Dynamic Equilibria between Pentavalent Protonated Oxyphosphoranes and Their Isomeric Tetravalent Enol Phosphonium Ions via Inter- and Intramolecular Proton Transfer

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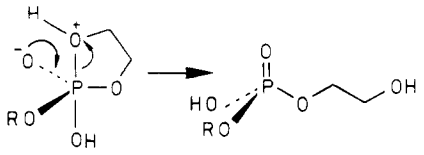
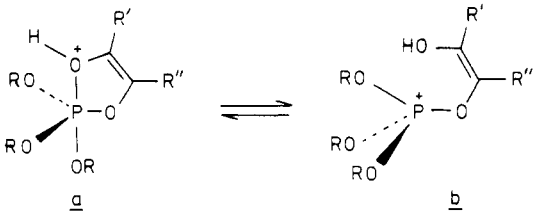
Low-temperature NMR (^1H, ^{13}C, ^{31}P) measurements of the reaction of several pentavalent oxyphosphoranes with FSO_3H in CH_2Cl_2 are described. Rapid equilibria between the neutral oxyphosphoranes and the enol phosphonium ions involving an intermolecular proton transfer can be obtained by implying certain structural constraints on the system, which means that less entropy has to be expended in order to obtain the rigid closed form of the protonated oxyphosphorane. Moreover, in one case evidence is presented for an intramolecular proton-exchange process which is also controlled by an intermediary pentavalent protonated oxyphosphorane. These reactions may be regarded as a model for intramolecular (biological) phosphorylation processes.

There is evidence that protonated pentacoordinated phosphorus intermediates play an essential role in many (bio)chemical reactions. For instance, the importance of pentavalent phosphorus, P(V), intermediates in the hydrolysis and alcoholysis of five-membered cyclic phosphates has been extensively discussed.[1] The phosphorane intermediates leading to decomposition in the acid-catalyzed processes are characterized by an apical protonated ligand. This ligand acts as the leaving group which is effectuated by the formation of the P=O bond. Similar



types of intermediates are involved in the intramolecular phosphorylation processes such as the hydrolysis of alkyl and aryl 2-hydroxyalkyl phosphates.[2] Closely related to these reactions is the hydrolysis of a ribonucleic acid or a nucleotide ester in the presence of RNase A by a two-stage mechanism.[3-5] The first stage, transphosphorylation, involves addition of the 2'-OH group (vicinal to the 3'-O-P bond) to the phosphate group with cleaving of the ribonucleic acid at the 5' end, yielding a 2'-3' cyclic phosphate. The second stage involves addition of H_2O to the cyclic phosphate, yielding a terminal 3'-phosphate monoester. The latter reaction is favored over the terminal 2'-phosphate since in the second stage His-12 is protonated, leading to 2'-O bridging and thus creating the opposite apical site for the incoming H_2O molecule. In the pentacoordinated intermediates there are two equatorial anionic oxygen atoms, shielded by protonated histidine and lysine residues.[5a]

This paper is concerned primarily with the generation of pentavalent protonated oxyphosphoranes under low nucleophilic conditions, which can provide more detailed information about the intramolecular phosphorylation which is strongly related to the transphosphorylation step in the first stage of the hydrolysis of a ribonucleic acid. Addition of acids to stable P(V) oxaphospholens yields type a phosphoranes which after apical leaving of the



protonated ligand result in the isomeric enol phosphonium ion. Effective shielding of the equatorial oxygen ligands, which is a prerequisite for stabilizing the trigonal-bipyramidal (TBP) intermediate, is effectuated in our model systems by methoxy groups. However, since previous investigations have demonstrated the extraordinary alkylation tendency of these types of compounds toward alcohols, phenols, and carboxylic acids,[6] the nucleophilic attack on the alkoxy ligands has to be suppressed. Therefore, the reactions and the kinetic studies were performed with FSO_3H.

Recently it has been shown that phosphorus in a tetrahedral configuration already bears a very high positive charge.[7] This was found by CNDO/2 calculations carried out on models for the enzymatic hydrolysis of dinucleoside phosphates. Therefore, the interesting suggestion was put forward that it would seem to be more important to activate the leaving group than to produce a more electrophilic phosphorus, especially if the transphosphorylation reaction is concerted. In our model systems, however, the phosphorylations involve attack on a phosphonium ion without transphosphorylation (expulsion of the opposite apical ligand). The products formed upon protonation are, in most cases, determined by *thermodynamic* factors, i.e., the relative stabilities of the products: c + MeOH vs. b. Only when there is a large difference in basicity between

(1) (a) Kumamoto, J.; Cox, J. R.; Westheimer, F. H. *J. Am. Chem. Soc.* **1956**, *78*, 4858. (b) Haake, P. C.; Westheimer, F. H. *Ibid.* **1961**, *83*, 1102. (c) Covitz, F.; Westheimer, F. H. *Ibid.* **1963**, *85*, 1773. (d) Eberhard, A.; Westheimer, F. H. *Ibid.* **1965**, *87*, 253. (e) Dennis, E. A.; Westheimer, F. H. *Ibid.* **1966**, *88*, 3432. (f) Westheimer, F. H. *Acc. Chem. Res.* **1968**, *1*, 70.

(2) For a review of this topic see: Bruice, T. C.; Benkovic, S. J. "Bio-organic Mechanisms"; W. A. Benjamin: New York, 1966; Vol. 2, p 37 et seq.

(3) Richards, R. F. M.; Wyckoff, H. "The Enzymes"; Boyer, P. D., Ed.; Academic Press: New York, 1971; Vol IV, Chapter 24.

(4) Hummel, J. D.; Kalnitsky, G. *Annu. Rev. Biochem.* **1964**, *33*, 15.

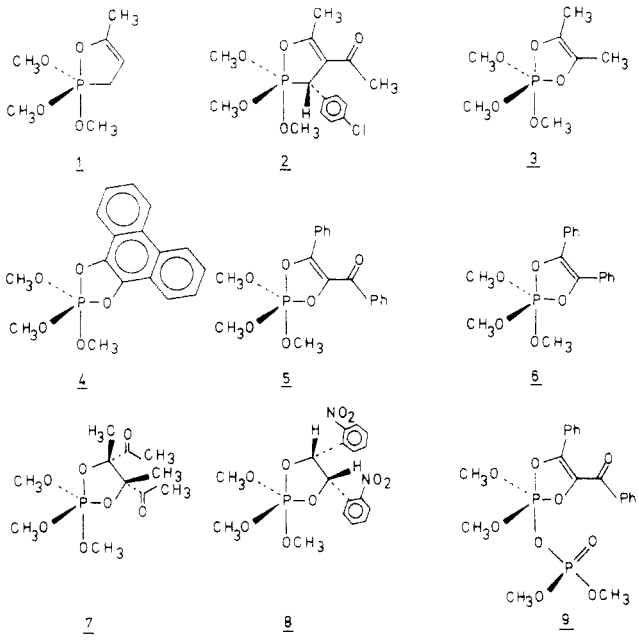
(5) (a) Gorenstein, D. G.; Wyrwicz, A. M.; Bode, J. *J. Am. Chem. Soc.* **1976**, *98*, 2308. (b) Holmes, R. R.; Deiters, J. A.; Galluci, J. C. *Ibid.* **1978**, *100*, 7393.

(6) (a) Voncken, W. G.; Buck, H. M. *Recl. Trav. Chim. Pays-Bas* **1974**, *93*, 14. (b) Voncken, W. G.; Buck, H. M. *Ibid.* **1974**, *93*, 210. (c) Voncken, W. G. Thesis, Eindhoven University of Technology, 1976. (d) Voncken, W. G.; Castelijns, A. M. C. F.; de Leeuw, S. J.; Buck, H. M. *Tetrahedron Lett.* **1977**, 729.

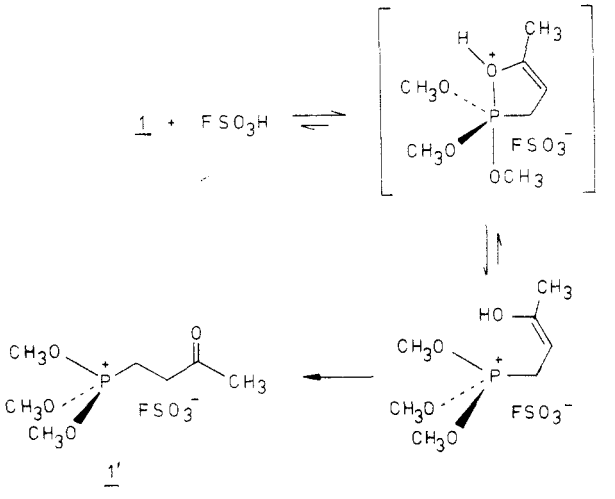
(7) Deakyne, C. A.; Leland, C. A. *J. Am. Chem. Soc.* **1979**, *101*, 3951.

0022-3263/81/1946-0047$01.00/0

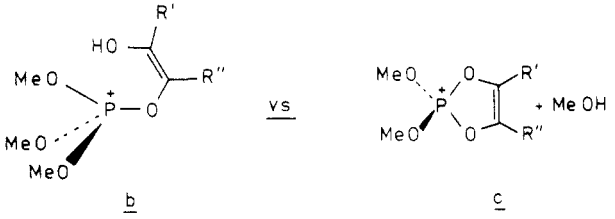
Chart I



Scheme I



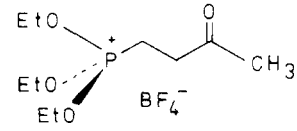
the apical ligands, as in compound **9** (vide infra), is *kinetic* control observed.



Results

(A) NMR Measurements. Variable-temperature NMR was used to study 1 M solutions of the oxyphosphoranes **1–9** (Chart I) in CH_2Cl_2 and the mixtures formed by the addition of various amounts of FSO_3H (for kinetic studies, 0.5 equiv of FSO_3H was used). In all cases except **9** (vide infra) apical ring oxygen protonation and ring opening were the primary reactions observed. In addition, most of the ring-opened phosphonium ions proved to be in equilibrium with the protonated phosphoranes as inferred from the temperature dependence of the NMR spectra.

Compound 1. The ^1H NMR spectrum of **1** at −80 °C reveals broadening of the methoxy doublet (δ 3.65, J_{PH} = 12.4 Hz) due to inhibited pseudorotation[8] (at −95 °C the structure is completely frozen, resulting in the occurrence of two methoxy doublets). When FSO_3H is added at −80 °C, an equivalent amount of **1** is immediately converted into the ketophosphonium ion **1′** (Scheme I): ^1H NMR δ 4.28 (J_{PH} = 11 Hz, d, CH_3O), 3.40–2.38 (m, CH_2CH_2), 2.28 (s, $CH_3C(O)$). The structure of **1′** is confirmed by the independent generation of the triethoxyphosphonium ion **10**, which displays completely analogous ^1H NMR reso-



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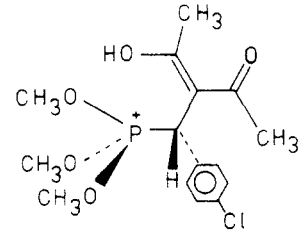
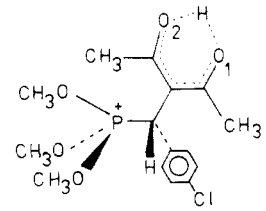
nances from the 3-oxobutyl group. In addition, the large downfield ^{31}P NMR shift of **1′** at −80 °C (δ 45 vs. H_3PO_4) is characteristic of a trialkoxyalkylphosphonium ion.[9]

Compound 2. In this case, the methoxy groups are magnetically different at −80 °C in CH_2Cl_2, indicating the inhibition of pseudorotation [^1H NMR δ 3.68 (d, J_{PH} = 14 Hz) and 3.63 (d, J_{PH} = 12.5 Hz) for the equatorial groups, δ 3.33 (d, J_{PH} = 10.5 Hz) for the apical group]. The methoxy groups become equivalent by the addition of FSO_3H; the doublet observed is located between the average position of the former doublets (δ 3.54) and the position expected for **2′** (about 4.28 ppm, by analogy to **1′**).



2′

The exact chemical shift is determined by the relative amounts of **2** and **2′** (i.e., by the amount of added FSO_3H). Thus, a very fast equilibrium must occur between **2** and **2′**, as the coalescence temperature of the methoxy doublets is ≪−80 °C. This is confirmed by the observation of a single ^{31}P signal for a mixture of **2** and **2′** at −80 °C, at a position between −30.5 ppm (**2**) and 40 ppm (**2′**) vs. H_3PO_4. In addition to these observations, coalescence of the ^1H NMR signals corresponding to the vinylic methyl group (δ 2.18) and the acetyl group (δ 2.63) occurs at −50 °C. This coalescence is explained by an equilibrium of the enol with its tautomer via intramolecular hydrogen transfer between O_1 and O_2.



intramolecular keto-enol tautomerization of **2′**

(8) Throughout this paper, the term pseudorotation is used to describe all regular permutational isomerizations of P(V) compounds. No particular mechanism is implied by this term.

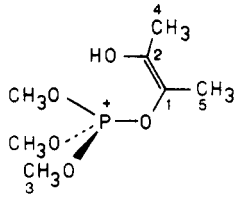
(9) Murray, M.; Schmutzler, R.; Gründemann, E.; Teichmann, H. *J. Chem. Soc. B* **1971**, 1714.

Table I. NMR Data of 3, 3', and 11[a]

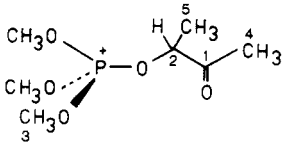
3	3'	11
	^{1}H NMR	
OCH_3, 3.57 (J_{PH} = 13)	OH, 7.92	$CHCH_3$, 5.60 ($J_{PH} = J_{HH}$ = 7)
CH_3, 1.83	OCH_3, 4.28 (J_{PH} = 11.5)	OCH_3, 4.28 (J_{PH} = 11.5)
	CH_3, 1.95	$COCH_3$, 2.28
		$CHCH_3$, 1.73 (J_{PH} = 2, J_{HH} = 7)
	^{13}C NMR	
C_1, 128.7 (J_{PC} = 3)	C_1, 138.8 (J_{PC} = 5)	C_1, 202.1
C_2, 55.0 (J_{PC} = 11)	C_2, 123.2 (J_{PC} = 9)	C_2, 85.3 (J_{PC} = 8)
C_3, 10.3 (J_{PC} = 13)	C_3, 59.7 (J_{PC} = 8)	C_3, 59.8 (J_{PC} = 7)
	C_4, 15.2	C_4, 25.0
	C_5, 14.3 (J_{PC} = 3)	C_5, 16.9
	^{31}P NMR	
^{31}P, −49.3	^{31}P, −1.0	^{31}P, −0.6

[a] Chemical shifts are given (in δ units) after the atoms to which they pertain. Coupling constants (in hertz) are given in parentheses.

Compound 3. By the addition of FSO_3H (up to 1 equiv) to a solution of **3** in CH_2Cl_2 at −100 °C, a corresponding amount of **3** is converted into a new species, to which is assigned the enol phosphonium structure **3'** on the basis

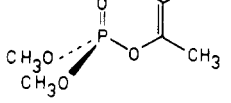


3'



11

of its ^{1}H, ^{31}P, and ^{13}C NMR parameters[10] (Table I). The peak of the vinylic methyl groups is sharpened on going from −100 to −80 °C. In contrast, the ^{1}H NMR spectrum[11] of the enol phosphate **12** shows one broad peak at −80 °C



12

but two peaks at 0 °C, reflecting the difference in shielding between these methyl groups. We therefore conclude that in **3'** the methyl groups are interchanging; this is confirmed by ^{13}C NMR where the difference in chemical shifts of the methyl groups decreases when the temperature is raised. In the mixture of **3** and **3'**, the resonances of the two species are seen separately at −100 °C; at higher temperatures first the vinylic methyl groups (at −70 °C) and then the methoxy groups (at −50 °C) of **3** and **3'** become magnetically equivalent, indicating an equilibrium between the two compounds. Consistently, the ^{31}P and ^{13}C spectra of the mixture show line-broadening effects in the temperature range −100 to 0 °C. Above 0 °C, enol **3'** undergoes irreversible rearrangement to its keto tautomer **11**. This ketophosphonium ion is also formed immediately when more than 1 equiv of FSO_3H is added to a solution of **3**, indicating that free protons accelerate the conversion of **3'** into **11**. After addition of the strong base trimethylamine to **3'**, the ^{1}H NMR at −70 °C shows a complete recovery of the neutral oxyphosphorane **3**, indicating that deprotonation of **3'** results in ring closure.

Table II. Coalescence Temperatures and Chemical Shifts of Phosphoranes and Phosphonium Ions

compd[a]	T_c,[b] °C	δ_{OCH_3}[c]	δ ^{31}P[d]
4	≃−60	3.72 (J_{PH} = 13)	−44.8
4'		4.22 (J_{PH} = 12)	−1.6
5	≃−40	3.72 (J_{PH} = 13)	−49.5
5'		4.37 (J_{PH} = 11.5)	−1.9
6	≃−20	3.76 (J_{PH} = 13)	−49.8
6'		4.20 (J_{PH} = 11.5)	+1.0
7	≃0	3.58 (J_{PH} = 12.5)	−54.0
7'		4.22 (J_{PH} = 11)	−2.5
8	>0	3.75 (J_{PH} = 12.5)	−50.7
8'		4.33 (J_{PH} = 12)	+0.5

[a] 4'-8' are the corresponding phosphonium ions formed by protonation of the endocyclic apical oxygen, followed by ring opening; cf. **3** and **3'**. [b] Coalescence temperature. [c] ^{1}H NMR chemical shift at −80 °C. Coupling constants are in hertz. [d] ^{31}P NMR chemical shift at −80 °C.

Compounds 4-8. The results for these compounds are similar to those for **3**. The coalescence temperatures (T_c) of the methoxy doublets of the oxyphosphorane and the (enol) phosphonium ion increase in the direction **4 < 5 < 6 < 7 < 8** which indicates a slower equilibrium going from **4** to **8** (see Table II).

Compound 9. In this compound, which can be regarded as a model for the intermediates generated by nucleophilic attack on pyrophosphates (e.g., ADP or ATP),[12] the phosphate group exhibits a strong preference for an apical position at the pentacoordinated phosphorus atom. This fact is evident from the temperature dependence of the ^{1}H NMR spectrum of **9**. At room temperature, the P(V)- and P(IV)-bonded methoxy groups give rise to doublets at δ 3.87 (J_{PH} = 15.75 Hz) and δ 3.70 (J_{PH} = 11.25 Hz), respectively; at temperatures below −80 °C the former doublet is broadened and finally split into two new doublets, both with a large phosphorus coupling characteristic for equatorial methoxy ligands. This behavior is interpreted as the inhibition of pseudorotation resulting in nonequivalent, equatorial methoxy groups.[13] The phosphorus resonances of compound **9** are doublets (J_{PP} = 27 Hz) at δ −7.65 for P(IV) and δ −57.65 for P(V).

Addition of less than 1 equiv of FSO_3H to a solution of **9** in CH_2Cl_2 at −80 °C causes a downfield shift for all methoxy doublets, which is primarily demonstrated by the P(IV)-bonded groups; at −55 °C, the two doublets are coincident. The phosphorus NMR spectrum reveals a new compound at δ 2.5, apart from the broadened original resonances. When the sample is warmed to −60 °C, the J_{PP} in compound **9** disappears, while the resonances at δ −7.65 and δ 2.5 coalesce. This process appears to be completely reversible with temperature. These observations indicate that protonation of **9** results in the formation of

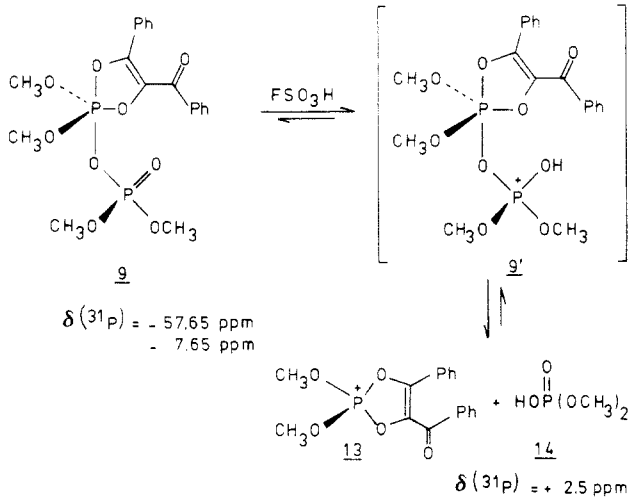
(10) (a) Castelijns, A. M. C. F.; Schipper, P.; Buck, H. M. *J. Chem. Soc., Chem. Commun.* **1978**, 382. Castelijns, A. M. C. F. Thesis, Eindhoven University of Technology, 1979.

(11) Compound **12** was prepared by the reaction of 2-methoxy-4,5-dimethyl-1,3,2-dioxaphospholene 2-oxide with 1 equiv of methanol at 0 °C. The enol phosphate is the initial product, which is gradually transformed to the keto isomer.

(12) Ramirez, F.; Chaw, Y. F.; Marecek, J. F.; Ugi, I. *J. Am. Chem. Soc.* **1974**, *96*, 2429.

(13) The plane of symmetry in compound **9** probably disappears at low temperature when the rotation of the large phosphate ligand is frozen. The preferred conformation of the phosphate group may be anti with respect to one of the methoxy ligands, since the latter groups offer more steric hindrance than the ring.

Scheme II



the protonated intermediate **9'** (Scheme II) which is immediately transformed into the species **13** and **14** which have similar chemical shifts (δ 2.5). Thus, at low temperatures, compounds **9**, **13**, and **14** are observed. When the temperature is raised, compounds **9**, **13**, and **14** equilibrate via the intermediate **9'**, as indicated by the disappearance of J_{PP} in **9** and the coalescence of the low-field resonances. The deviating behavior of this compound (exocyclic cleavage) compared to that of compounds **1–8** (ring cleavage) can be explained by the greater basicity of the exocyclic phosphato group with respect to the methoxy group.

(B) Kinetic Studies and Discussion. As is pointed out, addition of FSO_3H to a solution of **1** in CH_2Cl_2 immediately results, even at −80 °C, in protonation of the apical ring oxygen atom and a subsequent ring opening, generating the enol phosphonium ion which in turn is rapidly transformed into its thermodynamically more stable keto isomer **1'** (Scheme I). In addition, when the keto–enol tautomerization is suppressed, a rapid equilibrium is established between the enol phosphonium ion and the neutral oxyphosphorane as is demonstrated for the compounds **2–6**. The saturated compounds **7** and **8** also give rise to the formation of the phosphonium ions. However, an exchange with the neutral oxyphosphoranes is very slow.

For compounds **2–6** the equilibria are observed in the temperature range of −80 to −10 °C, and the order for the interconversion rate is **2** ≫ **4** > **3** > **5** > **6**. The equilibria between the enol phosphonium ions and the neutral oxyphosphoranes can be represented by an overall equation [eq 1, where P^+(IV) is the enol phosphonium ion and P(V) is the neutral oxyphosphorane] which includes a bimolecular proton transfer. For compound **2** a much faster rate is observed than for the other oxyphosphoranes **3–6** ($k_2/k_3 = 5.6 \times 10^3$) for which the mutual differences in rate are relatively small.

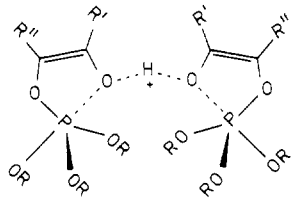
$$P^+(IV)^* + P(V) \rightleftharpoons P(V)^* + P^+(IV) \qquad (1)$$

In order to obtain a better understanding of the observed phenomena, we determined the Arrhenius parameters for the equilibria of **2** and **3** with their corresponding enol phosphonium ions from line-broadening experiments (Table III).[14] The large negative values for the entropy

Table III

compd	$\Delta H^{\ddagger}$, kJ/mol	$\Delta S^{\ddagger}$, J/(deg mol)	$\Delta G^{\ddagger}$, kJ/mol	k, L mol^{-1} s^{-1} (−25 °C)
3	11.5	−155.4	51.2	5.7×10^2
2	12.40	−75.6	31.5[15]	3.2×10^6

of activation of these reactions indicate a rate-determining bimolecular process which involves the proton-transfer step. The values for compound **2** correspond with that found for oxonium–water proton exchange processes.[16] The $\Delta H^{\ddagger}$ value for **3** is also comparable; however, its $\Delta S^{\ddagger}$ value is anomalously large and negative. Apparently, the bond-making and bond-breaking processes for proton transfer in both compounds are very similar ($\Delta H^{\ddagger}$), whereas the structural factors to attain the transition state differ significantly ($\Delta S^{\ddagger}$). Since the starting materials and products are identical (eq 1), a symmetric transition state is expected, as depicted in structure I, which shows the



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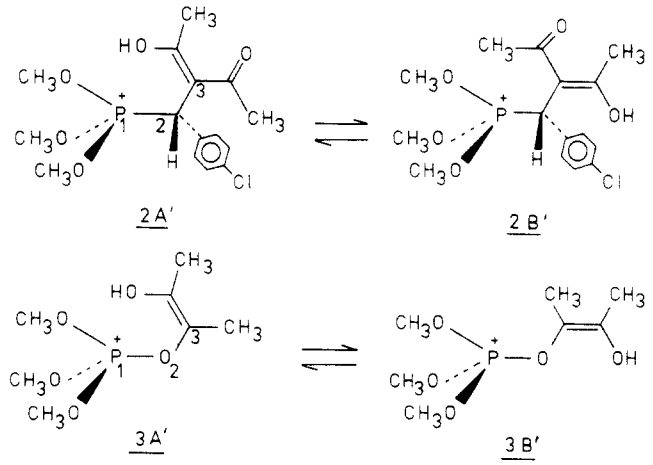
features of a ring-protonated oxyphosphorane. It will be obvious that whenever the enol phosphonium ions which are involved in the equilibria possess more rotational degrees of freedom, more entropy has to be suspended to attain the rigid closed form as depicted in structure I. The correspondence of $\Delta S^{\ddagger}$ of compound **2** with simple proton-transfer reactions (vide supra) implies a structural rigidity at the stage of the enol form which resembles the protonated oxyphosphorane ($P(V)H^+$). In contrast, compound **3** shows excess loss of entropy with respect to **2**. Therefore, **2'** occurs preferentially as conformer **2A'**,



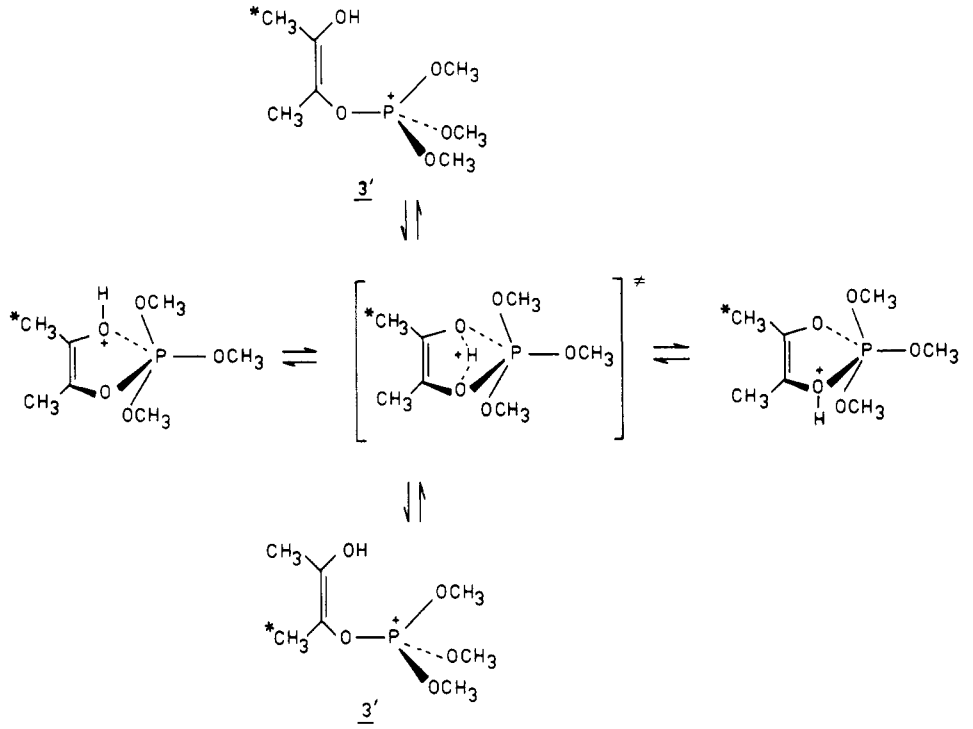
whereas in **3'** the enolic OH group to a certain extent is turned away from the phosphorus atom (the largest P–OH distance is obtained in conformer **3B'**). These structural differences may arise from steric factors. Due to the more bulky substituents in **2A'** compared to **3A'** and the smaller P(1)–C(2)–C(3) angle in **2A'** with respect to the P(1)–O(2)–C(3) angle in **3A'**, rotation around the C(2)–C(3) bond of **2A'** will be more difficult to accomplish than the analogous rotation around the O(2)–C(3) bond of **2A'**. Moreover, the interconversion of **2A'** and **2B'** does not

(14) Anbar, M.; Loewenstein, A.; Meiboom, S. *J. Am. Chem. Soc.* **1958**, *80*, 2631.

(15) The given Gibbs free energies of activation ($\Delta G^{\ddagger}$) in ref 10a must be substituted for the free energies of activation (E_a).

(16) Loewenstein, A.; Szöke, A. *J. Am. Chem. Soc.* **1962**, *84*, 1151.

Scheme III. Interchange of the Vinylic Methyl Groups of 3' Involving an Intramolecular Proton Transfer



necessarily have to imply rotation around the C(2)–C(3) bond but can also be achieved by an intramolecular keto–enol tautomerization. An analogous mechanism is possible for enol **5'** which might explain the faster equilibrium of **5** with respect to **4**. In addition, the smaller P–OH distance in **2A'** with respect to **3A'** might result in an additional stabilization of the former conformer by means of electronic interactions between the enol oxygen and the phosphorus atom.

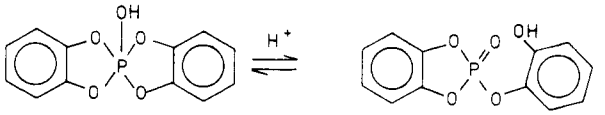
The slower interconversion observed for the saturated compounds **7** and **8** can now be understood on the basis of their larger entropy contents relative to the unsaturated analogues, originating from an increase in their rotational degrees of freedom. This implies that the probability for P(V) to encounter P^+(IV) in its isomeric P(V)H^+ form decreases, which is reflected in a slower exchange process.

In conclusion, the neutral oxyphosphoranes and their corresponding (enol) phosphonium ions equilibrate as a result of ring closure of the phosphonium ion, generating a pentacoordinated protonated intermediate which then transfers its proton to a neutral oxyphosphorane via a symmetric transition state such as depicted in structure I. Subsequent ring opening of the protonated species results in a new phosphonium ion.

Moreover, it is established that the vinylic methyl groups of the enol phosphonium ion **3'** can interchange in the absence of neutral oxyphosphorane which can only be explained by assuming an intramolecular proton-transfer mechanism (Scheme III). For the elimination of high-energy TBP configurations, the transition state for intramolecular proton transfer presumably involves a deformed TBP (e.g., a square-pyramidal configuration).

The experimental demonstration of intermolecular dynamic equilibria involving protonated oxyphosphoranes supports the intermediates which have been postulated to occur in the acid-catalyzed equilibrium between hydroxyphosphorane **15** and hydroxyphosphate **16** (Scheme IV).[17]

Scheme IV



It should be mentioned that if one of the catechol groups of **16** is substituted by an aliphatic diol, which implies an increase in $\Delta S^{\ddagger}$, it becomes much more difficult to obtain the corresponding oxyphosphorane, and under neutral or acidic conditions only the phosphate is observed.[18] This is also consonant with other literature data.[19]

The intramolecular proton exchange process of Scheme III is comparable with the mechanism of the cyclization of iminophosphorane to benzoxazaphospholine.[20]

Conclusions

It has been clearly shown that protonated oxyphosphoranes are real intermediates in the reversible interconversion between P(V) oxaphospholens and the isomeric enol phosphonium ions. The rate of these intramolecular processes can be modulated by structural manipulation within the five-membered ring. Consequently, alterations in rate are completely reflected in $\Delta S^{\ddagger}$.

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All the observed equilibria can be regarded as examples of intramolecular phosphorylation, in the sense that ring closure is accomplished by nucleophilic attack on a phosphonium ion. As expected, these phosphorylations can be very fast, in principle, due to the strongly electrophilic phosphorus atom; the rate is limited only by the orientation of the incoming nucleophile and by proton transfer from this nucleophile to neutral species. The ring closure is not accompanied by transphosphorylation involving the expulsion of methoxide or methanol. This might be expected for methoxide; however, protonation of this exocyclic group would result in a much better leaving group, methanol. There may be two explanations for the absence of methanol expulsion. (1) The resulting *cyclic* phosphonium ion is highly energetic due to considerable strain; this strain is relieved by an increase in the coordination number of phosphorus. Only in the case of a very good leaving group (e.g., the phosphate group in **9**) is a cyclic phosphonium ion (**13**, Scheme II) formed, but an equilibrium with phosphorane is still observed. (2) In comparison to the transphosphorylation step in the RNAse A reaction, the two exocyclic oxygen anions in our model systems have been shielded most effectively by means of methyl groups. This reduces the basicity of both apical oxygen atoms, but the experiments suggest that the ring oxygen is more basic than the exocyclic one.

Experimental Section

Apparatus. ^{1}H NMR spectra were recorded on a Varian Model T-60A spectrometer equipped with a Varian Model T-6080 variable-temperature accessory. Chemical shifts are reported relative to Me_4Si as the internal standard.

^{31}P and ^{13}C NMR spectra were obtained by using a Varian Model HA-100 spectrometer with a Digilab FT-NMR-3 pulsing accessory and a variable-temperature probe. Chemical shifts are reported relative to 85% H_3PO_4 and Me_4Si, respectively, as external standards.

Preparations and Reactions. 2,2,2-Trimethoxy-5-methyl-2,2,3,3-tetrahydro-1,2-oxaphosphole (1). For the preparation of **1** the method given by Westheimer[21] was slightly modified. A mixture of equivalent amounts of freshly distilled trimethyl phosphite and methyl vinyl ketone was allowed to stand for 10 days at room temperature under N_2. The product was distilled at 59–60 °C (4 mm) [lit.[21] 56–57 °C (3 mm)]: yield 60% of theory; ^{1}H NMR (CD_2Cl_2, −80 °C) δ 1.87 (m, 3 H, methyl H), 2.57 (dm, 2 H, J_{PH} = 19.5 Hz, methylene H), 3.65 (d, broadened, 9 H, J_{PH} = 12.4 Hz, methoxy H), 4.65 (dm, 1 H, J_{PH} = 49 Hz, olefinic H); ^{31}P NMR (CD_2Cl_2, −80 °C) δ −24.

2,2,2-Trimethoxy-3-(*p*-chlorophenyl)-4-acetyl-5-methyl-2,2,2,3-tetrahydro-1,2-oxaphosphole (2). To a solution of 5 g (22.5 mmol) of 3-(*p*-chlorobenzylidene)-2,4-pentanedione (prepared from *p*-chlorobenzaldehyde and 2,4-pentanedione)[22] in 50 mL of dry CH_2Cl_2 was added 2.8 g (22.5 mmol) of freshly distilled trimethyl phosphite under N_2. The reaction mixture was allowed to stand for 3 days at room temperature. The solvent was evaporated in vacuo, and the resulting oil was crystallized from hexane at 0 °C: 7 g (90% of the theory); mp 62–63 °C (lit.[6c] mp 62–63 °C); ^{1}H NMR (CD_2Cl_2, −80 °C) δ 1.95 (s, 3 H, acetyl H), 2.55 (d, 3 H, J_{HH} = 1 Hz, ring methyl H), 3.33 (d, 3 H, J_{PH} = 10.5 Hz, apical methoxy H), 3.68 (d, 3 H, J_{PH} = 14 Hz, equatorial methoxy H), 3.63 (d, 3 H, J_{PH} = 12.5 Hz, equatorial methoxy H), 4.17 (dq, 1 H, J_{PH} = 23 Hz, J_{HH} = 1 Hz, ring methine H), 7.33 (m, 4 H, phenyl H); ^{31}P NMR (CD_2Cl_2, −80 °C) δ −30.5.

2,2,2-Trimethoxy-4,5-dimethyl-2,2-dihydro-1,3,2-dioxaphosphole (3). This compound was prepared from freshly distilled biacetyl and trimethyl phosphite in a dry N_2 atmosphere:[23] yield 86%; bp 68–70 °C (1.5 mm) [lit.[23] bp 45–55 °C (0.2–0.5 mm)]; ^{1}H NMR (CD_2Cl_2, −80 °C) δ 1.85 (s, 6 H, methyl H), 3.58 (d, 9 H, J_{PH} = 13 Hz, methoxy H); ^{31}P NMR (CD_2Cl_2, −80 °C) δ −49.3.

2,2,2-Trimethoxy-4,5-(2′,2″-biphenyleno)-2,2-dihydro-1,3,2-dioxaphosphole (4). This compound was prepared according to the procedure of Ramirez[24] from trimethyl phosphite and phenanthrenequinone: yield 50%; mp 72–73 °C (lit.[24] mp 74–75 °C); ^{1}H NMR (CD_2Cl_2, −80 °C) δ 3.72 (d, 9 H, J_{PH} = 13 Hz, methoxy H), 7.93 (m, 8 H, aromatic H); ^{31}P NMR (CD_2Cl_2, −80 °C) δ −44.8.

2,2,2-Trimethoxy-4-benzoyl-5-phenyl-2,2-dihydro-1,3,2-dioxaphosphole (5). This compound was prepared from trimethyl phosphite and diphenylpropanetrione in a dry N_2 atmosphere.[19k] However, distillation of the yellow glass which ultimately is obtained only gave rise to decomposition of the product. Therefore, the synthesis was performed with a slight excess of trimethyl phosphite which after the reaction was completed could easily be removed under reduced pressure (0.1 mm). The product appeared to be NMR pure and was obtained in a quantitative yield. Due to its hygroscopicity a satisfactory elemental analysis could not be obtained. However, the physical data agree excellently with literature values:[19k] ^{1}H NMR (CD_2Cl_2, −80 °C) δ 3.72 (d, 9 H, J_{PH} = 13 Hz, methoxy H), 7.45 (m, 4 H, aromatic H), 7.75 (m, 6 H, aromatic H); ^{31}P NMR (CD_2Cl_2, −80 °C) δ −49.5 (lit.[19k] −49.3).

2,2,2-Trimethoxy-4,5-diphenyl-2,2-dihydro-1,3,2-dioxaphosphole (6). Reaction of equimolar amounts of trimethyl phosphite with solid benzil, followed by recrystallization from hexane, resulted in a nearly quantitative yield of the adduct:[24] mp 47–48 °C (lit.[24] mp 47–49 °C); ^{1}H NMR (CD_2Cl_2, −80 °C) δ 3.76 (d, 9 H, J_{PH} = 13 Hz, methoxy H), 7.18 and 7.07 (m, 10 H, aromatic H); ^{31}P NMR (CD_2Cl_2, −80 °C) δ −49.8.

***meso*-2,2,2-Trimethoxy-4,5-dimethyl-4,5-diacetyl-1,3-dioxaphospholane (7).** Reaction of adduct **3** with freshly distilled biacetyl yielded after distillation a mixture of diastereomeric 2:1 adducts.[25] Pure product with the meso configuration was obtained by fractional crystallization from pentane: yield 40%; mp 31–32 °C (lit.[25] mp 31–32 °C); ^{1}H NMR (CD_2Cl_2, −80 °C) δ 1.40 (s, broadened, 6 H, acetyl H), 2.32 (s, 6 H, methyl H), 3.58 (d, 9 H, J_{PH} = 12.5 Hz, methoxy H); ^{31}P NMR (CD_2Cl_2, −80 °C) δ −54.

***meso*-2,2,2-Trimethoxy-4,5-bis(*o*-nitrophenyl)-1,3,2-dioxaphospholane (8).** Addition of trimethyl phosphite to a solution of *o*-nitrobenzaldehyde in dry CH_2Cl_2 (1 M) at 0 °C gave rise to the formation of the dioxaphospholane.[26] The pure meso configuration was obtained by recrystallization from benzene–hexane: yield 50%; mp 120–121 °C (lit.[26] mp 120–121 °C); ^{1}H NMR (CD_2Cl_2, −80 °C) δ 3.75 (d, 9 H, J_{PH} = 12.5 Hz, methoxy H), 6.13 (d, 2 H, J_{PH} = 12 Hz, ring methine H), 7.60 (m, 8 H, aromatic H); ^{31}P NMR (CD_2Cl_2, −80 °C) δ −50.7.

2,2-Dimethoxy-2-(dimethylphosphato)-4-benzoyl-5-phenyl-2,2-dihydro-1,3,2-dioxaphosphole (9). Addition of dimethylphosphorochloridite[27,28] to an equimolar solution of the sodium salt of dimethyl phosphate[29] in ether resulted in an exothermic reaction with formation of sodium chloride. The mixture was stirred for 2 h at room temperature. The sodium chloride was filtered off with suction and thoroughly washed with ether. The ether was removed under reduced pressure, and the residue was submitted to short-path distillation (bath temperature ±90 °C). The yield of dimethylphosphorus dimethylphosphoric anhydride was nearly quantitative [bp ≃70 °C (0.05 mm)]. No satisfactory elemental analysis could be obtained, probably due to partial hydrolysis of the phosphite moiety: ^{1}H NMR ($CDCl_3$, 35 °C) δ 3.57 (d, 6 H, J_{PH} = 10.8 Hz, phosphite methyl H), 3.75

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(d, 6 H, J_{PH} = 11.4 Hz, phosphate methyl H).

Compound **9** was obtained as follows. A solution of 2.86 g of diphenylpropanetrione in 4 mL of anhydrous CH_2Cl_2 (3 M solution) was added dropwise to a solution of 2.33 g of dimethylphosphorus dimethylphosphoric anhydride in 1 mL of CH_2Cl_2 (12 M solution) at 0–5 °C with stirring under a dry N_2 atmosphere. After the reaction was completed, the solution became yellow and the solvent was removed at 20 °C under reduced pressure. The product could not be distilled but was NMR pure. Due to its hygroscopic nature no satisfactory elemental analysis could be obtained: ^{1}H NMR ($CDCl_3$, 35 °C) δ 3.70 (d, 6 H, J_{PH} = 11.25 Hz, P(IV) methoxy H), 3.87 (d, 6 H, J_{PH} = 15.75 Hz, P(V) methoxy H), 7.35 (m, 6 H, aromatic H), 7.80 (m, 4 H, aromatic H); ^{1}H NMR (CD_2Cl_2, −80 °C) δ 3.75 (d, 6 H, J_{PH} = 11.25 Hz, P(IV) methoxy H), 3.90 (d, broadened, J_{PH} = 15.75 Hz, P(V) methoxy H), 7.47 (m, 6 H, aromatic H), 7.85 (m, broadened, 4 H, aromatic H); ^{31}P NMR (CD_2Cl_2, −80 °C) δ −57.7 (d, J_{PP} = 27 Hz, P(V)), −7.7 (d, J_{PP} = 27 Hz, P(IV)).

Triethoxy-3-(oxobutyl)phosphonium Fluoroborate (10). Diethyl 3-(oxobutyl)phosphonate was obtained as follows. Addition of an equivalent amount of acetic acid to a solution of 2,2,2-triethoxy-5-methyl-2,2,3,3-tetrahydro-1,2-oxaphosphole in hexane (~0.1 M solution) resulted in an exothermic reaction with formation of ethyl acetate and the phosphonate. After evaporation of the hexane the residue could be distilled to give pure phosphonate in a nearly quantitative yield: ^{1}H NMR ($CDCl_3$, 35 °C) δ 1.27 (t, 6 H, J_{HH} = 7 Hz, ethoxy methyl H), ca. 1.90 (m, 2 H, PCH_2), 2.15 (s, 3 H, CH_3CO), ca. 2.71 (m, 2 H, CH_2CO), 4.07 (dq, 4 H, J_{PH} = J_{HH} = 7 Hz, ethoxy ethyl H).

Reaction of equivalent amounts of diethyl 3-(oxobutyl)-phosphonate and triethyloxonium fluoroborate[30] in dry CH_2Cl_2 (0.1 M solution) at room temperature for several hours resulted in the formation of the phosphonium salt **10**. The pure compound could be isolated by precipitation in ether, followed by thorough washing with ether. The compound was very hygroscopic, and elemental analysis constantly gave low C and N values: ^{1}H NMR (CH_2Cl_2, 35 °C) δ 1.47 (t, 9 H, J_{HH} = 7 Hz, ethoxy methyl H), 2.21 (s, 3 H, CH_3CO), 3.30–2.30 (m, 4 H, PCH_2CH_2), 4.55 (dq, 6 H, J_{PH} = J_{HH} = 7 Hz, ethoxy ethyl H).

Spectroscopic Study of the Reactions of Compounds 1–9 with FSO_3H in CH_2Cl_2. Fluorosulfonic acid was distilled at atmospheric pressure under a stream of dry nitrogen (bp 167 °C). Due to the very hygroscopic nature of this acid, the storage time is limited, and therefore mainly freshly distilled acid was used. For all the compounds investigated, 1 M solutions were made in CH_2Cl_2 and an aliquot (~0.4 mL) was transferred to an NMR sample tube, after which it was cooled to −85 °C. Next, approximately 0.5 equiv of FSO_3H was added, and after thorough mixing of the sample the NMR spectra of the sample were investigated in the temperature range of −80 to −10 °C. It should be mentioned that product formation (dealkylation) and keto–enol tautomerization could never be completely eliminated, and therefore, especially at higher temperatures, the measurement times were limited. Therefore, several aliquots of each compound were investigated independently. The activation energy for the equilibrium of **3** and **3′** was determined from line-broadening measurements of the methoxy doublets of both compounds in the temperature range of −50 to −15 °C in which a coalescence of these signals was observed. This experiment was repeated for a large number of independent samples in order to eliminate secondary effects due to decomposition as much as possible. The activation energy for the equilibrium of **2** and **2′** was determined from line-broadening measurements of the ^{31}P NMR signal in the temperature range of −90 to −60 °C.

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Registry No. **1**, 26192-22-3; **1′**, 75421-19-1; **2**, 75444-60-9; **2′**, 75421-20-4; **3**, 1665-79-8; **3′**, 75444-07-4; **4**, 4903-06-4; **4′**, 75421-21-5; **5**, 2908-28-3; **5′**, 75421-22-6; **6**, 4850-55-9; **6′**, 75421-23-7; **7** (isomer 1), 4130-26-1; **7** (isomer 2), 75444-08-5; **7′** (isomer 1), 75421-24-8; **7′** (isomer 2), 75444-09-6; **8**, 16190-84-4; **8′**, 75421-25-9; **9**, 75421-26-0; **10**, 75421-28-2; **11**, 75421-29-3; trimethyl phosphite, 121-45-9; methyl vinyl ketone, 78-94-4; 3-(*p*-chlorobenzylidene)-2,4-pentanedione, 19411-75-7; biacetyl, 431-03-8; phenanthrenequinone, 84-11-7; diphenylpropanetrione, 643-75-4; benzil, 134-81-6; *o*-nitrobenzaldehyde, 552-89-6; dimethylphosphorochlorite, 813-77-4; dimethyl phosphate, 813-78-5; dimethylphosphorus dimethylphosphoric anhydride, 1067-83-0; diethyl 3-(oxobutyl)phosphonate, 1067-90-9.

Relation of the Transition-State Structure for the Water-Catalyzed Hydrolysis of 1-Acetylimidazolium Ion to Solvent Hydrophobicity: Proton Inventories in Water–Acetonitrile Mixtures[1]

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The transition-state structure for the water-catalyzed hydrolysis of 1-acetylimidazolium ion has been probed in solvent systems which may mimic the hydrophobic nature of an enzyme's active site. The kinetic solvent deuterium isotope effects, k_{H_2O}/k_{D_2O}, are 2.58, 2.49, and 2.10 in water, in 0.5 vol fraction of acetonitrile in water, and in 0.9 vol fraction of acetonitrile in water, respectively. The proton inventory investigations suggest all three solvent systems entertain a transition-state structure composed of a catalytic proton bridge between the reorganizing substrate and a water molecule acting as a general-base catalyst. A "compression" of the transition-state structure in the solvent system containing the largest amount of acetonitrile is suggested to be responsible for the diminished kinetic solvent deuterium isotope effect. The reaction has been shown to be second order with respect to water.

The proton inventory technique has recently been used to help elucidate transition-state structures for a number of organic[3-12] and enzyme-catalyzed reactions.[13-20] There is no doubt that the enzymes for which the organic reac-

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