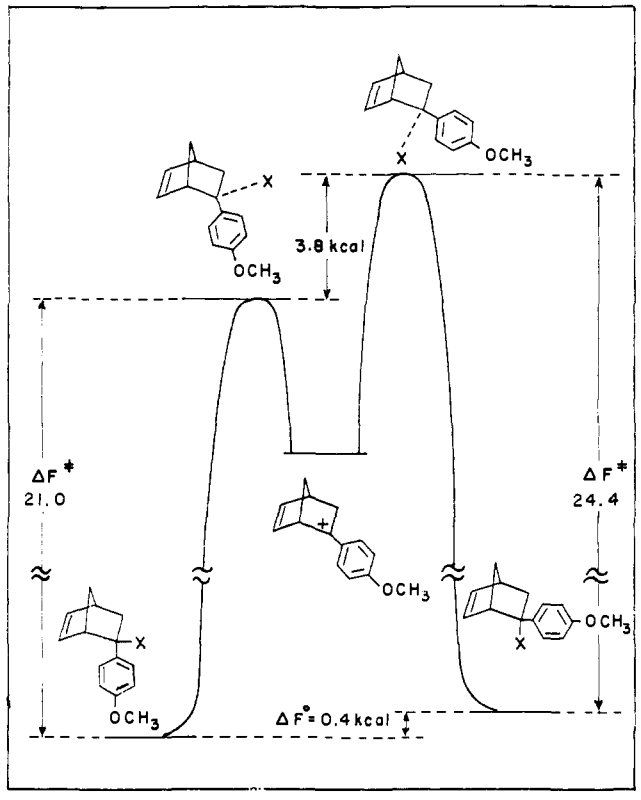


Figure 1. Goering–Schewene diagram for the solvolysis of 2-*p*-anisyl-2-norbornenyl *p*-nitrobenzoates in 80% acetone at 25.0° (X = OPNB or OH).

bornenyl benzoate (VII) in 80% acetone (containing a 10 mol % excess of sodium acetate) at 25.0° were analyzed by nmr. No products with the structure corresponding to $\pi$ participation, 1-*p*-anisyl-3-nortricyclanol, were observed. Both esters gave only 2-*p*-anisyl-2-*exo*-norbornenol.[6]

These results clearly establish that $\pi$ participation is not significant in the solvolysis of these 2-*p*-anisyl-2-norbornenyl derivatives. Consequently, the high exo:endo rate ratio must be due to some other factor. Possibly this factor is steric hindrance to ionization, such as has been proposed previously to account for the behavior of the 2-arylnorbornyl compounds.[5,7] If this interpretation is valid, it would mean that the $\pi$ cloud of the double bond in the rigid bicyclic system resists the departure of the anion in the same manner as the endo 6 hydrogen in the saturated derivative.[7a,8,9]

The Goering–Schewene diagram for the 2-*p*-anisyl-2-norbornenyl system (Figure 1) was constructed assuming the differences in the ground-state free energy of III and IV is the same as the difference in ground-state free energy for the 2-phenyl-2-norbornyl system.[10] This diagram makes it clear that the cation formed reacts preferentially with the solvent (or anion) to give predominantly the exo product.

Clearly the Goering–Schewene diagram shows that the factors responsible for the difference in energy between the exo and endo transition states in the 2-*p*-anisyl-2-norbornenyl system must likewise be responsible for the stereoselectivity leading to the almost exclusive formation of the exo product in this system. Since $\pi$ participation is evidently absent, some other factor, presumably steric effects, must be making a major contribution to the exo:endo rate ratio in the stabilized 2-*p*-anisyl-2-norbornenyl system. It follows that this factor must also be contributing at least in part to the higher exo:endo rate ratio in the parent secondary 2-norbornenyl system.[11]

(6) 2-*p*-Anisyl-2-*endo*-norbornenol, bp 110.5° (0.15 mm); 2-*p*-anisyl-2-*exo*-norbornenol, mp 65.4–66.5°.

(7) (a) H. C. Brown, "Boranes in Organic Chemistry," Cornell University Press, Ithaca, N. Y., in press (Chapters 9–11); (b) H. C. Brown and K.-T. Liu, *J. Amer. Chem. Soc.*, **91**, 5909 (1969); (c) H. C. Brown, S. Ikegami, and K.-T. Liu, *ibid.*, **91**, 5911 (1969).

(8) It has been shown that attack of borohydride ion on norcamphor and dehydronorcamphor is 86% exo and 95% exo, respectively: H. C. Brown and J. Muzzio, *ibid.*, **88**, 2811 (1966).

(9) H. C. Brown, F. J. Chloupek, and M.-H. Rei, *ibid.*, **86**, 1248 (1964).

(10) Determined from the equilibration of 2-phenyl-2-norbornanol: M.-H. Rei and H. C. Brown, *ibid.*, **88**, 5335 (1966).

(11) Our conclusion that $\pi$ participation cannot be a significant factor in the high exo:endo rate ratio in the 2-*p*-anisyl-2-norbornenyl system should not be extrapolated to the position that $\pi$ participation cannot be a factor in the large exo:endo rate ratio, 7000, in the parent 2-norbornenyl system. If we assume that the present factor of 312, attributed to steric effects, is present in the secondary system, this leaves a factor of approximately 20 attributable to $\pi$ participation in this system.

(12) Proctor and Gamble Fellow in Chemistry, 1970–1971.

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## Influence of Lone-Pair Electrons on Carbon-13–Phosphorus-31 Nuclear Spin Couplings in Aromatic Phosphines

*Sir:*

In recent years there has been an increasing interest in the effect of the orientation of lone-pair electrons on two-bond nuclear spin–spin coupling constants with special attention being paid to the effect on $^2J(^1H-^{15}N)$ and $^2J(^{13}C-^{15}N)$.[1-6] In phosphines it has previously been shown that the $^2J(^1H-^{31}P)$ coupling exhibits a dihedral dependence,[7] and recently a similar stereospecificity was also noted for the two-bond $^{13}C-^{31}P$ couplings, $^2J(^{13}C-C-^{31}P)$, in some four-membered cyclic phosphines (methyl-substituted phosphetans).[8] We wish to report on the observation of an extraordinarily large influence of ortho substituents on some of the $^{13}C-^{31}P$ couplings in triarylphosphines. The results have been interpreted in terms of a lone-pair effect on the $^{13}C-^{31}P$ couplings. This appears to be the first observation of its kind in $^{13}C$ nmr of nonrigid structures.

The magnitudes and, in most cases, the signs of the $^{13}C-^{31}P$ couplings for some ortho methyl and ortho bromo substituted trithienylphosphines (**1**, **3**, and **4**)

(1) J. P. Kintzinger and J. M. Lehn, *Chem. Commun.*, 660 (1967).
(2) D. Crepaux and J. M. Lehn, *Mol. Phys.*, **14**, 547 (1968).
(3) T. Yonezawa, I. Morishima, K. Fukuta, and Y. Ohmori, *J. Mol. Spectrosc.*, 31, 341 (1969).
(4) M. S. Gopinathan and P. T. Narasimhan, *Mol. Phys.*, **22**, 473 (1971).
(5) R. L. Lichter and J. D. Roberts, *J. Amer. Chem. Soc.*, **93**, 5218 (1971).
(6) P. S. Pregosin, E. W., Randall, and A. I. White, *J. Chem. Soc., Perkin Trans. 2*, 1 (1972).
(7) J.-P. Albrand, D. Gagniare, J. Martin, and J.-B. Robert, *Bull. Soc. Chim. Fr.*, 40 (1969).
(8) G. A. Gray and S. E. Cremer, *J. Chem. Soc., Chem. Commun.*, 367 (1972).

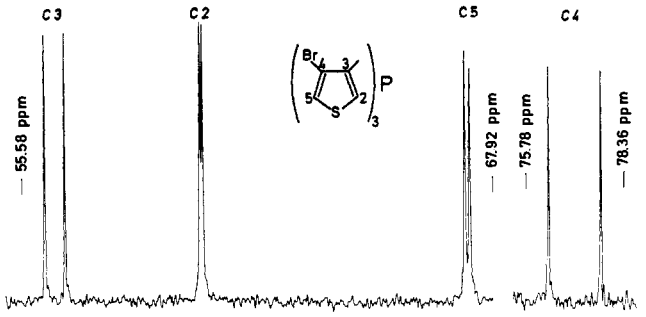



Figure 1. Natural abundance $^{13}C$ nmr spectrum ($^1H$ noise decoupled; 50 scans) of tri-(4-bromo-3-thienyl)phosphine (**4**). The ppm scale is upfield from internal carbon disulfide.

and triphenylphosphines (**6** and **7**) are given in Tables I and II along with the data for the parent phosphines

**Table I.** $^{13}C-^{31}P$ Coupling Constants in Some Ortho-Substituted Tri-3-thienylphosphines[a]

| | **1** | **2**[b] | **3** | **4** |
|---|---|---|---|---|
| $^2J_{C-2-P}$ | +33.88 | +23.09 | 0.25 | −1.66 |
| $^1J_{C-3-P}$ | −11.83 | −14.00 | −12.48 | −13.08 |
| $^2J_{C-4-P}$ | +1.09 | +17.50 | +27.38 | +35.10 |
| $^3J_{C-5-P}$ | +3.66 | +6.28 | +5.29 | +3.32 |
| $^3J_{C-\alpha-P}$ | 15.17 | | 10.60 | |

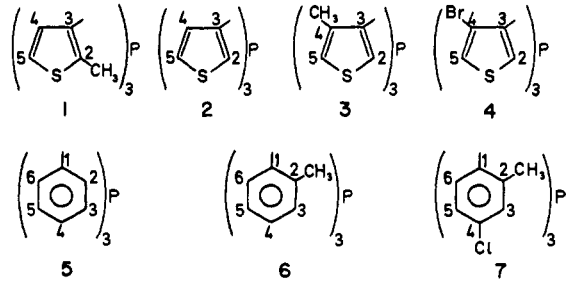
[a] Coupling constants are given in hertz and have been obtained from single scan spectra using a sweep width of 0.5 Hz/cm. Uncertainties in the parameters are ±0.03 Hz. Where not indicated the signs have not been determined. Solutions are *ca.* 40% w/w in $CS_2$–acetone-$d_6$ (47:13 w/w) and were contained in 12-mm tubes. Acetone-$d_6$ was used as an internal lock signal source. The temperature of the samples was 32°. [b] Reference 9.

**Table II.** $^{13}C-^{31}P$ Coupling Constants in Some Ortho-Substituted Triphenylphosphines[a]

| | **5**[b] | **6** | **7** |
|---|---|---|---|
| $^1J_{C-1-P}$ | −12.51 | −11.44 | −11.99 |
| $^2J_{C-2-P}$ | +19.65 | +26.44 | +27.90 |
| $^3J_{C-3-P}$ | +6.80 | +4.75 | +4.85 |
| $^4J_{C-4-P}$ | 0.33 | <0.2 | <0.2 |
| $^3J_{C-5-P}$ | +6.80 | 0.74 | 0.90 |
| $^2J_{C-6-P}$ | +19.65 | 0.41 | 0.63 |
| $^3J_{C-\alpha-P}$ | | 21.82 | 21.66 |

[a] As for Table I. [b] See ref 10.

(**2**[9] and **5**[10]), for purposes of comparison. The data were obtained from natural abundance $^{13}C$ nmr spectra (Figure 1) recorded on a Varian XL-100-15 spectrometer (25.2 MHz, continuous wave mode) using noise and single-frequency proton decoupling. Signs of the




(9) H. J. Jakobsen, T. Bundgaard, and R. S. Hansen, *Mol. Phys.*, 23, 197 (1972).
(10) T. Bundgaard and H. J. Jakobsen, *Acta Chem. Scand.*, in press.

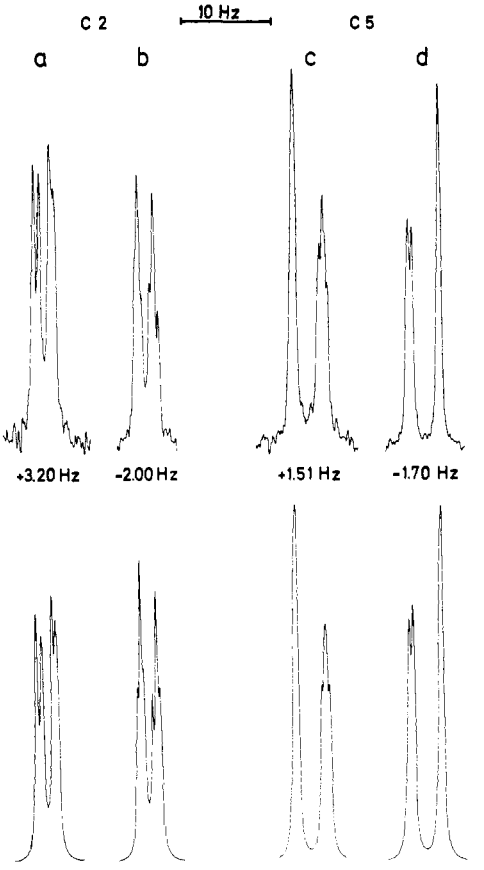



Figure 2. Experimental (upper part) and calculated (lower part) $^{13}C-\{^1H\}$ double resonance spectra for C-2 and C-5 in **4** (see text). The experimental parameters used for the simulation of the double resonance spectra are: $\gamma_{^1H}H_2/2\pi$ = 850 (a and b) and 900 Hz (c and d) for the amplitudes of the irradiation field; $\nu_2$ = 674.90 (a), 669.70 (b), 734.21 (c), and 731.00 Hz (d) for the irradiation frequencies; $\nu_{H-2}$ = 671.70 Hz, $\nu_{H-5}$ = 732.70 Hz, $J_{H-2-H-5}$ = +3.33 Hz, $J_{P-H-2}$ = +0.70 Hz, $J_{P-H-5}$ = +2.58 Hz, $J_{C-2-H-2}$ = +190.53 Hz, $J_{C-2-H-5}$ = +5.42 Hz, $J_{C-2-P}$ = −1.66 Hz, $J_{C-5-H-5}$ = +191.87 Hz, $J_{C-5-H-2}$ = +4.29 Hz, and $J_{C-5-P}$ = +3.32 Hz. The irradiation frequencies and proton chemical shifts are relative to TMS (100.1 MHz). Offsets (Hz) in the decoupling frequencies from $\nu_{H-2}$ and $\nu_{H-5}$ are given below the experimental spectra.

$^{13}C-^{31}P$ coupling constants were determined from off-resonance and/or selective proton decoupling experiments as recently described.[9] In several cases the spectra were compared with computer simulated double resonance $^{13}C$ spectra (Figure 2) obtained for different sets of relative signs of the coupling constants. Full experimental details for the $^{13}C-^{31}P$ coupling assignments, sign determinations, and syntheses will be provided in a subsequent publication.

Inspection of the $^{13}C-^{31}P$ coupling constants in Tables I and II shows that $^2J_{CCP}$ is very sensitive to the introduction of ortho substituents. For both the tri-3-thienylphosphines and triphenylphosphines it is observed that $^2J_{CCP}$ involving the ortho-substituted ring carbon atom increases, whereas this coupling for the unsubstituted ortho carbon markedly decreases as compared to the values for the parent phosphine. These changes in $^2J_{CCP}$ may even lead to a sign reversal as observed for $^2J_{C-2-P}$ in **4**. Minor decreases and differences are also observed for the $^3J_{CCCP}$ couplings, whereas $^1J_{CP}$ and $^4J_{CCCCP}$ appear to be least affected.

The observed influence of ortho substituents on $^2J_{CCP}$ may be explained as a geometrical dependence of

this coupling on the orientation of the nonbonded electrons on phosphorus with respect to the ring planes. The insignificant changes observed for all $^{13}C-^{31}P$ couplings in going from **6** to **7** (*i.e.*, upon introduction of a para chlorine substituent) are in support of this explanation as are the results for some other non-ortho-substituted triarylphosphines. Thus, evidence has been obtained for a steric interaction caused by the ortho substituents and resulting in different conformational preferences of the aryl rings in some of these phosphines (*e.g.*, in **1**, **2**, and **3**).

The same interpretation was recently invoked to explain the observation of a marked dependence of the ring $^{1}H-^{31}P$ coupling constants on ortho substitution in trithienylphosphines[11] (and also noted for **6** and **7**). CNDO/2 calculations performed for different geometries (rotational isomers) of the primary phosphines, 3-thienylphosphine, 2-thienylphosphine, and phenylphosphine, clearly indicate a considerable angular dependence of the ring $J(^{1}H-^{31}P)$ couplings. Furthermore, taking the experimental data[11] into account these calculations seem to indicate a preferred conformation for the ortho-substituted arylphosphines in which the ring planes are twisted so as to align the substituent toward the phosphorus lone pair of electrons. In view of the recently reported stereospecificity of $^{2}J_{CCP}$ in some cyclic phosphines[8] this predicted conformation is in accordance with the changes observed in this work for $^{2}J_{CCP}$.

In conclusion, the stereospecificity observed for $^{2}J_{CCP}$ appears to be especially useful in conformational analysis of phosphines and proves to be an alternative to the use of $^{1}H-^{31}P$ couplings which are often tedious to obtain.

**Acknowledgment.** CNDO/2 calculations were kindly performed by Dr. P. Rahn.

(11) H. J. Jakobsen and M. Begtrup, *J. Mol. Spectrosc.*, 40, 276 (1971).

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## Hydratase Activity of a Hydrolase. Adenosine Deaminase

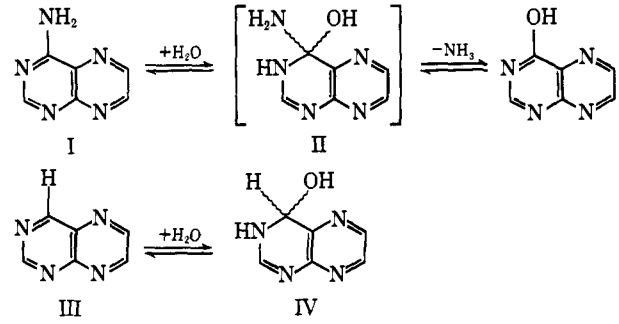
*Sir:*

In hydrolytic enzyme reactions, one may inquire whether the substrate water enters the reaction (in a chemical sense) before, during, or after the departure of the leaving group from the substrate. For adenosine deaminase, the possibility of direct water attack[1] gained support when it was found that 1,6-dihydro-6-hydroxymethylpurine ribonucleoside, an analog of the hypothetical intermediate formed by addition of water to the substrate adenosine, was an unusually potent inhibitor.[2] We wish to report a novel reaction of this enzyme which strengthens the likelihood that water attacks the substrate directly, resulting in an addition–elimination mechanism without the intervention of a purinyl–enzyme intermediate.

(1) R. Wolfenden, *Biochemistry*, 7, 2409 (1968).
(2) B. Evans and R. Wolfenden, *J. Amer. Chem. Soc.*, 92, 4751 (1970).

Noting that 4-aminopteridine (I) is a substrate for adenosine deaminase,[3] we chose to study the interaction of this enzyme with pteridine, a known inhibitor.[3] In neutral aqueous solution, pteridine (III) exists in stable equilibrium (in a molar ratio of 3.5:1)[4,5] with its 3,4-monohydrate IV (Scheme I). The rate of approach to

**Scheme I**




equilibrium has been studied in detail by Inoue and Perrin.[6]

In the present experiments, anhydrous pteridine ($10^{-4}$ *M*), freshly dissolved in a buffer (0.1 *M* potassium phosphate, pH 7.5, at 25°), was found to be converted to the equilibrium mixture by a first-order process with a half-time of 22 min; this hydration reaction was followed spectrophotometrically at 318 nm, and gave initial and final spectra identical with those reported.[4] In the presence of calf duodenal adenosine deaminase (33 μg/ml of the enzyme supplied by Boehringer Mannheim Corp.) under conditions which were otherwise identical, conversion of anhydrous pteridine to the equilibrium mixture was found to proceed very much more rapidly with approximately 50% conversion in 30 sec. The enzymatic reaction occurred in two phases, the first considerably more rapid than the second and representing approximately half-conversion to the final equilibrium mixture. To permit study of the reverse reaction, pteridine was first converted to the 3,4-monohydrate by momentary exposure to dilute acid[4] (1–2 sec in HCl, pH 2), then quenched by dilution in buffer (0.1 *M* potassium phosphate, pH 7.5 at 25°). The hydrate reverted to the usual equilibrium mixture with a half-time of approximately 22 min. In the presence of enzyme, this reaction also was found to be markedly more rapid, again following a biphasic course. Both the enzymatic hydration and dehydration reactions were effectively inhibited by competitive inhibitors of adenosine deaminase, indicating that they proceed at the active site of this enzyme.

In the absence of spectrophotometric evidence for any reaction intermediates, it seemed possible that the biphasic nature of these enzymatic reactions might be attributed to a stereochemical preference of the enzyme for one or the other enantiomer of pteridine hydrate (IV). This was substantiated by polarimetric observation (Figure 1). The hydration reaction showed a wave of *levorotation* reaching a maximum on a time scale comparable with that of the spectrophotometric burst, decaying more slowly to zero rotation. The dehydration

(3) R. Wolfenden, J. Kaufman, and J. B. Macon, *Biochemistry*, 8, 2412 (1969).
(4) D. D. Perrin, *J. Chem. Soc.*, 645 (1962).
(5) A. Albert, T. J. Batterham, and J. J. McCormack, *J. Chem. Soc. B*, 1105 (1966).
(6) Y. Inoue and D. D. Perrin, *J. Chem. Soc.*, 2648 (1963).