Kinetic Isotope Effects on Ethyl Metaphosphate Transfer from a Phosphoramidate to Ethanol

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Abstract: Kinetic isotope effects of nitrogen and hydrogen on thermolysis of *O*-ethyl *N*-mesityl- (**1**) and *O*-ethyl *N*-phenylphosphoramidates (**2**) in anhydrous ethanol at 80 °C are reported. The solvent hydrogen effect k_{EtOH}/k_{EtOD} is equal to 0.62 ± 0.03 for **1** and 0.67 ± 0.05 for **2**. The kinetic nitrogen isotope effect k_{14}/k_{15} was found to be equal to 1.0056 ± 0.0011 for **1** and 0.9925 ± 0.0024 for **2**. These results are consistent with a mechanism which involves proton transfer from the OH group to the nitrogen moiety. The recalculated nitrogen kinetic effect for the second step (amine departure) is equal to 1.021 for **1** and 1.008 for **2**. On this basis a metaphosphate-like transition state or "exploded" $S_N2(P)$ transition state is proposed for solvolysis of **1**. With its less bulky substituent, an earlier transition state in the unimolecular process or a change into the addition–elimination mechanism is considered for phosphoramidate **2**.

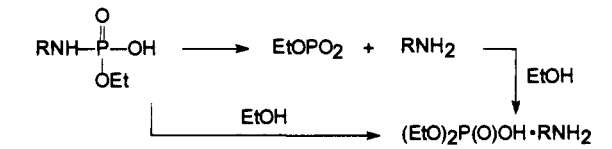
The intermediacy of ethyl metaphosphate for thermal fragmentation of *O*-ethyl phosphoramidates (EtO)P(O)(NRH)(OH), in anhydrous media was proposed on the basis of kinetics and trapping experiments.[1,2] The reaction was found to follow an elimination–addition mechanism (upper pathway on Scheme 1) when sterically demanding groups (mesityl, 1-adamantyl) were attached to nitrogen. An addition–elimination process (lower pathway on Scheme 1) is also allowed with the less bulky phenyl group.

On the basis of kinetic evidence, it was postulated[1] that the proton transfer from the OH group to the nitrogen atom is achieved in a fast preequilibrium step which precedes fragmentation of zwitterionic forms of **1** or **2** as illustrated in Scheme 2. The dipolar form of the phosphoramidic acid, which can be regarded as a "metaphosphate-base complex", decomposes to ethyl metaphosphate. The purpose of the studies described herein was to explore the metaphosphate intermediacy using isotope effects of nitrogen and hydrogen, which were measured during the thermolysis of *O*-ethyl *N*-mesitylphosphoramidate (**1**) and *O*-ethyl *N*-phenylphosphoramidate (**2**).

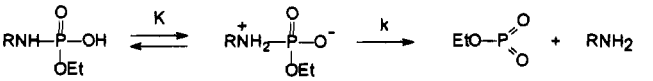
Experimental Section

Materials. Ethanol (Pharmaco Products, Inc., anhydrous) was used without purification. Ethanol-*d* (Aldrich, 99.5+ % D) was dried over magnesium. *tert*-Butyl alcohol (POCh, Poland, analytical grade) was dried over CaH_2. A solution of diazomethane in ether was prepared from Diazald (Aldrich). Substrates **1** and **2** were prepared from Na salts immediately before use according to the method described previously.[1] The sodium salt of **1** or **2** (0.5 mmol) was dissolved in methanol (15 mL) and passed through Amberlyst H^+ (Fluka). Elution was completed with 30 mL of methanol. The eluate was evaporated to dryness, and the residue was dissolved in 5 mL of CCl_4. Some solids were filtered off, and the filtrate was evaporated to dryness and then kept at low pressure (0.01 mmHg) for 30 min (yield 75%). A flask with acid **1** or **2** was purged with dry argon and weighed, and the desired amount of alcohol was added. The solution was then sealed in an NMR tube. The same procedure was applied with 5 mmol of Na salts to prepare substrates for nitrogen kinetic isotope effect experiments.

Scheme 1



Scheme 2



Isotope Effects. The solvent hydrogen isotope effect was measured in independent kinetic runs. Samples were placed in NMR tubes and kept at a constant temperature, and the rate of disappearance of substrate was determined from the diminution of the ^{31}P NMR signals.[3] The ^{31}P NMR spectra were recorded on a Bruker MSL 300 spectrometer. Only signals of substrate, product, and standard (Ph_3PO) were detected (samples that were not protected against moisture yielded additional signals around 0 ppm). Rate constants were evaluated on the basis of integration of substrate and standard.

For determination of the kinetic nitrogen isotope effect, samples of 0.2 M ethanol solutions of acids **1** or **2** were sealed under argon in glass ampules (5 mL) and kept at 80 °C. The reaction was then quenched by cooling to 0 °C, the ampules were opened, and an ethereal solution of excess diazomethane was added to convert acids into methyl esters. After 30 min the solvents were evaporated and the product (RNH)(EtO)(MeO)P=O was isolated by PLC on silica gel plates (Merck) with benzene–acetone (4:1) as an eluent (R_f = 0.54 for the mesityl derivative and R_f = 0.42 for the phenyl derivative). The methylated phosphoramidates were extracted from silica with isopropyl alcohol. The solution containing the methyl derivative of substrate (purity confirmed with GC on a Perkin-Elmer 8410 instrument equipped

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(3) Jankowski, S.; Quin, L. D. *J. Am. Chem. Soc.* **1991**, *113*, 7011.

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Table 1. Kinetic Nitrogen Isotope Effect for Thermolysis of **1** and **2** in Ethanol at 80 °C

compound	time (min)	f^a	δ_f	k_{14}/k_{15}
1	1	0.26	−6.299	1.0056 ± 0.0011[b]
	2	0.45	−5.685	
	3	0.59	−4.404	
	4	0.70	−1.066	
	5	0.78	−0.430	
2	15.5	0.31	5.043	0.9925 ± 0.0024[b]
	30	0.51	−0.479	
	45	0.66	−3.806	
	60	0.73	−4.037	
	75	0.83	−7.336	

[a] Value calculated from the rate constant. [b] The error reported is the standard deviation.

with a 6 ft by $^1/_8$ in. column of 10% SP-1000) was evaporated to dryness. Every sample contained at least 100 μmol of substrate. The phosphoramidate obtained in this way was combusted and the isotopic composition of nitrogen was measured with a Finnigan Delta S isotope ratio mass spectrometer combined on-line with a Heraeus elemental analyzer as described elsewhere.[4]

The nitrogen kinetic isotope effect was calculated from the slope of the linear dependence given below,

$$\ln(1000 + \delta_f) = \left(\frac{1}{k_{14}/k_{15}} - 1\right)\ln(1-f) + \ln(1000 + \delta_0) \quad (1)$$

where $y = \ln(1000 + \delta_f)$ and $x = \ln(1 - f)$. Values of fractions of reaction, f, were calculated for each sample using the rate constant. $\delta_f = (R_f/R_{st} - 1)1000$ is the relative isotope composition of substrate after fraction of reaction, f. R is the isotopic ratio ($^{14}N^{15}N$):($^{14}N_2$) for substrate (f) and for the standard (st), which was N_2 from air. Measured values of isotope effects are given in Table 1.

Thermolysis of 2 in *tert*-Butyl Alcohol. The solution of **2** (0.075 mol/L) in *tert*-butyl alcohol was heated to 80.0 °C in an NMR tube as in kinetic experiments described above. The thermolysis followed first-order kinetics for 1 half-life with a rate constant of (0.382 ± 0.017) × 10^{-4} s^{-1}. The ^{31}P NMR ($CDCl_3$) spectrum taken after 260 min showed resonances at δ 1.42 (52.5%) for substrate and δ −0.35 (8.7%), probably for an ethyl phosphate from the reaction of metaphosphate with traces of water, and a singlet at δ −5.11 (20.0%) for products and a doublet of doublets for the pyrophosphate type of product (δ −8.09 and δ −11.76 with J = 18.7 Hz) as were reported[1] for thermolysis of **2** in toluene. The reaction products were not isolated. We attribute a singlet at δ −5.11 to an aniline salt of (EtO)(*t*-BuO)P(O)OH.[5]

Results

The thermolysis of acids **1** and **2** in ethanol is a pseudo-first-order reaction with rate constants of (49.8 ± 0.90) × 10^{-4} s^{-1} and (4.06 ± 0.28) × 10^{-4} s^{-1}, respectively, at 80.0 °C.[1] In ethanol-*d* the corresponding rate constants are (80.8 ± 3.9) × 10^{-4} s^{-1} and (6.06 ± 0.12) × 10^{-4} s^{-1}. The solvent hydrogen isotope effect k_{EtOH}/k_{EtOD} is equal to 0.62 ± 0.03 for **1** and 0.67 ± 0.05 for **2**. The nitrogen kinetic isotope effect is k_{14}/k_{15} = 1.0056 ± 0.0011 for **1** and 0.9925 ± 0.0024 for **2** (Table 1).

Discussion

Overall, thermal fragmentation of *O*-ethyl phosphoramidates, (EtO)P(O)(NRH)(OH), involves formation of the N−H bond and P−N breakage (Scheme 2). The solvent hydrogen isotope effect remains unperturbed by the change of substituents while the nitrogen kinetic isotope effect changes significantly. The inverse deuterium solvent effect supports a previous[1] suggestion that proton transfer to nitrogen precedes the rate-determining step. Similar to our findings, an inverse or a very small deuterium solvent isotope effect had also been observed for hydrolysis of phosphoramidic acids, $RNHP(O)(OH)_2$.[6]

The observed nitrogen isotope effect for the reaction described by Scheme 2 is given by eq 2,

$$(k_{14}/k_{15})_{obs} = (K_{14}/K_{15})(k_{14}/k_{15}) \quad (2)$$

where K_{14}/K_{15} is an equilibrium isotope effect of the first step of the reaction and k_{14}/k_{15} is the kinetic isotope effect on the departure of the amine moiety. The magnitude of the equilibrium nitrogen effect can be estimated on the basis of literature data. Equilibrium ^{15}N isotope effects equal to 0.981 for $NH_3 \leftrightarrows NH_4^+$,[7] 0.984 for $RNH_2 \leftrightarrows RNH_3^+$,[7] and 0.988 for $R_3N \leftrightarrows R_3NH^+$ [8] have been reported earlier. Thus, the equilibrium nitrogen isotope effect for $RNHR' \leftrightarrows RNH_2^+R'$ can be safely estimated to be about 0.985.

The second step involves the departure of amine, and the kinetic isotope effect of nitrogen should be larger than unity. The large value of this effect is expected for an $S_N1(P)$ process, with advanced bond cleavage in the transition state and metaphosphate as an intermediate. A similar isotope effect can be expected for the concerted $S_N2(P)$ mechanism with an "exploded" transition state in which the P−N bond breaking is nearly complete and bond making has barely begun.

The observed kinetic isotope effects, corrected for the preequilibrium, give kinetic nitrogen isotope effects on the departure of the amine moiety 1.021 for ethanolysis of **1** and 1.008 for **2**. The typical range of nitrogen isotope effects on simple carbon−nitrogen bond breaking reactions[9] is 1.010−1.025.

From the large value of the nitrogen isotope effect, we conclude that the fragmentation of the zwitterionic form of **1** proceeds, consistent with kinetic data,[1] via a unimolecular process with a metaphosphate-like intermediate and with advanced phosphorus−nitrogen bond breakage in the transition state, or through an "exploded" S_N2-like transition state. For the zwitterion of **2** the nitrogen effect is much smaller. This can be interpreted in terms of an earlier transition state in the unimolecular process. The earlier transition state for **2** compared to **1** is against the Hammond postulate because the fragmentation of **2** has a larger activation energy.[10] Alternatively, thermolysis of **2** can proceed by the bimolecular mechanism with ethanol attack on the phosphorus atom before P−N bond breaking. We hoped to distinguish between these two possibilities by using *tert*-butyl alcohol to suppress an attack of solvent on a "metaphosphate-base complex," $PhNH_2^+P(O)(OEt)O^-$. *tert*-Butyl alcohol has been successfully applied as a probe of the intermediacy of monomeric metaphosphate.[11] The thermolysis of **2** followed the first-order kinetics for 1 half-life with a rate constant of (0.382 ± 0.017) × 10^{-4} s^{-1} at 80.0 °C. The reaction in the more weakly solvating *tert*-butyl alcohol is about 15 times slower than in ethanol and, contrary to the reaction in ethanol, more than one product of thermolysis was present (Scheme 3).

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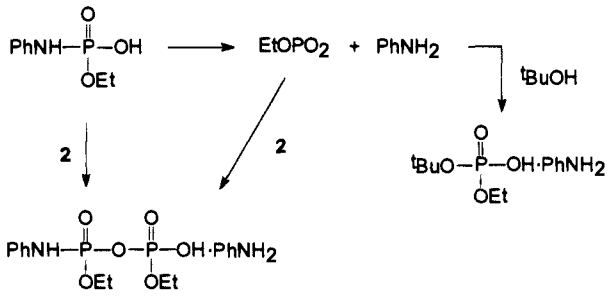
(10) The enthalpy of activation at 80 °C was reported as 67.0 ± 1.1 kJ/mol for **1** and 79.8 ± 4.7 kJ/mol for **2**, respectively (ref 1).

Scheme 3



The involvement of the phosphoramidate **2** in two competitive reactions prevents the determination of nitrogen kinetic isotope effects in *tert*-butyl alcohol.

Conclusions

The intermediacy of ethyl metaphosphate in thermal decomposition of *O*-ethyl *N*-mesityl- (**1**) and *O*-ethyl *N*-phenylphosphoramidates (**2**) in anhydrous ethanol was examined by means of kinetic isotope effects of hydrogen and nitrogen. This is the first measurement of the kinetic isotope effect of nitrogen on the phosphorus−nitrogen bond breakage process. Overall, the reaction involves formation of the N−H bond and P−N bond breakage. The solvent hydrogen isotope effect is inverse and unperturbed by the change of substituents, and leads to the conclusion that proton transfer precedes the rate−limiting step. The large value of the nitrogen isotope effect on the departure of sterically hindered mesitylamine in **1** supports a unimolecular process with a metaphosphate-like intermediate and advanced phosphorus−nitrogen bond breakage in the transition state. The alternative explanation that the reaction proceeds through an "exploded" S_N2 like transition state cannot be excluded, however. The smaller nitrogen effect for **2**, which has a less demanding substituent at nitrogen, can be interpreted as a unimolecular process with an earlier transition state or as a change into the addition−elimination mechanism.

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