Table I. Summary of Measurements at 25° of Inhibition Constants and Rate Constants for the Binding of Sulfonamides to Carbonic Anhydrases

Inhibitor	k_1, M^{-1} sec^{-1}	k_{calcd}, M^{-1} sec^{-1}	K_I, M^{-1}	pH of reaction solution	pK_a for sulfonamide group	Enzyme species
4-Hydroxy-3-nitrobenzenesulfonamide[a]	3.7×10^4	2.2×10^8	3.8×10^{-6}	7.6	10.9[d]	Bovine A + B
	7.5×10^4	4.5×10^8		7.6	10.9	Human B
Benzenesulfonamide	7×10^4 [b]	2.8×10^8	3.2×10^{-6} [b]	6.7	10.2	Bovine B
	1.6×10^5	1.8×10^8		7.7	10.2	Bovine B
Sulfanilamide	7×10^4 [c]	2.2×10^8	1.2×10^{-6} [c]	7.9	10.7	Co(II)-bovine B
Acetazolamide	5×10^6 [b]	2.6×10^7	2.2×10^{-8} [b]	6.7	7.2	Bovine B
	4×10^6 [c]	2.4×10^7	1.2×10^{-8} [c]	7.9	7.2	Co(II)- and Zn(II)-bovine B

[a] Results of this work. [b] Reference 5. [c] Reference 6. [d] Spectrophotometric titration gave a pK_a value of 4.89 ± 0.04 for the phenolic group and 10.9 ± 0.2 for the sulfonamide group in this inhibitor.

k_{meas} is the pseudo-first-order rate constant measured for the enzyme-catalyzed hydrolysis of the sultone,

$$\frac{[\mathrm{E}]_0}{(k_{\text{meas}} - k_{\text{spont}})} = \frac{K_M}{k_{\text{cat}}} + \frac{K_M}{k_{\text{cat}}}\frac{[\mathrm{I}]}{K_I} \qquad (4)$$

and k_{spont} is the first-order rate constant observed for the spontaneous hydrolysis reaction at the same pH in the same buffer system. A value of K_I of $(3.2 \pm 0.3) \times 10^{-6}$ M at 25.0°, pH 7.45, and $\mu = 0.125$ was obtained in good agreement with the equilibrium dialysis results.[9]

Since $K_I = k_{-1}/k_1$ (see eq 1), if we take our average K_I value of 3.8×10^{-6} M, we calculate that k_{-1} for the bovine enzyme complex is 0.14 sec^{-1}. A really reliable intercept cannot be calculated from the plot shown in Figure 1 since a considerable extrapolation of the data points is required. Nevertheless, we have estimated from this plot that $k_{-1} \approx 0.17$ sec^{-1} which corresponds well with the value calculated above.

From Table I it can be seen that the K_I and k_1 values we obtained for the reported group labeled inhibitor 4-hydroxy-3-nitrobenzenesulfonamide are similar to those found for two other inhibitors whose sulfonamide groups have comparable ionization constants.[5,6] The pH dependencies reported for the quantities K_I[5,6] and k_1[5] can be accounted for by postulating that the enzyme-sulfonamide complexes are formed by the reaction of the ionized sulfonamides with the form of the enzyme in which the water ligand bound to the active site is un-ionized.[10] The k_{calcd} values listed in Table I are based on this hypothesis, and they have been calculated from the k_1 results with the assumption that the pK_a for the ionization of the water ligand in the enzyme is approximately 7.3.[3] The variation in k_{calcd} values is tenfold at most although the pK_a values for the ionization of the sulfonamide groups in acetazolamide and 4-hydroxy-3-nitrobenzenesulfonamide differ by 3.7 pH units. This kind of invariance of k_{calcd} and the k_{calcd} values themselves are reminiscent of the rate data measured for the reactions of various anionic ligands with Zn(II) to form inorganic complexes.[11] Therefore, we suggest that the carbonic anhydrase-sulfonamide complex generation may be described in terms of rapid preequilibrium formation of an outer sphere complex between the sulfonamide anion and the Zn(II) ion at the active site which then loses water in the rate-determining step of inner sphere enzyme-inhibitor complex formation.

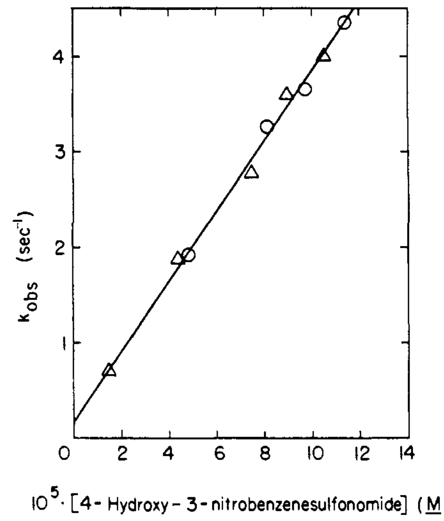

Figure 1. Rate data observed on mixing 4-hydroxy-3-nitrobenzenesulfonamide with bovine carbonic anhydrase: circled points, $\mu = 0.25$; triangles, $\mu = 0.11$; acetone concentration, 0.12-0.28%; temperature 25.0°; pH 7.6; Tris-sulfate buffer.

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[9] In ref 3 a K_I value of 7.38×10^{-7} M was reported for the sulfonamide inhibitor. However, for a variety of reasons we do not consider the results of these earlier inhibition experiments to be satisfactory.

[10] The alternative hypothesis that the un-ionized sulfonamides react with the ionized form of the enzyme cannot be discounted, however.

[11] M. Eigen and R. G. Wilkens, *Advan. Chem. Ser.*, **No. 49**, 55 (1965).

[12] Fellow of the Alfred P. Sloan Foundation; to whom correspondence should be addressed.

Intermolecular Exchange in Phosphorus(V) Fluorides

Sir:

Facile ligand exchange is a well-recognized feature of pentacoordinate phosphorus compounds.[1] Gen-

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(1) For pertinent reviews, see (a) E. L. Muertterties and R. A.

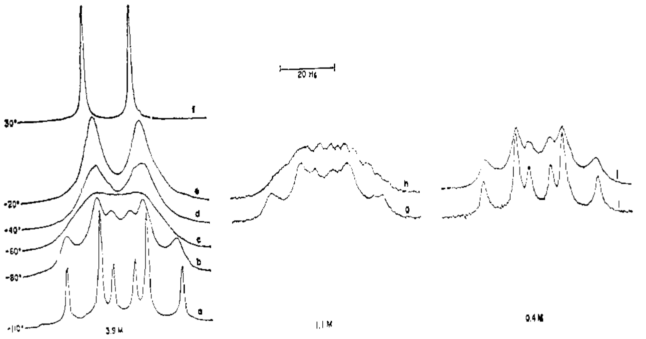


Figure 1. Proton magnetic resonance spectra of trimethyldifluorophosphorane (I) in $CHCl_2F$ solution at various temperatures and molar concentrations: (a) 3.9 *M*, −110°; (b) 3.9 *M*, −80°; (c) 3.9 *M*, −60°; (d) 3.9 *M*, −40°; (e) 3.9 *M*, −20°; (f) 3.9 *M*, 30°; (g) 1.1 *M*, −40°; (h) 1.1 *M*, −20°; (i) 0.4 *M*, −40; (j) 0.4 *M*, −20°.

erally, the stereolability of such species has been attributed to an intramolecular "pseudorotation" process of the type first envisoned by Berry.[2] A recent detailed study by Whitesides and Mitchell[3] has confirmed this view in the case of the fluorophosphorane, $(CH_3)_2NPF_4$. The purpose of this communication is to present what appears to be convincing evidence for an intermolecular exchange process[4] in the phosphorus(V) fluorides $(CH_3)_3PF_2$ (I) and $(CH_3)_2PF_3$ (II).

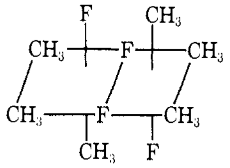
Compounds I and II were prepared by treatment of $(CH_3)_3P$ and $(CH_3)_4P_2S_2$, respectively, with SF_4 at −78°, and purified by fractional vacuum condensation until they were tensimetrically homogeneous. Very good agreement was noted with the previously published infrared spectra.[5] The nmr samples were prepared by condensing I or II with $CHCl_2F$ and sealing the nmr tube off *in vacuo* at −196°. The observation of a pair of overlapping triplets centered at τ 8.48 in the pmr spectrum of I at low temperature and/or low concentration (Figure 1a, i) with $J_{PCH} = 17.3$ and $J_{FPCH} = 12.8$ Hz is indicative of a D_{3h} trigonal-bipyramidal instantaneous structure in which the methyl groups assume the equatorial positions.[6] Upon raising the temperature at a fixed concentration or increasing the concentration at a fixed temperature the proton spectrum collapses (Figure 1) and a sharp doublet of spacing 17.3 Hz, which is assignable to the P–C–H coupling, gradually emerges at τ 8.45.

Theoretical line shapes were calculated for a variety of inverse mean lifetimes ($1/\tau$) using the NMRLS many-site exchange program which is based on the equations of Anderson and Kubo.[7] Detailed comparisons between the observed and computed spectra afforded a $1/\tau$ value for each temperature and molar concentration, *M*. A plot of log τ *vs.* log *M* gave a slope of −1.1, which corresponds to a molecularity of 2.1.[8] For a bimolecular process the rate constant, *k*, is related to inverse mean lifetime by the equation

$$k = \frac{1}{\tau}\frac{e - 1}{M} \tag{1}$$

An Arrhenius plot of ln *k* *vs.* reciprocal temperature yielded an activation energy of 3.4 kcal/mol. The activation parameters $\Delta H^{\ddagger} = 3.72$ kcal/mol, $\Delta S^{\ddagger} = -43$ eu at 300°K, and $\Delta G^{\ddagger} = 16.6$ kcal/mol at 300°K were obtained by standard procedures.[8] The observation that the P–C–H coupling is maintained while the F–P–C–H coupling is lost at higher temperatures and concentrations suggests that P–F bonds are broken in the exchange process. Since the P–F coupling is 545 Hz in the instantaneous structure of I this means that, according to the Gutowsky–Holm equation,[9] a $1/\tau$ value of 2404 sec^{-1} would be required for coalescence of the ^{19}F peaks. Thus, *e.g.*, for a 3.9 *M* solution of I a temperature of 99.2° would be required for collapse of the ^{19}F spectrum. The experimental ^{19}F spectrum of I (3.9 *M* in α,α,α-trifluorotoluene) collapsed at ~100° and a very broad singlet (peak width at half-height ~ 200 Hz) was observable at ~140°. Unfortunately, some decomposition takes place at these temperatures as evidenced by the deposition of traces of a white solid and the appearance of spurious doublet [$(CH_3)_3PO$?] in the ambient-temperature pmr spectrum. However, the bulk of the solute can be recovered unchanged; hence the ^{19}F nmr spectral observations are probably valid.

In view of the foregoing, the most likely transition state for the second-order exchange process in I is the fluorine-bridged dimer, III. An analogous bridged dimer has been invoked[10] to explain the intermolecular exchange in, *e.g.*, ClF_3, BrF_3, and SF_4.



III

Great interest was associated with $(CH_3)_2PF_3$ (II) because it appeared to be a likely candidate for a "non-Berry" intramolecular exchange.[3] However, this is not the case and, in fact, II undergoes an intermolecular exchange process. The experimental activation parameters $\Delta H^{\ddagger} = 3.9$ kcal/mol, $\Delta S^{\ddagger} = -41$ eu at 300°K, and $\Delta G^{\ddagger} = 16.4$ kcal/mol at 300°K are very similar to those obtained for I.

In the fluorophosphoranes which undergo exchange by the intramolecular "pseudorotation" process, the energies of activation (and approximately free energies of activation, since $\Delta S^{\ddagger} \sim 0$) are in the range 6–12

Schunn, *Quart. Rev., Chem. Soc.*, 20, 245 (1966); (b) F. H. Westheimer, *Accounts Chem. Res.*, **1**, 70 (1968); (c) R. Schmutzler in "Halogen Chemistry," Vol. 2, V. Gutmann, Ed., Academic Press, New York, N. Y., 1967; (d) J. I. Musher, *Angew. Chem., Int. Ed. Engl.*, **8**, 54 (1969).

(2) R. S. Berry, *J. Chem. Phys.*, 32, 933 (1960).

(3) G. M. Whitesides and L. Mitchell, *J. Amer. Chem. Soc.*, **91**, 5389 (1969).

(4) On the basis of preliminary experimentation, Brownstein [*Can. J. Chem.*, **45**, 1711 (1967)] has suggested that intramolecular exchange in PF_5 may be assisted by an intermolecular process. This interpretation has been criticized, however; see J. D. Macomber, *J. Magn. Resonance*, 1, 677 (1969).

(5) A. J. Downs and R. Schmutzler, *Spectrochim. Acta, Part A*, **23**, 681 (1967).

(6) Electron diffraction studies indicate that the methyl groups in $(CH_3)_2PF_3$ adopt equatorial sites of a trigonal bipyramid [see K. W. Hansen and L. S. Bartell, *Inorg. Chem.*, **4**, 1775 (1965)]. Vibrational spectroscopic data (ref 5) strongly support the D_{3h} model for $(CH_3)_3PF_2$.

(7) P. W. Anderson, *J. Phys. Soc. Jap.*, **9**, 316 (1954); R. Kubo, *Nuovo Cimento, Suppl.*, **6**, 1063 (1957). The program was devised by M. Saunders, *Tetrahedron Lett.*, 1699 (1963); M. Saunders, *Proc. Int. Conf. Magn. Resonance Biol. Systems, 2nd, 1966*, 85 (1967).

(8) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," 2nd ed, Wiley, New York, N. Y., 1961, pp 41–43.

(9) H. S. Gutowsky and C. H. Holm, *J. Chem. Phys.*, **25**, 1228 (1956).

(10) E. L. Muetterties and W. D. Phillips, *J. Amer. Chem. Soc.*, **79**, 322 (1957); **81**, 1084 (1959).

kcal/mol.[11] The failure of I and II to undergo intramolecular exchange reactions is consistent with the Muetterties polarity rule[1a,b] which states that electropositive substituents preferentially occupy the equatorial sites of a trigonal bipyramid. Presumably the reluctance of the methyl groups to occupy axial sites raises the $\Delta G^{\ddagger}$ for pseudorotation above 16 kcal/mol, thus making the intermolecular process the energetically favored route.

While the present evidence does not completely eliminate the possibility of an impurity-catalyzed exchange process, we consider that such a mechanism is highly unlikely for the following reasons. (i) Consistent activation parameter data were obtained for three different samples for both I and II. In the case of I, one of the samples was prepared by an alternative synthetic procedure.[12] If the reaction were catalyzed by adventitious impurity, one would expect the rates and consequent activation parameters to vary incoherently. (ii) The results were unaffected by the presence of NaF. While NaF does not completely eliminate fluoride impurity from solution, one would, nevertheless, anticipate a sensitivity of the rate to the presence of the scavenger if the observations were due to fluoride ion catalysis. (iii) The reactions are second order in the phosphoranes I and II. Although it might be possible to devise a series of steps for a catalyzed reaction which resulted in a second-order dependence on phosphorane, we consider that such a sequence is improbable.

Acknowledgment. The authors are grateful to the Robert A. Welch Foundation and to the National Science Foundation (Grant No. GP 9518) for financial support.

[11] *E.g.*, the E_a's for Cl_2PF_3 and $(C_2H_5)_2NPF_4$ are 6.5 ± 2 and 12.8 ± 2 kcal/mol, respectively: E. L. Muetterties, W. Mahler, K. J. Packer, and R. Schmutzler, *Inorg. Chem.*, 3, 1298 (1964); R. Schmutzler, *Angew. Chem., Int. Ed. Engl.*, 4, 496 (1965).

[12] The reaction of $(CF_3)_3P$ with $(CH_3)_3P$ produces useful yields of I. This reaction and other oxidative fluorinations with $(CF_3)_3P$ will be the subject of a forthcoming publication.

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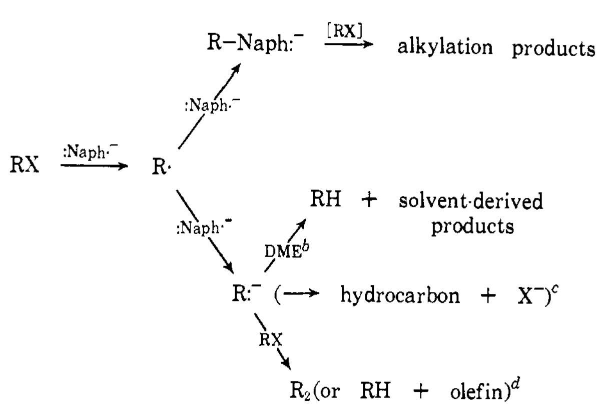
Unusual Chemically Induced Nuclear Spin Polarization in Reactions of Sodium Naphthalene with Alkyl Halides

Sir:

There is strong chemical evidence that reactions of sodium naphthalene with alkyl halides proceed through intermediate alkyl radicals (Scheme I).[1] Acting on the presumption that this was sufficient grounds for seeking chemically induced nuclear spin polarization phenomena in these reactions, we sought and found them.[2] The conditions under which the polarizations appear to be maximal and the nature of the polarizations are of interest in connection with the theory of the phenomenon. In particular, they differ from those predicted using the model of Closs[3,4] and Kaptein and Oosterhoff[5] in its approximation intended for reactions carried out in large magnetic fields, thus experimentally confirming the prediction that this approximate theory would fail for reactions carried out in small magnetic fields.[4a]

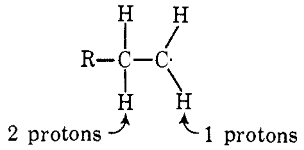
Scheme I[a]



[a] Metal counterions are omitted, but aggregates at least as high as ion pairs are considered to be involved for all anions considered. [b] DME = 1,2-dimethoxyethane. Other ethers, *e.g.*, tetrahydrofuran, may be used. [c] This pathway is available when R itself contains a halogen atom, so that RX is really a dihaloalkane. [d] This pathway is of major importance only for reactions of alkyl iodides.

The CKO model is one in which nuclear polarization is brought about through competitive processes of associated radical pairs. The rates of collapse of radical pairs to singlet products are considered to be nuclear spin state dependent, while the rates of diffusive separation of radical pairs are independent of their nuclear spin states. In the t_0–s approximation, mixing of electronic singlet states (s) of radical pairs with two of the electronic triplet states, those with $m_s = \pm 1$ (t_+ and t_-), are neglected, the only singlet–triplet mixing considered being that of singlet states with triplet states of $m_s = 0$ (t_0) This approximation is explicitly justifiable only for reactions run in large magnetic fields. Nonetheless, it might have proved sufficient for reactions run in any field.

Two predictions of the t_0–s CKO model are: (1) if Δg, the g-value difference for the radicals of the critical pairs, is very small, then maximal net ("energy")[3] polarization of products is predicted for reactions run in very large magnetic fields. (2) For reactions proceeding through critical pairs containing alkyl radicals, any energy polarization in the products should be of opposite sign for protons which were 1 and 2 protons in the radicals. This stems from the fact that the nuclear-electron hyperfine coupling constants of 1 protons are negative, while those of 2 protons are positive.



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[1] J. F. Garst, *Polym. Prepr., Amer. Chem. Soc., Div. Polym. Chem.*, 11, 8 (1970); J. F. Garst and J. T. Barbas, *Tetrahedron Lett.*, 3125 (1969); and references cited therein.

[2] This is apparently the first report of nuclear spin polarization induced in a reaction involving a paramagnetic initial reactant.

[3] G. L. Closs, *J. Amer. Chem. Soc.*, **91**, 4552 (1969); G. L. Closs and A. D. Trifunac, *ibid.*, **91**, 4554 (1969).

[4] (a) G. L. Closs and A. D. Trifunac, *ibid.*, **92**, 2183 (1970); (b) G. L. Closs, C. E. Doubleday, and D. R. Paulson, *ibid.*, **92**, 2185 (1970); (c) G. L. Closs and A. D. Trifunac, *ibid.*, **92**, 2186 (1970).

[5] R. Kaptein and J. L. Oosterhoff, *Chem. Phys. Lett.*, **4**, 195, 214 (1969).