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Participation of the β Phosphonate Group in Carbocation Formation

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Diethyl (2-(tosyloxy)cyclohexyl)phosphonates have been prepared to test the hypothesis that the strongly electron-withdrawing phosphonate group can stabilize the formation of a β carbocation through hyperconjugation. Systems were constructed with the 180° dihedral angle between phosphonate and tosyloxy that is optimal for such participation and with the 60° dihedral angle that minimizes it. Reactions were carried out in aqueous mixtures of ethanol, trifluoroethanol, and hexafluoro-2-propanol. The 60° case had the standard profile for bimolecular reaction with solvent (k_s), with a slower rate that is sensitive to solvent nucleophilicity. The 180° case had the standard profile for a carbocation pathway (k_c), with a faster rate that is independent of solvent nucleophilicity and with products that are possible only with a carbocation intermediate. These results suggest that the phosphonate group is capable of stabilizing a carbocation, presumably through hyperconjugation, relative to the expectation based solely on its polar effect.

In recent years there have been numerous studies of the effect of electron-withdrawing groups attached directly to carbocations (α effects).[2] Such groups, including trifluoromethyl, sulfonyl, and nitro, in general have a profound destabilizing influence through their polar effects on the already electron deficient positive charge center. In some cases, however, the destabilization is less than expected from polar effects as measured for example by σ constants. For cyano,[2,3] the destabilization is partially offset by positive charge delocalization, $>C^+C\equiv N \leftrightarrow >C{=}C{=}N^+$, reminiscent of the more standard cases of methoxyl and halogen.

Whereas such α effects of substituents on carbocations are almost always a tradeoff between a destabilizing polar effect and a stabilizing π resonance effect, the situation is quite different for a β substituent. The polar effect is much diluted and may become secondary. The major β effect for electron-donating substituents such as silicon and tin[4] is their ability to delocalize σ electrons through hyperconjugation (vertical stabilization), **1**. The desirable property of the substituent here is very high polarizability. In addition, there is a large group of β substituents capable of classical anchimeric assistance (nonvertical stabilization), including hydroxyl, alkoxyl, halogen, amino, phenyl, and alkenyl, e.g., **2**. The desirable property here is strong nucleophilicity derived from the presence of either a lone pair or a π pair.

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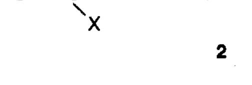

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All the existing examples of β stabilization involve net electron donors. Is it possible, as with α cyano, for a net electron-withdrawing β substituent to stabilize positive charge? Such a possibility is unprecedented and as yet unstudied except in a single case of β carbonyl, in which the dihedral dependence expected of vertical participation was not explored.[5] We have sought to determine whether there are β groups for which hyperconjugation might compensate to some extent for high electronegativity and provide some stabilization of carbocations. To avoid the mechanism involving anchimeric assistance (**2**), we excluded groups with lone pairs or strong π bonds. This exclusion applies to most unsaturated carbon-containing groups, to Group VII (halogens), to divalent Group VI (ethers, sulfides, etc.), and to trivalent Group V (amines, phosphines, etc.). Consequently, we directed our attention to high valent examples from Groups V and VI, as represented, respectively, for example, by phosphonates and sulfonates. Although there is the possibility of anchimeric assistance from the oxygen atoms, the main group element has no lone pairs and only weak π bonds. Of these groups, the phosphonate is less electron withdrawing than the sulfone or sulfonate (respective σ constants[6] about 0.51 for $(EtO)_2P{=}O$ and 0.64 for $MeSO_2$).

Consequently, we have chosen to explore the question of whether the phosphonate group is capable of providing β stabilization, whereby the polarizability of high valent phosphorus in part compensates for polar destabilization. The work of Mastalerz and co-workers has provided some precedent for such a phenomenon.[7] They found that $NH_2CH_2C(OH)(Ph)PO_3H_2$ when diazotized rearranged fully to $Ph(C{=}O)CH_2PO_3H_2$, in which the phosphonate has undergone a Wagner−Meerwein shift intact. In particular, there was no involvement of the oxygen atoms. In this case the driving force for phosphonate migration was formation of the oxonium ion. The work of Warren et

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[1] This work was supported by the National Science Foundation (Grant CHE-9302747).

[2] Creary, X. *Chem. Rev.* **1991**, *91*, 1625−1678.

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[6] Freedman, L. D.; Jaffe, H. H. *J. Am. Chem. Soc.* **1955**, *77*, 920−921.

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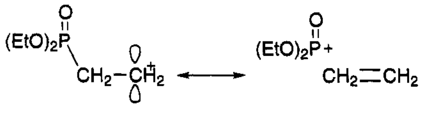
al. also found that phosphine oxides undergo Wagner–Meerwein rearrangements, again with the C—P bond intact (no P to O rearrangement).[8] In both cases the observation of a phosphorus 1,2 shift implies some ability of high valent phosphorus to stabilize positive charge on a β carbon. We have undertaken the evaluation of the ability of the phosphonate group to provide this stabilization, which can be represented by the hyperconjugative interaction **3**.



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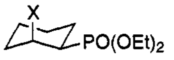
For such an interaction to be significant, the polarizability of the C—P bond must to some extent compensate for the destabilizing inductive effect. An interaction such as that shown in **3** is subject to a dihedral angle dependence in the starting material. The largest effect will be exerted when the P—C—C—X dihedral angle is 180° (parallel orbitals) (P represents the phosphonate group, X is a leaving group) and the smallest at 90° (orthogonal orbitals), with a cosine-squared gradation in between.

To test for the existence of this novel β effect, we have prepared three stereoisomers based on the cyclohexyl framework, **4**–**6**. In the cis isomer **4** the dihedral angle



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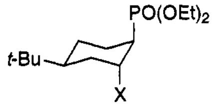
is about 60°, and the phosphonate group should provide little hyperconjugation. The trans isomer **5** is in equilibrium with the diaxial form, in which the optimal antiperiplanar (180°) stereochemistry is present. The biased trans isomer **6** has been frozen into the diaxial form. As with silicon,[9,10] it is expected that the unbiased



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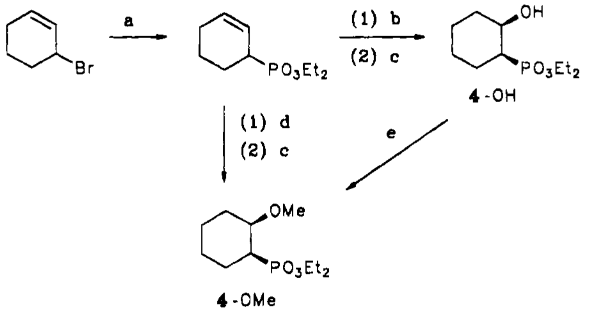
trans form readily interconverts between the diequatorial and diaxial forms but the biased form provides the better model for a β effect. We report herein the preparation of **4**–**6** and the subjection of suitable derivatives to conditions conducive to carbocation formation. By kinetics, solvent variation, and product structures, we assess the ability of the phosphonate group to exert a stabilizing β effect.

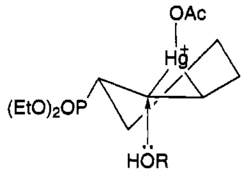
Results

Diethyl (*cis*-2-hydroxycyclohex-1-yl)phosphonate (**4**-OH) was prepared by the procedure given in Scheme 1. The phosphonate group was introduced by treatment of 3-bromocyclohexene with triethyl phosphite in the absence of solvent. The resulting diethyl (2-cyclohexen-1-yl)phosphonate was oxymercurated to give either the alcohol (**4**-OH) or the methyl ether (**4**-OMe), depending on conditions. Of the four possible regio- and stereoisomers, the desired cis-1,2 isomer was formed in predominance. The intermediate mercuronium ion for steric reasons apparently is formed preferentially trans to the existing phosphonate group, so that the incoming hydroxy or methoxy group then enters cis to phosphonate. In six-membered rings, the opening of fused three-membered rings such as epoxides occurs preferentially in a diaxial fashion, the microscopic reverse of the ring formation. Axial attack by solvent at the 3 position would result in an axial phosphonate group, whereas axial attack at the 2 position results in an equatorial phosphonate group. After mercury is removed by reduction, the resulting product is the cis-1,2 isomer. These steric considerations are summarized by structure **7**.

Scheme 1[a]



[a] Key: (a) $P(OEt)_3/\Delta$; (b) $Hg(OAc)_2/H_2O$–THF; (c) $NaBH_4/NaOH$; (d) $Hg(OAc)_2/MeOH$; (e) MeI/K_2CO_3.



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The reaction actually produced three of the four possible 1,2 and 1,3 isomers. The 1,2 isomers were easily distinguished from the 1,3 isomers by ^2J(CCP), which connects the oxygen-substituted carbon with the phosphorus. The 1,3 isomers do not have such a coupling. Our assignments follow those of Buchanan and Bower,[11] who studied ^{13}C—^{31}P couplings in phosphonates. Most of the structural work was carried out on the methoxy derivatives, which were more soluble and gave easily recognized methoxy resonances. Once **4**-OMe had been identified, **4**-OH was proved analogously and by conversion to **4**-OMe. The stereochemistry of the alcohol also was proved by comparison with the trans-1,2 isomer (below).

Diethyl (*trans*-2-hydroxycyclohex-1-yl)phosphonate (**5**-OH) was prepared straightforwardly by the treatment of cyclohexene oxide with diethyl phosphonate (Scheme 2). This previously unknown procedure was patterned after a low yield reaction of aldehydes with diethyl phosphonate.[12] The use of a stoichiometric amount of ethoxide as base greatly improved the reported yield. The isomeric nature of the cis and trans alcohols was evident from the ^1H NMR spectra. The expected trans stereochemistry from the epoxide ring opening (**5**) confirmed

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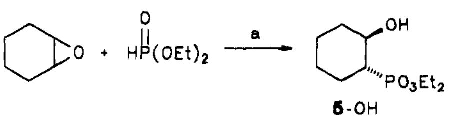
Scheme 2[a]



[a] Key: (a) NaOEt/EtOH/Δ.

Table 1. Rate Constants

	solvent[a]	temp, °C	rate, s^{-1}
4-OTs (*cis*)	97% TFE	80.0	5.12×10^{-5}
		70.0	1.04×10^{-5}
		60.0	3.16×10^{-6}
		25.0	9.22×10^{-9} [b]
	80% TFE	70.0	2.31×10^{-5}
	60% TFE	70.0	8.88×10^{-5}
	80% EtOH	70.0	2.05×10^{-5}
	70% EtOH	70.0	3.03×10^{-5}
	60% EtOH	70.0	5.22×10^{-5}
	97% HFIP	70.0	1.37×10^{-5}
5-OTs (*trans*)	97% TFE	80.0	5.13×10^{-5}
		70.0	2.49×10^{-5}
		60.0	4.33×10^{-6}
		25.0	2.95×10^{-8} [b]
	80% TFE	70.0	2.62×10^{-5}
	60% TFE	70.0	3.46×10^{-5}
	80% EtOH	80.0	2.26×10^{-5}
		70.0	1.14×10^{-5}
	70% EtOH	70.0	1.82×10^{-5}
	60% EtOH	70.0	2.79×10^{-5}
	97% HFIP	70.0	6.65×10^{-5}
6-OTs (biased *trans*)	97% TFE	86.0	2.06×10^{-4}
		80.0	1.04×10^{-4}
		70.7	4.02×10^{-5}
		70.0	3.67×10^{-5} [b]
		25.0	1.17×10^{-7} [b]
	80% TFE	80.0	1.26×10^{-4}
	60% TFE	80.0	1.47×10^{-4}
	80% EtOH	80.0	2.79×10^{-5}
	70% EtOH	80.0	4.29×10^{-5}
	60% EtOH	80.0	6.81×10^{-5}
	97% HFIP	70.0	2.66×10^{-4}

[a] Percentages are weight/weight for trifluoroethanol (TFE) and hexafluoro-2-propanol (HFIP) and volume/volume for ethanol. [b] Calculated from the Arrhenius parameters.

the original assignment of the product of the oxymercuration reaction to the cis stereochemistry (**4**). The biased trans alcohol **6**-OH was prepared in a slightly different fashion[13] by the ring opening of *trans*-4-*tert*-butylcyclohexene oxide.[10]

For the purposes of kinetic measurements, the alcohols were converted to their respective tosylates (**4**-OTs–**6**-OTs). Rates were measured in seven solvents (aqueous mixtures of ethanol, trifluoroethanol (TFE), and hexafluoro-2-propanol (HFIP)) by NMR spectroscopy at 70 °C and additionally at 60 and 80 °C in 97% TFE and 80 °C in 80% ethanol (Table 1). Arrhenius plots (correlation coefficients 0.995 for cis, 0.98 for trans, 0.999 for biased trans) from these data yielded activation parameters in 97% TFE (Table 2). Products were determined in 97% TFE and in 80% ethanol (Table 3).

Discussion

The three substrates include a material in which phosphonate is stereoelectronically available for hyperconjugation in an intermediate carbocation (the biased trans form, **6**-OTs), a second material with minimal hyperconjugation that would react directly with solvent (the cis isomer, **4**-OTs), and a third material that is a mixture of conformations and might react by a mixture of mechanisms (the trans isomer, **5**-OTs). The carbocation pathway is referred to as k_c and the direct reaction with solvent as k_s. The latter reaction encompasses solvent displacement at carbon, elimination by reaction of solvent with a hydrogen β to tosylate, and solvent attack on other atoms of the nucleofuge (more common for hydrolysis of carboxylate leaving groups). If all three substrates reacted by the k_s mechanism, and if the phosphonate provides the common function of slowing down departure of the nucleofuge through σ electron withdrawal, they should all have the same reactivity profile. Consequently, our objective was to see if there are mechanistic differences between the cis and the biased trans molecules, with the unbiased trans molecule serving as an intermediate case. We have used three lines of evidence to characterize the systems: (1) relative rates, (2) response to changes in solvent nucleophilicity and ionizing power, and (3) product structures.

Table 2. Activation Parameters in 97% Trifluoroethanol (25 °C)

	4-OTs (cis)	**5**-OTs (trans)	**6**-OTs (biased trans)
E_a, kcal/mol	32.5	29.0	26.1
log A	15.77	13.73	12.16
$\Delta H^{\ddagger}$, kcal/mol	31.9	28.4	25.4
$\Delta S^{\ddagger}$, cal/deg mol	11.6	2.3	−5.2
$\Delta G^{\ddagger}$, kcal/mol	28.4	27.7	26.9

Table 3. Product Studies at 70 °C

substrate	product	97% TFE	80% EtOH
4-OTs (*cis*)	**8**-H	73	83
	5-OEt		8
	5-OCH_2CF_3	8	
	5-OH	19	9
5-OTs (*trans*)	**8**-H	12	11
	9-H	45	54
	4-OEt		27
	4-OCH_2CF_3	20	
	4-OH	23	8
6-OTs (biased *trans*)	**8**-*tert*-butyl	2	2
	9-*tert*-butyl	52	65
	10-OEt		9
	10-OCH_2CF_3	18	
	10-OH	26	21
	11	2	3

The β effect of silicon is the classic example of hyperconjugative stabilization of an adjacent carbocation.[4] Whereas cyclohexyl tosylate reacts in aqueous media by a standard k_s pathway, introduction of a β silyl group changes the mechanism to k_c.[10] The presence of a trans β silyl group imparts an enormous rate acceleration to the system.[9,10] For this reason, we examined the present phosphonates for kinetic evidence of hyperconjugation. The appropriate point of comparison again is cyclohexyl tosylate (k(25 °C) = 1.70×10^{-6} s^{-1} and k(70 °C) = 2.77×10^{-4} s^{-1} by our own measurements in 97% TFE). At 25 °C in 97% TFE, the cis tosylate reacts 0.0054 times as fast as cyclohexyl, because of the very large rate depressing effect of phosphonate through its polar effect (positive charge is developed in the k_s transition state). The biased trans form reacts 0.069 times as fast as cyclohexyl and the unbiased trans form 0.0174 times as fast. Thus, there is a biased trans/cis acceleration of 12.7 (the acceleration ratio for the unbiased trans form is 3.2). These numbers are diluted to 3.5 and 2.4 at 70 °C, but the trend is the same. The modest acceleration of 12.7 corresponds to a 1.5 kcal mol^{-1} free energy difference

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(Table 2) or a 6.5 kcal mol^{-1} enthalpic difference, as the cis form has a more favorable entropy of activation. We also examined the three systems in 97% HFIP at 70 °C and found a biased trans/cis ratio of 19.4 and an unbiased trans/cis ratio of 4.9. These accelerations are suggestive of but not compelling for a mechanistic change.

If the change in the rate acceleration from 3.2 for the unbiased trans tosylate to 12.7 for the biased form is due entirely to a freezing in of the diaxial conformation, the small increase implies that there already is a substantial amount of diaxial form present in the unbiased case. Although the A values of phosphonate at about 2.5 and of tosylate at about 1.0 imply a large diequatorial proportion, the interaction between the two groups militates against this form. Thus, introduction of the biasing *tert*-butyl group has a smaller effect on the rate than expected from the A values. Consistent with this observation, the line width for the proton α to phosphonate changes only from 16.1 Hz for the unbiased **5**-OTs to 13.2 Hz for the biased **6**-OTs. These observations may even imply anomeric-effect-like ground-state stabilization of the antiperiplanar form, as found for β-silyl esters.[14]

In order to explore differences in molecularity, we utilized the Raber–Harris[15–17] approach, which exploits the differences in nucleophilicity and ionizing power of aqueous ethanol and of aqueous TFE. Whereas variation of the proportion of ethanol with water changes the ionizing power but not the nucleophilicity, variation of the proportion of TFE with water changes the nucleophilicity but not the ionizing power. Raber, Harris, and their co-workers plotted the logarithm of the rate of a given substrate versus that of 1-adamantyl bromide, which must react by a carbocation mechanism (k_c). If the substrate also reacts by a k_c mechanism, the plot yields a straight line (the TFE points cluster in the upper righthand corner, as there are no rate changes with nucleophilicity along either axis). On the other hand, if the substituent reacts by a solvent participation (k_s) mechanism, the two solvents give different lines: the ethanol points stretch out along the x axis as the adamantyl rate varies with ionizing power, whereas the trifluoroethanol rates stretch out along the y axis as the substrate rate varies with nucleophilicity.

The Raber–Harris plot for the cis substrate (Figure 1) contains the two lines (r = 0.989 and 0.9999) that are diagnostic for solvent participation (k_s), similar to cyclohexyl tosylate. In particular, the rate in the TFE mixtures varies about 1 order of magnitude in response to changes in solvent nucleophilicity. On the other hand, the plot for the biased trans substrate (Figure 2) has the classic form for a carbocation pathway (k_c), a single line (r = 0.995) with the TFE points bunched because the rate is not sensitive to solvent nucleophilicity, similar to the plots for β-silyl esters.[10] It is clear that there has been a mechanistic change between the two structures. It is interesting that the unbiased trans case exhibits an intermediate form (Figure 3). The TFE points here are bunched for **5**-OTs, suggesting that in this solvent the mechanism is k_c, but the ethanol points are not on the same line. By themselves, the ethanol points of **5**-OTs give a linear plot with r = 0.9997, but with the TFE

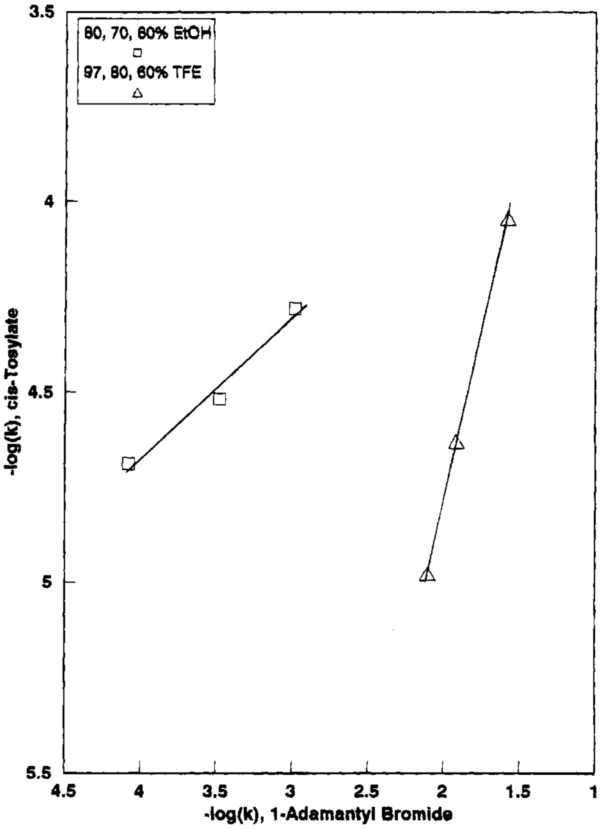

Figure 1. Raber–Harris plot for diethyl (*cis*-2-(tosyloxy)-cyclohex-1-yl)phosphonate (**4**-OTs).

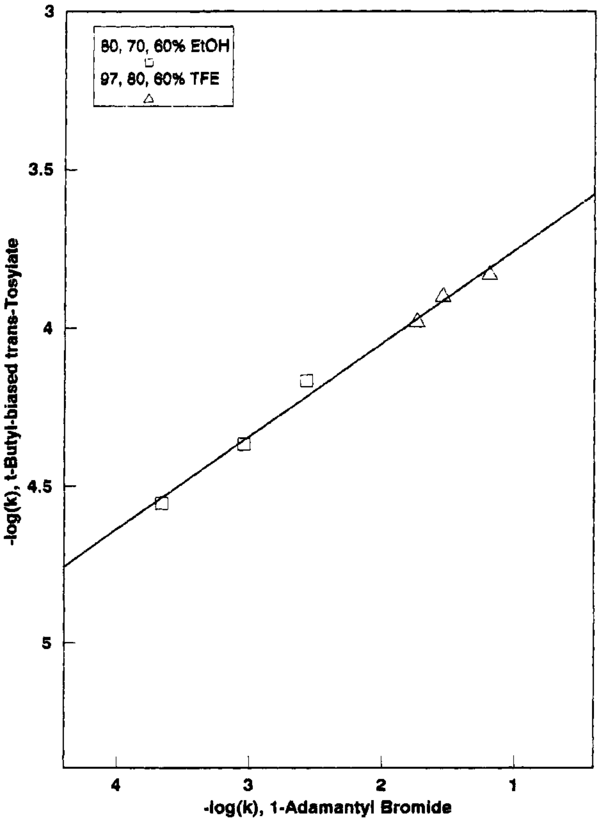

Figure 2. Raber-Harris plot for diethyl (*r*-4-*tert*-butyl-*t*-(tosyloxy)-*c*-1-yl)phosphonate (**6**-OTs).

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[14] Kuan, Y. L.; White, J. M. *J. Chem. Soc., Chem. Commun.* **1994**, 1195–1196.

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[17] For limitations of this method, see: McManus, S. P.; Neamati-Mazrael, N.; Hovanes, B. A.; Paley, M. S.; Harris, J. M. *J. Am. Chem. Soc.* **1985**, *107*, 3393–3395.

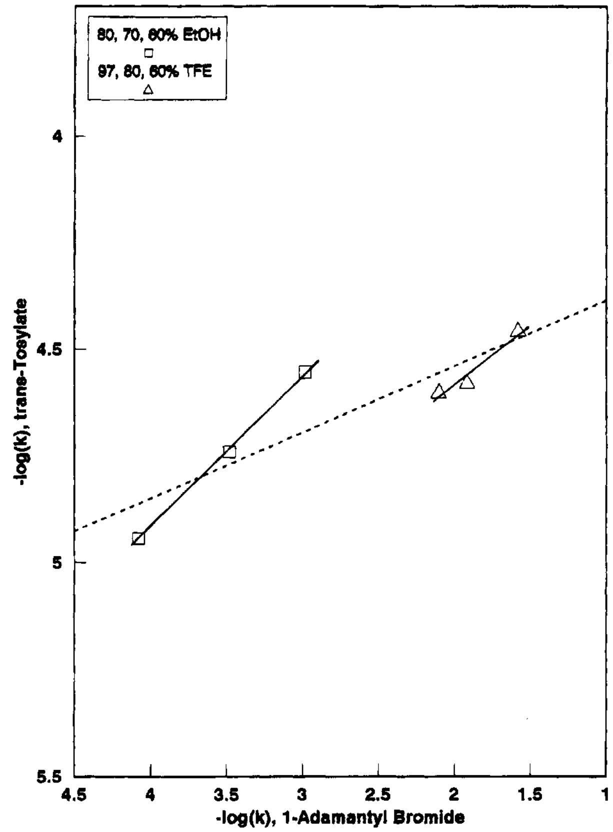
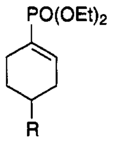


Figure 3. Raber–Harris plot for diethyl (*trans*-2-(tosyloxy)cyclohex-1-yl)phosphonate (**5**-OTs).

points $r = 0.88$ (the dotted line in Figure 3). Examination of the data indicates that linearization for the biased trans tosylate occurs because the rate in TFE becomes faster. The Raber–Harris plots therefore support a change of mechanism, whereby an antiperiplanar geometry between phosphonate and tosylate leads to a carbocation mechanism.

The products from the cis tosylate are straightforwardly explained in terms of a k_s process (Table 3). The vinyl phosphonate **8**-H is formed by removal of the proton that is geminal to phosphonate and trans to tosylate. It is the only observed alkene product. The remainder of the product is from substitution with inversion. In the trans substrates there is no proton that is geminal to phosphonate and trans to tosylate, as phosphonate itself resides at the trans position. Nonetheless, the same product, **8**-H or **8**-*tert*-butyl, is observed, as well as **9**. In the absence of a syn elimination, **8** can only come from a carbocation intermediate. The remaining products are unremarkable for a carbocation mechanism, although it is noteworthy that the substitution products (**4** and **10**) are all formed with inversion. It is the expected result for ion pairs. The product-forming reaction with solvent occurs after the rate-determining step in a k_c reaction, so that these observations are entirely in accord with the Raber–Harris plots.



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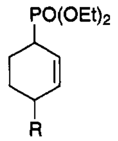

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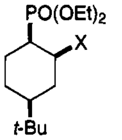

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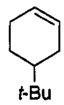

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The observation of the alkene **11** in the reaction of the biased trans substrate is extremely significant, as it is the expected product from the fragmentation that is implied by the hyperconjugative resonance structure **3**. In the systems lacking *tert*-butyl, the analogous product is cyclohexene, whose presence or absence could not be confirmed, since its retention time was obscured by solvent. The fragmentation product **11** cannot be rationalized by a k_s reaction, but is in accord with a mechanism with a carbocation stabilized through hyperconjugation with phosphonate. This reaction is formally analogous to the Conant–Swan fragmentation of β-bromo phosphonic acids.[18]

Conclusions

The Raber–Harris plots support a definite change in mechanism between the cis substrate (**4**-OTs, 60° dihedral angle between phosphonate and tosylate) (Figure 1) and the biased trans substrate (**6**-OTs, 180° dihedral angle) (Figure 2). The two-line plot for **4**-OTs is the standard appearance for a k_s pathway, which involves direct solvent attack in the transition state, leading to substitution and elimination. The one-line plot for **6**-OTs is the standard appearance for a k_c pathway, which involves a carbocation intermediate prior to solvent attack. The unbiased trans substrate **5**-OTs exhibits a Raber–Harris plot of intermediate form (Figure 3). The clustering of the TFE points for both trans substrates, however, indicates that in this solvent the rate has lost its dependence on solvent nucleophilicity, as expected for a k_c mechanism.

Although Figures 1–3 clearly demonstrate a change in mechanism that is stereoelectronically based, it is not possible to provide a definitive rationale. Hyperconjugative stabilization of the transition state leading to the carbocation, as in **3**, when the nucleofuge and electrofuge are antiperiplanar to each other provides one possible explanation. Product and kinetic studies support this interpretation, but by themselves are not compelling. The biased trans form reacts 12.7 times faster than the cis form in 97% TFE at 25 °C or 3.5 times faster at 70 °C. This modest rate acceleration is consistent with hyperconjugation that is not sufficiently strong to overcome the large electron-withdrawing effect of the phosphonate group that destabilizes the carbocation intermediate. The ratio is outside the usual range of structurally similar axial and equatorial systems, whereby the higher ground state of the axial system increases the k_s rate by a factor of 3–5 at 25 °C.[19] Moreover, the biased trans/cis rate ratio increases from 3.5 to 19.4 at 70 °C in the more ionizing HFIP, an observation that supports a k_c mechanism but is not expected for sterically based ground state differences in a k_s mechanism.

Stabilization of an α-CN carbocation with respect to a β-CN carbocation originally was described in terms of

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[18] Satterthwait, A. C.; Westheimer, F. H. *J. Am. Chem. Soc.* **1981**, *103*, 1177–1180.

[19] Lambert, J. B.; Salvador, L.; So, J.-H. *J. Org. Chem.* **1993**, *58*, 5428–5433.

resonance delocalization in the former case, $>C{=}C{=}N^+$.[2,3] It also, however, may be explained by relief of geminal destabilization of the ROCCN grouping.[20] Such electronically based ground state effects do not apply to the current situation. The dipoles (CO and CP) in fact are more repulsive in the gauche (60°) than in the anti (180°) form (compare the relative orientations of the dipoles or alternatively note that the negative end of the CP dipole in the anti form is closer to the positive end of the CO dipole and hence is stabilizing). The favorable interaction lowers the anti ground state with respect to the gauche form and hence serves to decrease the anti/gauche rate ratio. Moreover, such a ground state effect cannot explain the change in mechanism from k_s to k_c between cis and biased trans or the increase in the acceleration from 3.5 in 97% TFE to 19.4 in HFIP. Both observations require an explanation that stabilizes a carbocation transition state over one involving attack by solvent directly on the substrate.

Finally, the cis and trans systems have somewhat different product mixtures. Whereas the alkene product **8** from the cis tosylate is exclusively that expected for the E2 mechanism, the presence of the same vinylic product from the trans tosylates requires an E1 mechanism and hence a carbocation intermediate. Significantly, the biased trans tosylate produces the hydrocarbon **11**, which results from fragmentation and resembles the valence bond representation of hyperconjugation.

From these lines of reasoning but primarily from the change in mechanism documented by the Raber–Harris plots, we believe that we have found evidence for β stabilization of carbocations by the very unlikely phosphonate group, in comparison with expectations from polar factors alone. These observations comprise only a beachhead on the problem, but they indicate that a search of second generation systems may document more fully β stabilization of carbocations by highly electron withdrawing groups.

Experimental Section

Diethyl (2-Cyclohexen-1-yl)phosphonate. A dried, 25-mL, three-necked flask containing a magnetic stirring bar and fitted with a N_2 inlet adapter, a reflux condenser, and a rubber septum was charged with 3-bromocyclohexene (3.28 g, 20.0 mmol) and triethyl phosphite (7.04 mL, 60.0 mmol). The mixture was heated with stirring to 160 °C for 14 h. At that time, GC indicated no remaining starting material and the presence of only two major components. The crude mass balance was 7.51 g (83% of the combined mass of the phosphonate and the excess phosphite). Multiple chromatography on silica gel (60% acetone–hexane mobile phase) gave 3.43 g (79%) of product as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.30 (t, 6H), 1.51 (m, 1H), 1.85 (m, 3H), 2.01 (m, 2H), 2.60 (md, 1H, J_{HP} = 30 Hz), 4.09 (m, 4H), 5.69 (m, 1H), 5.88 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 16.4 (d, J_{CP} = 5.8 Hz), 20.7 (d, J_{CP} = 9.2 Hz), 22.4 (d, J_{CP} = 4.7 Hz), 24.4 (d, J_{CP} = 3.2 Hz), 34.4 (d, J_{CP} = 142.3 Hz), 61.6 (d, J_{CP} = 6.5 Hz), 61.9 (d, J_{CP} = 6.7 Hz), 121.2 (d, J_{CP} = 8.6 Hz), 130.8 (d, J_{CP} = 12.4 Hz); ^{31}P NMR ($CDCl_3$) δ 31.0; MS (EI) *m/z* 218 (92) (M^+), 190 (12), 162 (9), 139 (70), 138 (53), 111 (89), 93 (16), 83 (53), 82 (33), 81 (65), 81 (25), 80 (100).

Diethyl (*cis*-2-Methoxycyclohex-1-yl)phosphonate (4-OMe). A dried, N_2-flushed vial containing a magnetic stirring bar and fitted with a rubber septum was charged with mercuric acetate (0.38 g, 1.19 mmol) and CH_3OH (1.0 mL). To the rapidly stirring suspension was added diethyl (2-cyclohexen-1-yl)phosphonate (0.26 g, 1.19 mmol) as a solution in methanol (1.0 mL). The solid material gradually disappeared, and the solution became clear and nearly colorless. The demercuration step was carried out by cooling the solution to 0 °C and adding 3 N aqueous NaOH (0.4 mL, 1.19 mmol) followed by 0.5 M $NaBH_4$ (in 1 M aqueous NaOH, 1.19 mL, 2.38 mmol of hydride). The metallic Hg that was produced as a colloidal suspension was allowed to precipitate, and the solution was decanted off. The residue was rinsed with ether (5.0 mL), and the aqueous solution was extracted with ether (3 × 5 mL). The combined organic phases were dried with anhydrous $MgSO_4$ and concentrated to yield 0.74 g of a pale yellow oil. Chromatography on silica gel (70 g) (60% hexane–acetone as eluent) gave 0.28 g (93%) of a colorless oil containing the product and its trans isomer in a 92:8 ratio by GC and a 94:6 ratio by ^{1}H NMR: ^{1}H NMR ($CDCl_3$) δ 1.32 (t, 6H), 1.35–1.8 (m, 6H), 1.95 (br, 2H), 2.1 (m, 1H), 3.30 (s, 3H), 3.55 (m, 1H), 4.1 (m, 4H); MS (EI) *m/z* 250 (7.6) (M^+), 235 (100), 219 (24), 165 (70), 139 (16), 138 (13), 113 (32), 111 (28), 109 (10).

Diethyl (*cis*-2-Hydroxycyclohex-1-yl)phosphonate (4-OH). The same reaction conditions reported above for **4**-OMe were utilized, although the reaction was carried out at the 26.0 mmol scale and with H_2O instead of CH_3OH. The crude product (5.15 g, 84%) was pumped down overnight at 50 °C and then chromatographed three times on alumina (400 g) (slow $CHCl_3$ to CH_3OH gradient as eluent) to yield 3.49 g (57%) of a pale yellow oil, which was 94% pure by GC and 95.6% pure by ^{31}P NMR: ^{1}H NMR ($CDCl_3$) δ 1.27 (dt, 6H), 1.3–1.75 (m, 6H), 1.9 (br m, 2H), 2.21 (dtt, 1H, J_{HP} = 20 Hz), 2.6 (br, 1H), 4.04 (m, 4H), 4.10 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 16.4 (d, J_{CP} = 5.4 Hz), 19.5 (d, J_{CP} = 15.3 Hz), 25.2 (d, J_{CP} = 4.8 Hz), 29.2 (d, J_{CP} = 144.5 Hz), 30.2, 32.1 (d, J_{CP} = 3.8 Hz), 61.5 (d, J_{CP} = 6.8 Hz), 64.9, 65.0; ^{31}P NMR ($CDCl_3$) δ 34.5; MS (EI) *m/z* 236 (20) (M^+), 218 (20), 208 (8), 193 (10), 179 (12), 165 (100), 138 (55), 111 (40), 109 (20). Anal. Calcd for $C_{10}H_{21}O_4P$: C, 50.84; H, 8.96. Found: C, 50.66; H, 8.89.

Diethyl (*cis*-2-(Tosyloxy)cyclohex-1-yl)phosphonate (4-OTs). A dried, 50 mL, round-bottomed flask containing **4**-OH (1.69 g, 7.15 mmol) was flushed with N_2, cooled to 0 °C, and charged with pyridine (25 mL) and tosyl chloride (2.73 g, 14.3 mmol). The mixture was swirled at 0 °C until all had dissolved and was placed in the refrigerator until no additional pyridinium hydrochloride precipitated out. After 27 days the solution was poured onto ice (200 g) and ether (200 mL). The aqueous solution was extracted with ether (2 × 100 mL). The combined organic phases were washed with 2 N HCl (8 × 50 mL), dried with a 1:1 mixture of anhydrous Na_2SO_4 and anhydrous K_2CO_3, and concentrated to 2.83 g. By ^{1}H NMR, the mixture contained **4**-OTs and tosyl chloride with some excess pyridine. After the residual pyridine was pumped away, 2.72 g of a viscous oil was recovered. This material was triturated with pentane (5 × 200 mL). The insoluble material was pumped down for 18 h to yield 0.98 g (35%) of **4**-OTs: ^{1}H NMR ($CDCl_3$) δ 1.30 (t, 6H), 1.2–2.3 (m, 9H), 2.46 (s, 3H), 4.07 (m, 4H), 4.86 (s, 1H), 7.35 (d, 2H), 7.80 (d, 2H); ^{13}C NMR ($CDCl_3$) δ 16.3 (d, J_{CP} = 5.8 Hz), 19.4 (d, J_{CP} = 15.8 Hz), 21.6, 24.2 (d, J_{CP} = 4.6 Hz), 29.3 (d, J_{CP} = 163.0 Hz), 29.9, 30.1, 61.6 (d, J_{CP} = 6.9 Hz), 77.5, 127.5, 129.8, 134.1, 144.6; ^{31}P NMR ($CDCl_3$) δ 32.6; MS (EI) *m/z* 390 (28) (M^+), 235 (36), 219 (100), 218 (26), 191 (16), 163 (14), 155 (14), 139 (23), 138 (16), 111 (22); HRMS (M^+) calcd 390.1266, obsd 390.1251.

Diethyl (*trans*-2-Hydroxycyclohex-1-yl)phosphonate (5-OH). A dried, 25-mL, three-necked flask fitted with a reflux condenser, rubber septum, N_2 outlet adapter, and a magnetic stirring bar was charged with diethyl phosphonate (4.67 mL, 25 mmol), cyclohexene oxide (2.53 mL, 25 mmol), and sodium ethoxide (8 mL of a saturated solution in ethanol, >10 M) and heated to reflux overnight. The mixture was cooled to room temperature, diluted with ether–THF (1:1) (70 mL), and washed with 2 N HCl (12 mL). The aqueous phase was extracted with ether–THF (2 × 20 mL), and the combined organic solutions were dried (anhydrous Na_2SO_4). After removal of the solvent in vacuo, 13.67 g of a cloudy oil was recovered. Pumping overnight resulted in a mixture of solid and oil, 7.94 g. Column chromatography on alumina (600 g)

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[20] Wu, Y.-D.; Kirmse, W.; Houk, K. N. *J. Am. Chem. Soc.* **1990**, *112*, 4557–4559.

(slow $CHCl_3$ to CH_3OH gradient as eluent) yielded, after an additional overnight pumping, 2.58 g (44%) of a white solid, which was 96.9% pure by GC, mp 62–64 °C: ^1H NMR ($CDCl_3$) δ 1.08–1.40 (m, 4H), 1.32 (dq, 6H), 1.65–1.80 (m, 3H), 1.91 (dm, 1H), 2.08 (m, 1H), 3.68 (m, 1H), 3.81 (br s, 1H), 4.09 (dp, 4H); ^{13}C NMR ($CDCl_3$) δ 16.2 (d, J_{CP} = 5.4 Hz), 24.0, 24.9 (d, J_{CP} = 10.3 Hz), 25.1 (d, J_{CP} = 14.9 Hz), 34.4 (d, J_{CP} = 15.3 Hz), 43.1 (d, J_{CP} = 137.2 Hz), 61.6 (d, J_{CP} = 6.5 Hz), 61.9 (d, J_{CP} = 7.0 Hz), 68.5, 68.6; ^{31}P NMR ($CDCl_3$) δ 32.4; MS (EI) *m/z* 236 (11) (M^+), 218 (2), 208 (44), 207 (13), 193 (28), 180 (13), 179 (13), 166 (39), 165 (100), 152 (29), 139 (11), 138 (27), 137 (39). Anal. Calcd for $C_{10}H_{21}O_4P$: C, 50.84; H, 8.96; P, 13.11. Found: C, 50.69; H, 8.82; P, 12.59.

Diethyl (*trans*-2-(Tosyloxy)cyclohex-1-yl)phosphonate (5-OTs). A dried, 25-mL, three-necked flask containing **5**-OH (0.59 g, 2.50 mmol) was cooled to 0 °C and charged with pyridine (8.0 mL) and tosyl chloride (0.97 g, 5.00 mmol). After 1 day at 0 °C, the mixture was allowed to react at room temperature for 14 days and then was returned to 0 °C for an additional 7 days to complete the precipitation of the pyridinium hydrochloride. The crude product was isolated in the same manner as for **4**-OTs. After trituration with pentane, the soluble material was pumped down to yield pure **5**-OTs as a pale yellow, extremely viscous oil: ^1H NMR ($CDCl_3$) δ 1.26 (m, 6H), 1.2–1.75 (m, 4H), 1.98–2.23 (m, 3H), 2.43 (s, 3H), 4.03 (m, 4H), 4.79 (m, 1H), 7.32 (d, 2H), 7.81 (d, 2H); ^{13}C NMR ($CDCl_3$) δ 16.3 (d, J_{CP} = 5.6 Hz), 21.6, 21.9, 23.1 (d, J_{CP} = 8.3 Hz), 23.4 (d, J_{CP} = 4.5 Hz), 31.1 (d, J_{CP} = 6.5 Hz), 39.1 (d, J_{CP} = 139 Hz), 61.7 (d, J_{CP} = 7.5 Hz), 62.0 (d, J_{CP} = 6.5 Hz), 79.2, 127.0, 127.9, 129.6, 130.2; ^{31}P NMR ($CDCl_3$) δ 28.0; MS (EI) *m/z* 390 (4) (M^+), 345 (7), 327 (8), 326 (35), 299 (17), 298 (67), 284 (10), 283 (27), 256 (12), 255 (33), 242 (18), 235 (46), 220 (18), 219 (100), 218 (71), 207 (14).

***trans*-4-*tert*-Butylcyclohexene oxide** was prepared as before.[10]

Diethyl (*r*-4-*tert*-Butyl-*t*-hydroxy-*c*-1-yl)phosphonate (6-OH).[12] An oven-dried, N_2-flushed, 50 mL, round-bottomed flask was fitted with a rubber septum and a magnetic stirring bar and was charged with 1.93 mL (15 mmol) of diethyl phosphite in 15 mL of anhydrous THF. The solution was cooled to −75 °C, and 6 mL (15 mmol) of 2.5 M BuLi in hexane was introduced dropwise to the stirred solution through a syringe. The solution was stirred for 15 min, and 0.77 g (5 mmol) of *trans*-4-*tert*-butylcyclohexene oxide in 3 mL of anhydrous THF was added dropwise. The solution was stirred another 15 min, and 2.5 mL (20 mmol) of BF_3 etherate was introduced slowly. After being stirred at −75 °C for 2 h, the reaction was quenched with 10 mL of saturated aqueous NH_4Cl. The mixture was warmed to room temperature, the organic solvent was removed by rotary evaporation, and the water layer was extracted with 3 × 30 mL of ether. The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated by rotary evaporation. The residue was purified by column chromatography over silica gel with hexane/ethyl acetate (1/1) and pure ethyl acetate as eluents. The product was a very viscous, pale green oil: 1.19 g (82%); ^1H NMR ($CDCl_3$) δ 0.84 (s, 9H, *tert*-butyl), 1.30–1.40 (m, 6H), 1.40–2.18 (m, 9H), 4.02–4.22 (m, 5H), 4.40 (m, 1H); ^{13}C ($CDCl_3$) δ 16.5 (d, J_{CP} = 6.6 Hz), 20.5, 22.8, 27.4, 31.9 (d, J_{CP} = 79.6), 38.2, 40.0, 40.1, 61.5, 66.2 (d, J_{CP} = 5.2 Hz); ^{31}P NMR ($CDCl_3$) δ 32.0; MS (EI) *m/z* 292 (M^+, weak), 269 (11), 236 (28), 235 (100), 218 (50), 217 (12), 207 (24); HRMS (M^+) calcd 292.1803, obsd 292.1815. Anal. Calcd for $C_{14}H_{29}O_4P$: C, 57.52; H, 10.00. Found: C, 56.96; H, 9.97.

Diethyl (*r*-4-*tert*-Butyl-*t*-(tosyloxy)-*c*-1-yl)phosphonate (6-OTs) was prepared in the same fashion as **5**-OTs.

Product Studies. A 0.2–0.5 M solution of the substrate in 80% ethanol or 97% trifluoroethanol (0.7 mL) was prepared in a NMR tube. The tube was sealed and put into a constant temperature bath at 70 °C. After at least 10 half-lives, the samples were cooled and checked by ^{31}P NMR spectroscopy to ensure that the reaction was complete. The mixtures were then analyzed with GC and GC–MS. In the systems lacking *tert*-butyl, assignments were made by comparing the mass spectra with those of authentic materials. For the *tert*-butyl-biased system, characterizations were made by analyzing the mass spectra and by comparing the ^{31}P chemical shifts with those of the *tert*-butyl-free compounds. Quantifications were based on GC (FID detector) without correction.

NMR Kinetic Experiments. A series of 24 oven-dried 5-mm NMR tubes was charged with approximately 50 mg (0.12 mmol) of tosylate (**4**-OTs or **5**-OTs) and 0.70 mL of the appropriate solvent. The resulting solutions were 0.17 M in substrate. The tubes were sealed at room temperature and then stored at −78 °C until they were run. Reactions were followed by observing the changes in intensity of the aromatic resonances from the tosylates into tosic acid or the disappearance of the ^{31}P peak. The integral ratios were used to determine the extent of the reaction. Points were collected at various elapsed times. For ^1H spectra a point was defined as a 32 transient spectrum taken with an acquisition time of 2.675 s and a pulse delay of 2 s. The initial time zero was defined as the point at which the NMR probe had returned to thermal equilibrium after a new cold sample was inserted. Between acquisitions each sample was maintained at the temperature of the probe by means of a constant temperature bath. This procedure allowed for several samples to be run in parallel. For samples with more rapid rates of reaction, points were collected without removing the sample from the probe for at least 1 half-life. Kinetic data were analyzed with the LOTUS 123 package, and graphical presentations were prepared via the transmission of that data to the LOTUS FREELANCE PLUS program.

Variable Temperature NMR Calibration. The actual temperature in the NMR probe was determined and calibrated by means of the methanol calibration curve. The software of the XLA-400 includes a program, TEMCAL(M), that determines the temperature from the frequency difference between the two peaks of a neat sample of methanol. A calibration curve may be generated from several temperatures. In practice, however, it was simpler to use the curve only as a guide and to determine the actual temperature each day with the methanol sample.