 7



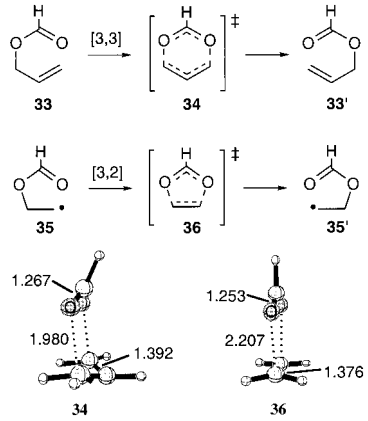
transition states **27** and **28**, respectively. In their discussion, the authors favor the concerted mechanisms and speculate that "the incipient radical-cation may not even have become a discrete species", but the experimental evidence is not sufficient to exclude either the $S_{RN}1$ or the $S_{RN}2/S_{RN}2^c$ pathway. One very recent example for a nucleophilic substitution process in open shell systems has been noted for β-phosphatoxy radical **29**, which rapidly rearranges to the benzylic radical **30** in a variety of solvents (Scheme 7).[21] Addition of small amounts of 1-octanol leads to the formation of a second benzylic radical **31**, which potentially derives from radical **29** through an $S_{RN}2^c$ process. Time-resolved measurements indicate that the rate of appearance of benzylic radicals is directly proportional to the concentration of 1-octanol, thus excluding C−O bond heterolysis in **29** as the rate-limiting step. A preparative scale experiment in octanol as the solvent and using thiols as hydrogen donors yields ether **32** in 60% yield.

A clear distinction between stepwise or concerted processes cannot be made in many of the experimental studies cited above, and unequivocal experimental evidence for the $S_{RN}2^c$ reaction mechanism is still lacking. There is, however, no doubt about the strong acceleration radical centers provide to ionic substitution processes in general.

Acyloxy Rearrangements Proceed More Readily in Radicals Than in Closed Shell Molecules

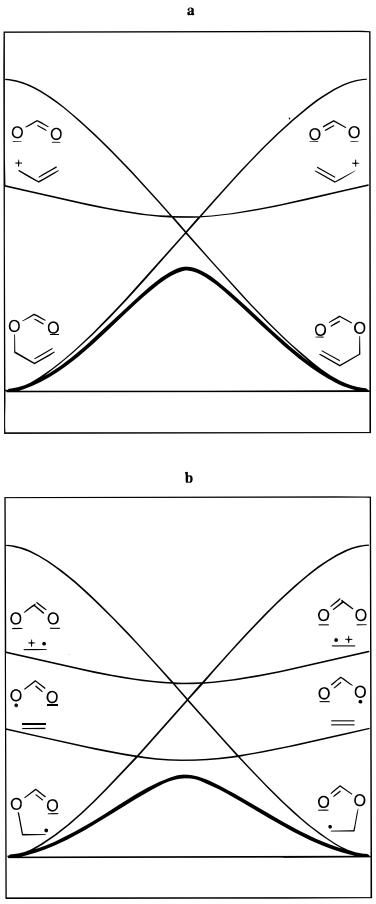
General Aspects. Rearrangement reactions involving the translocation of acyloxy groups are known in closed[22,23] and open[17,24−26] shell compounds. Both open and closed shell reactions have commonly been considered to be sigmatropic rearrangements (Scheme 8). The closed shell [3,3]-sigmatropic rearrangement in allylic esters has been studied in the gas[22b] as well as the condensed phase. The gas-phase barriers for a number of differently substituted systems range from 35 to 39 kcal/mol. The solution-phase reaction occurs more rapidly in more polar solvents than in less polar ones and shows acid catalysis. Experiments involving labeled carboxylates hint to a mainly intramolecular process. Activation barriers for the open shell [3,2]-acyloxy rearrangement in nonpolar solution range from 9 to 18 kcal/mol, the lowest values being found in highly substituted carbohydrate radicals.[17,25] The reaction shows moderate solvent effects in organic media, but proceeds much more rapidly in water.[25] Various experiments indicate the concerted, intramolecular nature of this reaction. Ab initio calculations[27] on the parent systems for both reaction types **33** and **35** are in full accord with the large barrier difference between the [3,3]- and [3,2]-rearrangement reactions and the concerted nature found experimentally. All theoretical methods considered predict the barrier for rearrangement of **35** to be lower than that for **33** by at least 22 kcal/mol.[27b]

Scheme 8



Is the dramatic change in barrier height associated with a change in mechanism? According to the ab initio studies, both reactions proceed through single transition structures (Scheme 8) from reactants to products. Most remarkably, the relative orientation of the carboxylate and alkyl groups precludes efficient overlap of the carboxylate group π-system and the π-systems of the allyl (in **34**) or ethylene (in **36**) fragment. The orbitals actively involved in the bond-making/breaking process in **35** are the carbonyl lone pair pointing toward the radical center, the singly occupied orbital, and the C−O bond linking the carboxylate group to the alkyl moiety. On the basis of these observations, both reactions should better be understood as intramolecular nucleophilic substitution reactions, in which the carboxylate group functions as the nucleophile as well as the leaving group. The rearrangement **33** → **34** → **33′** is then nothing else but an intramolecular S_N2' reaction, and the rearrangement **35** → **36** → **35′**, its methylenologic counterpart, the intramolecular $S_{RN}2^c$ reaction. The appropriate VBCM model for the closed shell

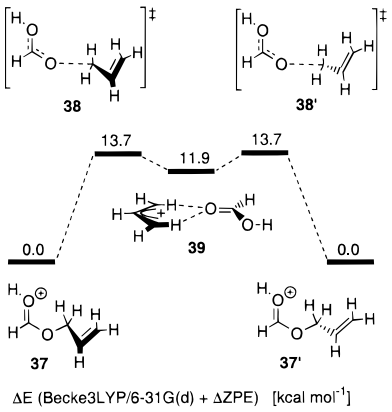
Scheme 9



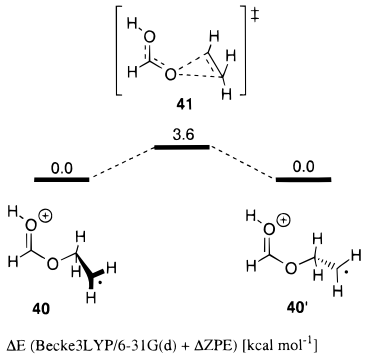
acyloxy rearrangement consists of the reactant and product VB curves as well as the triple ion configuration, which is responsible for charge polarization in the transition state (Scheme 9a). The much lower barrier in the open shell case is again due to the double bond configuration (Scheme 9b), which becomes more important in the transition-state than the ground-state region. In contrast to the anionic $S_{RN}2^c$ model system discussed before, however, the influence of the double bond configuration is not sufficiently large to force formation of a discrete intermediate in the gas phase. In both open and closed shell acyloxy rearrangement reactions, it is certainly conceivable that the influence of the triple ion configuration is enhanced through substituent or medium effects to such a degree that the overall reaction proceeds through a stepwise process involving ion pair intermediates.[17]

Does Acid Catalysis Play a Role in [3,2]-Acyloxy Rearrangements? The rate of [3,3]-acyloxy rearrangements is accelerated through the presence of acids.[22,23] The mechanistic basis of this effect is easily explored through comparison of **33** with the corresponding protonated form **37** (Scheme 10). While the [3,3]-acyloxy rearrangement in **33** proceeds in a single step and with a reaction barrier of around 39 kcal mol^{-1}, the proton-catalyzed version is a two-step reaction through intermediate **39** with a reaction barrier of around 14 kcal mol^{-1}. Even though catalysis through a free proton certainly represents an extreme way of acid catalysis, this result

Scheme 10



Scheme 11



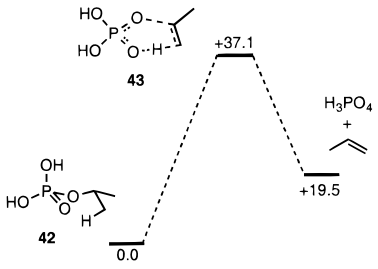
suggests that acid catalysis will be an efficient way to speed up acyloxy rearrangements in closed shell systems.

The possibility of acid catalysis for the analogous open shell [3,2]-rearrangement had not been considered to be important before. As a consequence, neither the pH dependence nor the influence of the salt or buffer concentration had been studied systematically in reactions performed in water, despite the large rate enhancement observed in this medium.[25a] Theoretical studies of model system **40**, which is derived from the neutral model system **35** through protonation of the carbonyl group, are, however, very suggestive of acid catalysis (Scheme 11): acyloxy migration in **40** faces a barrier of only 3.6 kcal mol^{-1}, more than 10 kcal mol^{-1} less than in the corresponding unprotonated system **35**. The prediction of acid catalysis of the [3,2]-acyloxy rearrangement has only recently been verified by Renaud et al., who obtained rate enhancements of up to 10^3 using Lewis acids such as scandium(III) triflate in nonpolar solution.[28] It is quite obvious that such a rate enhancement has the potential to significantly improve the synthetic utility of this reaction.

The *syn*-[1,3]-Elimination: A New Mechanism Derived from Closed Shell Analogues

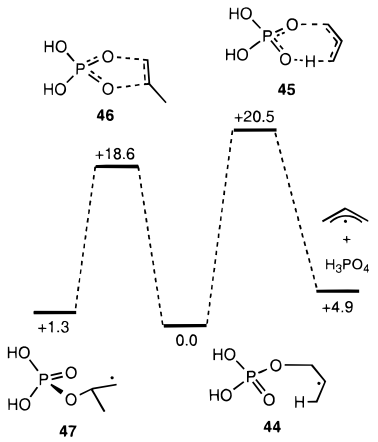
Theoretical Studies. Application of the methylenology principle to elimination reactions leads to the prediction of a [1,3]-elimination reaction. The first model systems chosen in the quest for [1,3]-*syn*-elimination reactions consisted of isopropyl phosphate **42** and the 2-(phos-

Scheme 12



ΔE (Becke3LYP/6-31G(d) + ΔZPE) [kcal/mol]

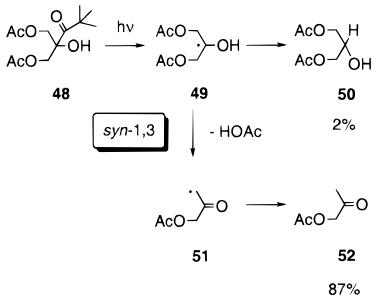
Scheme 13



ΔE (Becke3LYP/6-31G(d) + ΔZPE) [kcal/mol]

phatoxy)prop-1-yl radical **44**.[29] These small systems are models for biologically interesting organophosphates such as DNA or RNA building blocks or phospholipids. The *syn*-[1,2]-elimination of phosphate from **42** leads through transition state **43** to phosphoric acid and propene in a concerted fashion (Scheme 12). The high reaction barrier of 37.1 kcal/mol at the Becke3LYP/6-31G(d) level of theory is close to the experimentally determined "effective" activation barrier of 40 kcal/mol for elimination of butene from tri-*sec*-butyl phosphate.[30] Much like in other *syn*-elimination transition states,[31] the C−O bond in **43** is almost completely broken and the phosphate group carries a significant negative charge of −0.18e (including the migrating proton). In the open shell system **44** the *syn*-elimination occurs through transition state **45** to yield phosphoric acid and the allyl radical (Scheme 13). The reaction barrier for this step is +20.5 kcal/mol, significantly lower than for the elimination in the closed shell model system. The open shell transition structure **45** is similar to the closed shell transition structure **43** in that the C−O bond is almost completely broken and the phosphate group carries a significant negative charge of −0.14e (including the migrating proton). Considering the significantly different barriers and the fact that the phosphate group bridges across a C2-unit in **43** but a C3-unit in **45**, this similarity is quite surprising. *Syn*-elimination of phosphate from **44** competes with other low-barrier processes such as the 1,2-phosphatoxy migration through transition state **46**, yielding the primary radical **47**. Transition state **46** shows that esters of inorganic acids can also

Scheme 14



engage in the [3,2]-acyloxy rearrangement discussed before for organic esters.

On the basis of theoretical results, one can conclude that the methylenology principle is also applicable to syn-elimination reactions. As was observed already in substitution and acyloxy rearrangement reactions, the reaction barriers are again much lower in the open than in the closed shell cases. There is, however, significant similarity between the open and closed shell systems in terms of transition-state structure and charge distribution.

Experimental Examples. Given that phosphatoxy alkyl radicals such as **44** occur frequently as substructures of DNA and RNA radicals, signs of the concerted *syn*-[1,3]-elimination should surface in the chemistry of these reactive intermediates.[16,18,32,33] Most of the experimental results can, however, be explained assuming radical-induced heterolytic C−O bond fragmentation as the dominating process. The only experimental indication for the existence of *syn*-[1,3]-elimination reactions has been found in the chemistry of model systems for lipid radicals by Giese et al. (Scheme 14).[34] Photolysis of ketone **48** yields only minor amounts of the direct trapping product **50**. The main product **52** is obtained from intermediate radical **49** through elimination of acetic acid. Solvent effect data as well as theoretical results support together with rate constant measurements the *syn*-[1,3]-elimination mechanism as the most likely pathway for this process. A similar mechanistic picture has also been described for the elimination of phosphoric acids from phospholipids. The *syn*-[1,3]-elimination might also be responsible for the rapid elimination of phosphoric acid from substituted derivatives of radical **29** (Scheme 7).[21]

Limitations of the Methylenology Principle

Whether "methylenologous" variants of a given closed shell reaction mechanism can be observed experimentally depends not only on the rates of the modified process but also on the rates of competing processes. This is the main reason polar reactions in radicals are rarely observed. At least for synthetic purposes, most radicals are generated in chain processes. All elementary steps involved in a chain process have to occur at certain minimum rates for the chain to carry on.[35] Processes that are too slow will simply not be observed. The surprisingly large number of examples for elimination and substitution reactions observed in radicals of biochemical substrates can be well understood in this context as these radicals are usually

generated in a nonchain fashion. The main challenge in putting radical-induced polar reactions to work for synthetic purposes will be to either find polar processes that beat the chain or find well-working nonchain methods for radical generation and capture. A second limitation of the methylenology principle is that the newly predicted reactions might be too slow to compete with "normal" homolytic processes.

Conclusions

Using nucleophilic substitution reactions, acyloxy rearrangements, and elimination reactions as examples, we have investigated here the scope and the limitations of the methylenology principle. We have accumulated strong theoretical evidence for two new reaction types: the $S_{RN}2^c$ substitution reaction and the *syn*-[1,3]-elimination reaction. The existence of these new reaction types is also supported by some experimental evidence. In all three reactions studied here, theoretical and experimental evidence hints to considerable mechanistic analogies between the "methylenologic" variants of the reactions types, despite the fact that reaction barriers are dramatically lower in open than in closed shell systems. These results suggest that the methylenology principle can be applied to at least those reaction types, which show substantial charge separation along the reaction pathway. The root cause of significantly lower barriers of polar processes in open shell systems is the interplay of homolytic and heterolytic bond cleavage processes. The limits of this new principle are reached where "normal" homolytic reactivity wins out over radical-accelerated polar reactivity.

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