PERKIN 2 COMMUNICATION

Influence of strain on hydrolysis of five-membered sulfate and phosphate esters

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Relief of ring strain in the pentacoordinate state is supported by MO calculations as an explanation for rate enhancement in alkaline hydrolysis of five-membered sulfate diesters.

Alkaline hydrolysis of five-membered phosphate and sulfate esters proceeds orders of magnitude faster than that of the acyclic esters.[1–6] The explanation for this rate enhancement has been accepted to rest primarily on relief of ring strain in the trigonal bipyramidal (TBP) pentacoordinate intermediates and transition states. However, recent MO calculations on the alkaline hydrolysis of ethylene phosphate (EP) have been interpreted to contradict the ring-strain theory.[7] Application of similar MO methods to the alkaline hydrolysis of ethylene sulfate (ES), demonstrates that in this system, the cyclic pentacoordinate intermediate is indeed substantially stabilized relative to the acyclic pentacoordinate intermediate and provides support for the ring-strain rationale for rate enhancement in sulfate ester hydrolysis.

Nucleophilic substitution reactions of phosphate esters are of prime importance in biological systems.[8] Extensive experimental work on solution reactivity by many groups assisted in the formulation of a set of predictive rules of reactivity: Westheimer's Guidelines.[9,10] The reactivity of five-membered phosphate esters is particularly significant, not only because of the relevance to ribonuclease, but because rationalizations of cyclic phosphate reactivity underpin the Guidelines. The rate accelerations of *ca.* 10^7 observed for alkaline hydrolysis of five-membered cyclic, relative to acyclic, phosphates indicates a difference in $\Delta G^{\ddagger}$ of 10–11 kcal mol^{-1}.[1–3,6,9–11] † The rationale provided is that ring strain in the tetracoordinate reactant, as manifested by small endocyclic bond angles at P, is relieved in the TBP pentacoordinate states along the reaction profile.[1–3,6,9–11] Molecular orbital (MO) calculations, directed at the pentacoordinate reaction intermediates in nucleophilic substitution at phosphorus, have in some cases been supportive of the Guidelines.[12,13] However, recently it has been argued by Dejaegere and Karplus that aqueous solvation effects explain the observed high relative reactivity of five-membered phosphates with no role for ring-strain.[7]

Experimental evidence demonstrates a similarly enhanced reactivity of five-membered sulfate diesters towards alkaline hydrolysis as observed for phosphates. The cause has been argued to be identical to that for the comparable reactivity of cyclic phosphates.[4,5] In order to examine the rationale for the enhanced reactivity in sulfate hydrolysis using MO calculations, structures along the reaction pathway for reaction of ES with OH^- were thoroughly examined with full geometry optimization at the HF/3-21 + G(*) level using Gaussian92.[14,15] Three important structures in the gas phase reaction were located; the reactant (ES), the rate-determining transition state ($\mathrm{TS_c}$) and the pentacoordinate intermediate ($\mathrm{I_c}$) (Table 1).[14] For the comparable acyclic ester reaction of dimethyl sulfate (DMS) with OH^-, the reactant (DMS) and TBP intermediates ($\mathrm{I_{ac}}$ and $\mathrm{I'_{ac}}$) were located (Table 1).‡ The structures obtained by HF/3-21 + G(*) optimization were reoptimized at higher levels of calculation, incorporating DFT and MP2 energies with Gaussian94 (Table 2).[15]

Comparison of the energies of the equilibrium structures obtained for the cyclic and acyclic reactions clearly demonstrates that the five-membered ring causes a relative stabilization of the pentacoordinate state [Fig. 1(*a*), Table 1]. The magnitude of this stabilization free energy is *ca.* 12–13 kcal mol^{-1} and the energy difference is relatively independent of the level of calculation (Table 2). Importantly, it is comparable to the experimentally observed rate enhancement for hydrolysis of the cyclic sulfate esters.

An indication of ring strain comes from comparison of endocyclic bond angles at sulfur. The values suggest significant strain in the cyclic tetracoordinate state, in contrast to the strain-free cyclic pentacoordinate state (Table 1). Comparison of calculated enthalpies of ES with trimethylene sulfate (TMS) may provide a quantitative estimate of ring strain in ES [eqn. (1)]. The strain enthalpy, calculated in this way, is 4.6 kcal mol^{-1}. However, consideration of endocyclic bond angles makes it unlikely that TMS is strain-free (Table 1).§ The calculated value should be viewed as a lower limit for relief of ring strain in the pentacoordinate state. Thus relief of ring strain may be estimated to account for at least half of the observed stabilization of the pentacoordinate state. We arrive at a conclusion to which other paths have led: relief of ring strain is important, but other factors are required to account for the large observed rate enhancements. Cogent arguments have previously been made for hybridization, steric, stereoelectronic and solvation effects.[1–3,6,9–11,18,19]

$$E(\mathrm{strain}) = [E(\mathrm{ES}) - E(\mathrm{DMS})] - [E(\mathrm{TMS}) - E(\text{methyl ethyl sulfate, MES})] \quad (1)$$

The effects of aqueous solvation can be approximated by a continuum dielectric model (CDM).[20] Although such a model may be criticized since specific hydrogen bonds are not accounted for, a similar CDM was used in calculations on EP reactivity, thus allowing valuable comparison.[7] After 'solvation' of the equilibrium structures for ES and DMS hydrolysis, *in simile* with the treatment applied to EP hydrolysis, $\Delta G(\mathrm{ES} \rightarrow \mathrm{I_c})$ *ca.* 9 kcal mol^{-1} and $\Delta G(\mathrm{DMS} \rightarrow \mathrm{I_{ac}})$ *ca.* 21 kcal mol^{-1} [Table 1,

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† 1 cal = 4.184 J.

‡ The absence of activation barriers in gas phase reactions is not exceptional (see ref. 16 and refs. therein). In EP hydrolysis, a transition-state structure, but no TBP intermediate, can be located in the gas phase (ref. 7).

§ From crystal structure determination the TMS endocyclic ∠OSO = 102.6° (ref. 17). TMS optimization at the HF/6-311G* level yields ∠OSO = 100.2°. Although this is an imperfect estimation method, it was used in and allows comparison with calculations on EP, where a strain enthalpy of 3.3 kcal mol^{-1} was calculated by this method (ref. 7).

Table 1 Relative energies, enthalpies and bond angles for TMS and MES and for ES and DMS hydrolysis[a]

	∠O–S–O/degrees	$\Delta E + E_{zp}$/kcal mol^{-1}	ΔG_{solv}[b]/kcal mol^{-1}	ΔH/kcal mol^{-1}	ΔG/kcal mol^{-1}	ΔG_{aq}[c]/kcal mol^{-1}
ES + OH^-[d]	94.7	0.00	0.00	0.00	0.00	0.00
TS_c	90.4	−4.28	+20.52	−5.01	+4.24	+24.76
I_c	84.2	−36.78	+36.12	−37.72	−27.35	+8.77
DMS + OH^-[e]	101.6	0.00	0.00	0.00	0.00	0.00
I'_{ac}	82.9	−21.70	+34.65	−22.63	−13.24	+21.41
I_{ac}	84.4	−22.39	+35.51	−23.29	−14.12	+21.39
	∠O–S–O/degrees		Energy/au		H(total)/kcal mol^{-1}	
TMS	99.3		−815.235 543 8		74.886	
MES	101.7		−816.403 203 4		89.230	

[a] MP2/6-31 + G*//HF/3-21 + G(*); HF/3-21 + G(*) geometries were used to obtain analytical frequencies and thermochemical data. [b] Continuum dielectric (CDM) solvation energies. [c] ΔG with CDM energies added. [d] E(ES) = −776.056 483 1 au, $E(OH^-)$ = −75.588 364 1 au. [e] E(DMS) = −776.095 749 3 au. 1 au = 4.36 × 10^{-18} J.

Table 2 Energies of stabilization of the cyclic pentacoordinate state[a]

	$\delta(\Delta E)$	$\delta(\Delta E + E_{zp})$
MP2/6-31 + G*//HF/3-21 + G(*)	−14.69	−14.39
MP2/6-311 + G**//HF/6-31G*	−14.46	−13.99
B3PW91/6-311 + G**//HF/6-31G*	−13.88	−13.41
B3PW91/6-311G**	−15.07	—

[a] $\delta(\Delta E) = \Delta E(I_c - ES) - \Delta E(I_{ac} - DMS)$; E_{zp} from normal mode vibrational analysis at HF/6-31G*.

Fig. 1(*a*)].¶ The relative stabilization of the cyclic pentacoordinate state (12 kcal mol^{-1}) persists and again bears comparison with the experimental rate enhancement.

The previous calculations on EP reactivity took the gas phase transition-state structures for reaction of EP with hydroxide and a comparable acyclic system, and applied a CDM solvation correction to the energies of these structures, leading to rejection of the ring-strain rationale for the observed rate enhancement in phosphates.[7] In its place aqueous solvation was offered as the explanation. The present calculations on ES reactivity show a relative stabilization of the cyclic system in the TBP pentacoordinate intermediate that is quantitatively in agreement with solution reactivity. Relief of ring-strain is indicated as a significant component of this stabilization, and hence the enhanced reactivity, with little contribution from solvation.

There is a discrepancy between the results for the cyclic sulfate and phosphate systems which may be explained if the causes of the similar rate accelerations observed in hydrolysis of five-membered cyclic phosphates and sulfates are entirely different. The assumptions implicit in the EP treatment are: (*a*) that the structures of transition states obtained by MO calculations in the gas phase are identical to those in aqueous solution and (*b*) that aqueous solvation may be treated by applying a CDM. The structure of the long-range, rate-determining transition state calculated for ES hydrolysis in the gas phase (TS_c) has the sulfate moiety little distorted from the reactant and an S • • •O(H) distance of 2.9 Å [Fig. 1(*b*)]. Evidence is required that such transition-state structures mirror those in aqueous solution.[21] The ability to calculate such transition-state structures relaxed within a solvation sphere would be beneficial. However, calculations on the high energy pentacoordinate intermediates in sulfate ester hydrolysis provide a reasonable quantitative correlation with experimental data and support for the ring-strain rationale for rate enhancement.

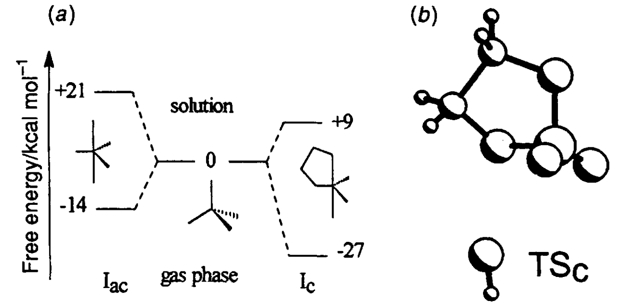

Fig. 1 (*a*) Free energies for TBP intermediates relative to reactants for ES and DMS hydrolysis (see Table 1). (*b*) Transition-state structure TS_c, $-\nu$ = 104 cm^{-1} (scaled).

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¶ The CDM algorithm of Lim and Shang was used (see ref. 20). This model is comparable to that used by Dejaegere and Karplus (ref. 7), but with atomic radii of 2.015 (S), 1.75 (O), 1.8 (C), 1.6 [H(C)] and 0.73 [H(O)]. Mulliken charges obtained at MP2/6-31 + G*//HF/3-21 + G(*) were used. Solvation energies in the monoanionic sulfate system are less than half of the values in the dianionic phosphate system (ref. 7).

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