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## Stereoelectronic Effects in the Reactions of Phosphate Diesters. Ab Initio Molecular Orbital Calculations of Reaction Profiles

*Sir:*

We have recently suggested that the selective weakening of P-O ester bonds which are trans, antiperiplanar (app) to lone pairs on directly bonded oxygen atoms may provide an important basis for further understanding enzymatic and nonenzymatic reactions of phosphate esters. Thus, we have suggested that a significant portion of the $10^6$–$10^8$-fold rate acceleration of five-membered cyclic phosphates relative to acyclic phophates derives from this stereoelectronic effect. We have also indicated that the preferential cleavage of yeast phenylalanyl transfer RNA by pancreatic ribonuclease A at only two positions along the chain originates from this stereoelectronic effect.[1]

These conclusions were based upon molecular orbital calculations on $O_I$–P–$O_2$ structural fragments in phosphate diesters and pentacovalent oxyphosphoranes. As has recently been demonstrated,[2-5] when the $O_I$ atom lone pair is app to the P–$O_2$ bond, the P–$O_I$ bond is strengthened (shown by an increase in the P–$O_I$ Mulliken overlap population) and the P–$O_2$ bond is weakened (shown by a decrease in the P–$O_2$ Mulliken overlap population).

Previous molecular orbital studies on this stereoelectronic effect have only utilized overlap population changes or bond length changes as a measure of the potential difference in reactivity of various conformations.[1-4] In this communication we wish to present the first ab initio molecular orbital study on a stereoelectronically controlled reaction surface.

Shown in Figure 1 is the reaction profile for the base-catalyzed hydrolysis of dimethyl phosphate in two different ester conformations:

$$(CH_3O)_2PO_2^- + {}^-OH \rightarrow [(CH_3O)_2PO_3H]^{2-}$$
$$\rightarrow (CH_3O)PO_3H^- + CH_3O^-$$

The points comprising the profile were computed with the Gaussian 70 series of programs, utilizing the minimal, STO-3G basis set.[6] Geometry optimization for the dimethoxyphosphorane structures shown in Figure 1 was performed in essentially the same fashion as that previously reported for dimethyl phosphate. All nonhydrogen bond lengths and bond angles $MeO_a$-P-$O^-$, $MeO_a$-P-$O_e$Me, and $^-O$-P-$O_eCH_3$ in the approximately trigonal-bipyramidal, $D_{3h}$, structures were optimized. $C_s$ symmetry for the array of five oxygens and phosphorus was assumed throughout the reaction profile. (Thus colinear $^-OH$ attack and $MeO^-$ leaving were assumed.) Extensive geometry optimization on the structure with $d_{P\text{-}OH} = 2.5$ Å was also performed for the t,g,−g conformation. The geometries for other reaction intermediates were obtained by interpolation. The same geometric parameters were assumed for the $^-OH$ attack reaction pathway involving the g,t,t intermediate. Geometries for the methoxide displacement re-

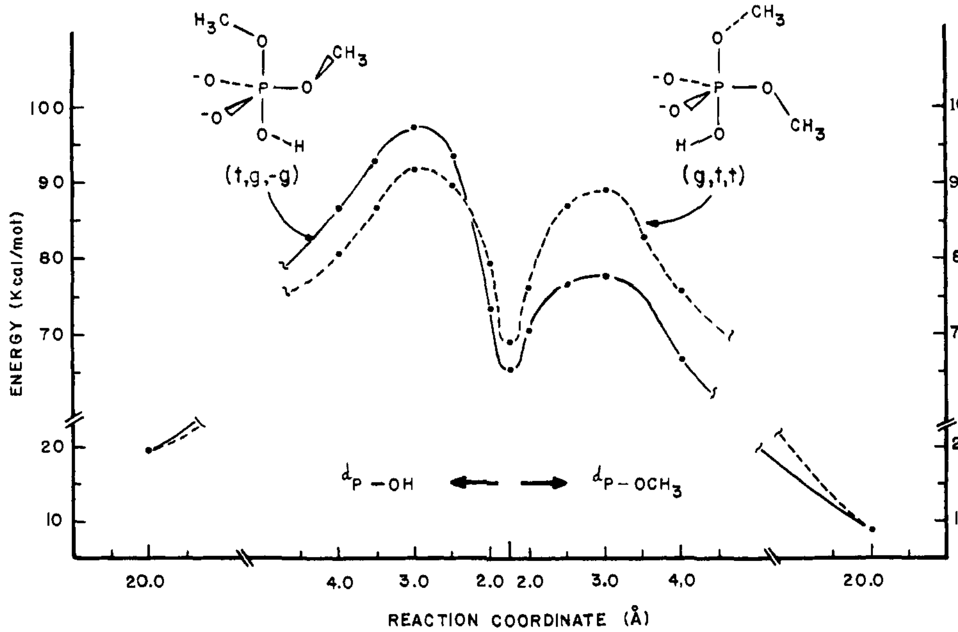

**Figure 1.** Reaction profiles for hydroxide-catalyzed hydrolysis of dimethyl phosphate in two different conformations. Torsional angles about the P-OMe bonds for the two phosphorane intermediates **1** and **2** are defined by the MeOPOMe structural fragment, and the torsional angle about the P-OH bond is defined by the $MeO_ePOH$ fragment. Conformers are defined by the following order for the torsional angles: apical ester, equatorial ester, and apical P-OH bonds. The reaction coordinate is defined by the P-OH distance ($d_{POH}$) and P-OMe distance ($d_{POMe}$) for the attack and displacement steps, respectively.

action were assumed to be identical with the $^-$OH attack pathway with OH replacing OCH$_3$. We emphasize that geometry optimization was performed on the reaction pathway involving the higher energy of the two attack transition states ($^-$OH attack, forming the t,g,−g intermediate). Thus the energy separation between the transition-state conformational isomers should only *increase* if geometry optimization was performed on the lower energy structures as well.

The reaction is computed to proceed via a metastable pentacovalent intermediate with separate transition states for the addition and elimination steps. Most significantly, for $^-$OH attack the g,t,t transition state is 5.5 kcal/mol lower energy than the t,g,−g transition state, while for CH$_3$O$^-$ displacement the t,g,−g transition state is 11.6 kcal/mol lower energy than the g,t,t transition state. These reversals agree nicely with our earlier CNDO and ab initio calculations of bond-order differences in the phosphoranes and also with the stereoelectronic effect theory. Thus for the second, displacement step the (t,g) transition state (we ignore the torsional angle designation for the other, *nontranslating,* P-OH, apical bond) is lower energy than the (g,t) transition state. We have previously shown[1,2] that the trans bond in a t,g phosphate diester or in a dimethoxyphosphorane is weaker than the gauche bond because of the app lone-pair interactions. In the $^-$OH attack step we must now relabel the torsional angles of the equatorial ester and translating apical bonds. Thus in the g,t,t structure, the translating, apical P-OH bond is trans while the equatorial ester bond is synperiplanar (spp) *to the P-OH bond,* and hence for the $^-$OH attack step the transition state in this conformer is properly designated (t,spp). Similarly, the transition state for the t,g,−g conformer is designated (−g,ac); anticlinal = (ac). The lower energy for the (t,spp), $^-$OH attack, transition state is consistent with our earlier finding that two partial app lone pairs are as effective as a single app lone pair (such as from a gauche equatorial bond) in facilitating bond translation.

These conclusions actually follow directly from a consideration of the principle of micoscopic reversibility. Since $^-$OH is chemically similar to $^-$OCH$_3$, stereoelectronic effects altering the activation energy for $^-$OH attack (or displacement) must be nearly identical with stereoelectronic effects in $^-$OCH$_3$ displacement (or attack). This rather obvious statement brings with it an important. though apparently previously unappreciated, consequence. For the stereoelectronic effect to alter the rate of a two-step reaction in which both attack and displacement steps are partially rate limiting, *rotation about the equatorial ester bond during the reaction is essential.* Otherwise, while an app lone pair on an equatorial ester bond will facilate attack, without rotation a lone pair will not be app to the leaving group. Hence the overall activation energy for the reaction will be essentially unaltered. Only with rotation about the equatorial ester bond during the reaction can the stereoelectronic effect lower the activation barrier for *both* steps and hence lower the overall activation barrier.

This rotation *during* reaction is not feasible for a concerted S$_N$2-type displacement reaction where the rotation rate will only be a fraction of the rate of translation across the top of the energy barrier. While an app lone-pair effect could facilitate the first, largely attack phase of the reaction, the latter, largely displacement stage of a single barrier pathway, cannot be helped by the now *spp* lone pair. We expect therefore that the app lone-pair effect cannot play an important role in S$_N$2-type reactions. If, however, an intermediate, no matter how high its energy, exists along the reaction pathway, bond rotation is allowed and "stereoelectronic catalysis" of both bond making and breaking is possible. The intermediate need only have a lifetime of a single bond rotation. Displacement reactions at tetrahedral carbon (S$_N$2-type) cannot be stereoelectronically catalyzed while those at tetrahedral phosphorus (and other second and third row elements) may well obey these principles since pentacovalent intermediates are realizable. In fact, we have proposed that these effects are responsible for much of the 6 kcal/mol extra stabilization of the five-membered cyclic vs. acyclic phosphate diester transition states. The substantial 5–11 kcal/mol lowering of the transition state energies for favorable app lone-pair interactions shown in Figure 1 demonstrates that effects large enough to account for the experimental observations may well be possible. It must also be emphasized that these *transition state energy differences are not due to simple steric interactions* since the lowest energy transition state for attack has the equatorial methoxyl group synperiplanar (eclipsed) to the translating apical hydroxyl group. The attack step transition state with the equatorial group staggered to the apical bonds and anticlinal to the hydroxyl group is higher energy. Note that the (g,t,t) metastable intermediate with the eclipsed bonds is 3.7 kcal/mol higher energy than the (t,g,−g) intermediate, likely attributable to the unfavorable *steric* interaction. The energies for the attack *transition state,* however, for these two isomers are thus *reversed* from their "ground-state" energies. This must reflect stereoelectronic effects.[9] These conclusions have been verified by calculations on the (t,spp,−g) conformer which again demonstrates that eclipsing of the equatorial group raises the energy of the metastable intermediate but lowers the energy of a transition state (for the displacement step now) by providing two partial app lone pairs to the translating methoxyl group.[10]

While app effects should not be important for carbon S$_N$2 reactions, they should operate in reactions involving trigonal or tetrahedral centers such as S$_N$1 and acyl addition/elimination reactions. The trigonal or tetrahedral intermediates in these reactions will generally have lifetimes long enough to permit single bond rotation. Our interpretation of the lysozyme catalyzed hydrolysis of an acetal and Deslongchamp's experimental verifaction of the stereoelectronic effect in the hydrolysis of amides and other systems[11] do not violate this requirement for bond rotation.[12]

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