920, 820, 730, 700, 680, 620, 470 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25–7.48 (m, 4 H), 6.08, 6.00 (s, 1 H), 5.42, 5.35 (t, J = 9 Hz, 1 H), 1.82–1.92 (m, 2 H), 1.00–1.11 (m, 3 H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 129.15, 128.93, 128.71, 128.64, 106.45, 106.18, 103.16, 102.57, 25.54, 24.12, 8.25, 7.76. Anal ($C_{10}H_{11}O_3Cl$) C, H, Cl.

3-Ethyl-5-[4-(trifluoromethyl)phenyl]-1,2,4-trioxolane (cis + trans isomers): IR (AgCl) 2990, 2900, 1925, 1620, 1520, 1460, 1420, 1320, 1210, 1160, 1120, 1070, 1020, 920, 880, 830, 760, 720, 680, 650, 640, 600, 430 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58–7.68 (m, 4 H), 6.17, 6.07 (s, 1 H), 5.43, 5.34 (t, J = 9 Hz, 1 H), 1.79–1.92 (m, 2 H), 0.98–1.07 (m, 3 H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 128.04, 127.41, 125.61, 125.56, 125.51, 106.50, 106.18, 102.76, 25.01, 24.12, 7.71. Anal ($C_{11}H_{11}O_3F_3$) C, H, F.

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Registry No. Propionaldehyde oxide, 627-39-4; 4-methoxybenzaldehyde, 123-11-5; 4-*tert*-butylbenzaldehyde, 939-97-9; 4-ethylbenzaldehyde, 4748-78-1; 4-methylbenzaldehyde, 104-87-0; 4-fluorobenzaldehyde, 459-57-4; 4-chlorobenzaldehyde, 104-88-1; 4-(trifluoromethyl)benzaldehyde, 455-19-6; *cis*-3-hexene, 7642-09-3; *cis*-3-ethyl-5-phenyl-1,2,4-trioxolane, 135658-31-0; *trans*-3-ethyl-5-phenyl-1,2,4-trioxolane, 135638-98-1; *cis*-3-ethyl-5-(4-methoxyphenyl)-1,2,4-trioxolane, 135638-99-2; *trans*-3-ethyl-5-(4-methoxyphenyl)-1,2,4-trioxolane, 135639-00-8; *cis*-3-ethyl-5-(4-*tert*-butylphenyl)-1,2,4-trioxolane, 135639-01-9; *trans*-3-ethyl-5-(4-*tert*-butylphenyl)-1,2,4-trioxolane, 135658-32-1; *cis*-3-ethyl-5-(4-ethylphenyl)-1,2,4-trioxolane, 135639-02-0; *trans*-3-ethyl-5-(4-ethylphenyl)-1,2,4-trioxolane, 135639-03-1; *cis*-3-ethyl-5-(4-methylphenyl)-1,2,4-trioxolane, 135639-04-2; *trans*-3-ethyl-5-(4-methylphenyl)-1,2,4-trioxolane, 135639-05-3; *cis*-3-ethyl-5-(4-fluorophenyl)-1,2,4-trioxolane, 135639-06-4; *trans*-3-ethyl-5-(4-fluorophenyl)-1,2,4-trioxolane, 135639-07-5; *cis*-3-ethyl-5-(4-chlorophenyl)-1,2,4-trioxolane, 135639-08-6; *trans*-3-ethyl-5-(4-chlorophenyl)-1,2,4-trioxolane, 135639-09-7; *cis*-3-ethyl-5-[4-(trifluoromethyl)phenyl]-1,2,4-trioxolane, 135639-10-0; *trans*-3-ethyl-5-[4-(trifluoromethyl)phenyl]-1,2,4-trioxolane, 135639-11-1.

Anomeric-like Substituent Effects on the Chair–Chair Conformational Equilibrium of the 2-Oxo-1,3,2-oxazaphosphorinane Ring System[1]

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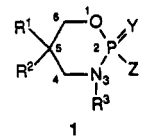
The chair–chair equilibria for a series of 5,5-dimethyl-2-oxo-(2-*p*-X-anilino)-1,3,2-oxazaphosphorinanes were determined by ^{1}H NMR. The percentage of chair conformer with the *p*-X-anilino group axial is increased by the presence of electron withdrawing X, while the opposite is true for electron-donor para X. Reasonably good linear plots of log K vs σ_p were obtained in the solvents acetone-d_6, CD_3CN, and CD_3NO_2 with ρ = 0.28–0.36. These results are interpreted in terms of the dominance of the endo anomeric effect involving overlap of the endocyclic N(3) and O(1) p lone pairs with the axial P–N σ^* orbital (*p*-XC_6H_4NHP).

1,3,2-Oxazaphosphorinanes **1** can be viewed as cyclohexanes in which carbon atoms have been replaced by oxygen, phosphorus, and nitrogen atoms. The effects on the conformational properties of cyclohexane of making such substitutions are of basic interest. These ring systems take on further significance since they are an integral structural part of the clinically valuable antitumor agent cyclophosphamide **2** and its congeners.[2] A thorough



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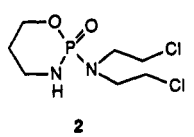

2

knowledge of the conformational properties of the 1,3,2-oxazaphosphorinane ring system should be beneficial to a detailed understanding of the effects of conformation on the oxidative metabolic activation of cyclophosphamide, the transport properties of the metabolites, and their breakdown to cytotoxic products.

In previous work,[3] it was shown that chair–chair and chair–twist equilibria are strongly influenced by the following (see structure **1**): (1) the size of substituent R^3 and (2) the steric and electronic properties of Z. The chair-to-twist free energy change was found to be remarkably

† Present address: Department of Chemistry, The University of Alabama in Huntsville, Huntsville, AL 38899.

(1) Presented in part at the First American Chemical Congress, San Juan, Puerto Rico, Nov 1985.

(2) Two reviews by chemists have emphasized both the chemical and pharmacological aspects of cyclophosphamide, its analogues, and related compounds: Zon, G. *Prog. Med. Chem.* **1982**, *19*, 205. Stec, W. *Organophosphorus Chem.* **1982**, *13*, 145. See also: Hill, D. L. *A Review of Cyclophosphamide*; Charles C. Spring: Springfield, IL, 1975. Calvin, M. In *Clinical Pharmacology of Anti-Neoplastic Drugs*; Pinedo, H. M., Ed.; Elsevier: Amsterdam, The Netherlands, 1978; pp 245–261. Friedman, O. M.; Myles, A.; Calvin, M. *Adv. Cancer Chemother.* **1979**, *1*, 143.

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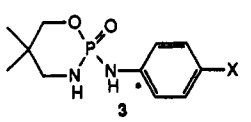
Table I. ^{1}H NMR Parameters for 3a–3e at 300 MHz, Ambient Temperature

		chemical shift (ppm)				J_{HP}, J_{HH} (Hz)						
compd	solvent	H_A	H_B	H_C	H_D	AB	AP	BP	CD	CP	DP	BD
3a	acetone-d_6	4.01	3.72	3.07	*a*	−11.0	3.9	20.0	−13.1	2.5	*b*	2.7
3b	acetone-d_6	3.99	3.73	3.07	2.83	−11.0	3.8	20.2	−13.1	2.6	23.3	2.7
3c	acetone-d_6	4.04	3.76	3.09	2.83	−11.0	3.6	20.4	−13.1	2.4	24.0	2.8
3d	acetone-d_6	4.00	3.75	3.29	3.10	−11.1	3.2	20.5	−13.0	2.0	*b*	3.1
3e	acetone-d_6	4.04	3.83	3.13	2.87	−11.1	2.8	21.2	−12.9	1.3	24.7	2.7
3a	CD_3CN	3.99	3.78	3.03	2.96	−11.0	3.9	20.0	*c*	*c*	*c*	2.7
3b	CD_3CN	3.94	3.74	2.99	2.75	−11.0	3.4	20.5	−12.9	2.6	23.9	2.7
3c	CD_3CN	4.00	3.80	3.05	2.81	−11.1	3.3	20.7	−13.1	2.5	24.3	2.8
3d	CD_3CN	3.95	3.75	3.01	2.76	−11.2	3.2	20.9	−12.9	2.1	24.6	2.8
3e	CD_3CN	3.98	3.79	3.04	2.79	−11.2	2.7	21.5	−12.6	*b*	25.1	2.9
3a	CD_3NO_2	4.04	3.80	3.10	2.87	−11.0	3.9	20.0	−13.0	3.3	23.1	3.9
3b	CD_3NO_2	4.04	3.79	3.09	2.87	−11.0	3.7	20.7	−13.1	3.4	23.6	2.9
3c	CD_3NO_2	4.05	3.82	3.11	2.89	−11.1	3.5	20.5	−13.0	2.4	23.9	2.5
3d	CD_3NO_2	4.06	3.82	3.13	2.89	−11.0	3.2	20.6	−13.4	2.4	24.2	2.7
3e	CD_3NO_2	4.09	3.86	3.15	2.93	−11.6	2.6	21.8	−13.2	1.3	24.9	2.7

[a] Overlapped with Me_2N signal. [b] Poorly resolved. [c] Closely coupled second-order spectrum.

small. Relatively small, electronegative substituents, such as Z = MeO and PhO,[3c] show a very strong axial preference. Even Me_2N displays a small axial preference when Y = O, R^3 = H, and R^1 = R^2 = Me. This may be attributable to orbital interactions similar to those thought to be primarily responsible for the endo anomeric effect[4] observed in other six-membered-ring heterocycles. Thus, the antibonding P–N orbital, when it is axial, is suitably aligned for stabilizing overlap with a neighboring electron lone pair on N(3) or O(1), an interaction that is not available when the P–N bond is equatorial.

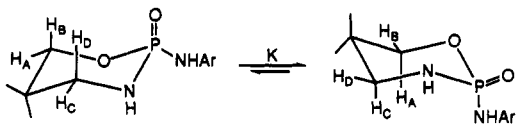
To explore the correctness of this idea, we have prepared a series of 2-anilino-2-oxo-5,5-dimethyl-1,3,2-dioxaphosphorinanes 3 and determined the effects of changing X on



3

a, X = NMe_2
b, X = OMe
c, X = F
d, X = H
e, X = NO_2

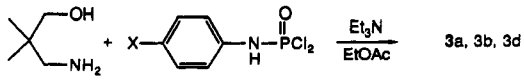
the equilibrium 4 ⇌ 5. In this way the electronic nature of the substituent on phosphorus can be varied without changing its steric demands. Results in accord with the electronic effects described above are indeed found.



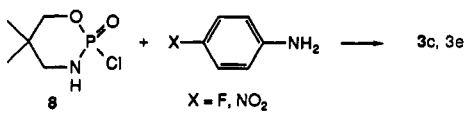
4 5

Results

Syntheses. 1,3,2-Oxazaphosphorinanes 3 were prepared,[5] as shown below, by the reaction of amino alcohol 6 with the appropriate phosphoramidic dichloride 7 (3a, 3b, and 3d) or from reaction of a substituted aniline with 2-chloro-2-oxo-5,5-dimethyl-1,3,2-oxazaphosphorinane 8.



6 7 X = Me, N, MeO, H



8 X = F, NO_2

Conformational Analysis. The equilibrium constants for the chair–chair process 4 ⇌ 5 for the series 3a–3e were determined by 300-MHz ^{1}H NMR analysis. The pertinent NMR parameters are given in Table I. Chemical shift dispersions were great enough to allow a first-order determination of coupling constants J_{AP} and J_{BP} to be made. The dominant conformer was assigned the structure 5. This is based on the well-demonstrated,[3] small preference of the Me_2N in 2-oxo-1,3,2-oxazaphosphorinanes with hydrogen at N(3) for the apical position and the obviously smaller steric size of the anilino group which was found in the X-ray structures published for 3c and 3d.[3a,3b] In those structures the PhNH is positioned with the N–H over the 1,3,2-dioxaphosphorinane ring. The axial preference of the anilino group is even evident in 2-oxo-1,3,2-dioxaphosphorinanes.[6] By contrast, the axial Me_2N attached to phosphorus is unstable by about 1 kcal/mol in the 1,3,2-dioxaphosphorinane[7] in contrast to its small preference to be axially attached to a 2-oxo-1,3,2-oxazaphosphorinane ring (R^3 = H). Thus, there can be no uncertainty as to the orientation of the ArNH (*p*-XC_6H_4NH) in the dominant conformer 5 for 3a–3e.

The mole fraction of 4 can be easily calculated from the observed, time-averaged, $^3J_{HP}$ values J_{AP} and J_{BP}. For J_{AP} eq 1 is readily derived.[3] A completely analogous equation

$$N(5) = \frac{J_{AP}(\text{obsd}) - J_{AP}(4)}{J_{AP}(5) - J_{AP}(4)} \quad (1)$$

relates J_{BP}(obsd) to assumed J_{BP}(4) and J_{BP}(5). Assumed values for J_{AP} and J_{BP} of 4 and 5 (22.0 and 2.0 Hz) were based on measured values for 2-oxo-1,3,2-dioxa- and oxazaphosphorinanes for which close to 100% of a single chair is populated.[3,8] As seen in Table I, the sum J_{AP} + J_{BP} is close to constant at 24.0 Hz. Small adjustments in assumed J_{HP} in model compounds were made so that their sum would be 24.0 Hz. (The assumed values 22.0 Hz and 2.0 Hz were used in measurements of similar chair equilibria published earlier from this laboratory.[3]) The assumed interconvertibility of J_{AP}(5) and J_{BP}(4), each 2.0 Hz, and, likewise, J_{BP}(5) and J_{AP}(4), each 22.0 Hz, is based on the failure of the observed, time-averaged sums of J_{AP}

(4) Kirby, J. J. *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*; Springer-Verlag: New York, 1983.
(5) Preparations of 3a, 3c, and 3d were reported previously.[6]
(6) Cameron, T. S.; Galdecki, Z.; Karolak-Wojciechowska, J. *Acta Crystallogr., Sect. B* **1976**, *B32*, 492.
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Table II. Estimated Equilibrium Constants (K = 5/4), Ambient Temperature

	solvent acetone-d_6 % 5 based on observed					solvent CD_3CN % 5 based on observed					solvent CD_3NO_2 % 5 based on observed		
compd	J_{AP}	J_{BP}	avg	K	$\Delta G°$	J_{AP}	J_{BP}	avg	K	$\Delta G°$	J_{AP}[a]	K	$\Delta G°$
3a	90.5	90.0	90.3	9.3	1.32	90.5	90.5	90.5	9.5	1.33	90.5	9.5	1.33
3b	91.0	91.0	91.0	10.1	1.37	93.0	92.5	92.8	12.9	1.51	91.5	10.8	1.41
3c	92.0	92.0	92.0	11.5	1.44	93.5	93.5	93.5	14.4	1.58	92.5	12.3	1.48
3d	94.0	92.5	93.3	13.9	1.55	94.0	94.5	94.3	16.5	1.66	95.0	19.0	1.74
3e	96.0	96.0	96.0	24.0	1.88	96.5	97.5	97.0	32.3	2.05	97.0	32.3	2.05

[a] J_{BP} values were not well ordered.

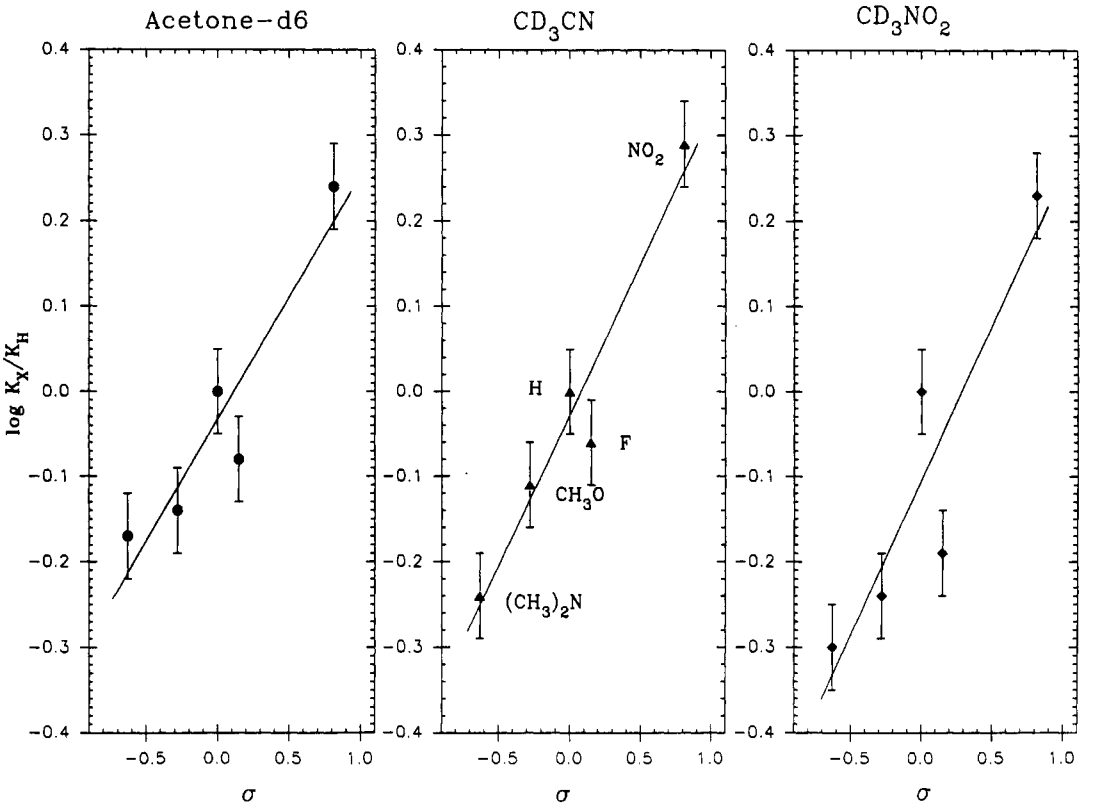


Figure 1. Hammett plots of equilibrium **5/4** for **3a–3e**.

+ J_{BP} for 2-oxo-1,3,2-dioxa-[8] and oxazaphosphorinanes[3] to change with perturbations in equilibria induced by solvent polarity variations. The good agreement of percentages of **5** calculated by use of J_{AP}(obsd) or J_{BP}(obsd), recorded in Table II, further attests to the correctness of the above assumptions. Finally, although the absolute values of the percentage of **5** populated change a few percent if the assumed J_{HP} values are varied by 0.5–1.0 Hz, the more important *differences* in population of **5**, as a function of substituent X, are little affected.

The coupling constants J_{CP} and J_{DP} also potentially could be used to determine the equilibrium **4** ⇌ **5**. However, we consider them less reliable since they are sensitive to the substituent on N(3) and perhaps to small changes in hybridization at N(3) that may accompany conformational change. Also, for a number of the examples in Table I, the spectra for H_C and H_D were poorly resolved or were second order in nature because $\Delta\nu_{CD}$ was relatively small.

The equilibrium constants determined in three solvents as a function of substituent *p*-X are recorded in Table II. Note that the electron-withdrawing *p*-NO_2 group increases the population of **5**, while electron-donor *p*-X substituents have the opposite effect. Although these changes are small, overall ΔJ_{HP} are 1.2–1.9 Hz, and the corresponding ratio of **5/4** ranges from 90.5/9.5 to 97/3 in CD_3CN, the solvent in which the equilibrium is most responsive. This is seen to correspond to a $\Delta\Delta G°$ of about 0.7 kcal/mol (Table II), a not large but certainly real effect. (Errors in these measurements will be addressed in the Discussion). Inspection of the J_{CP} and J_{DP} values of Table I show that they follow the same trend as do J_{AP} and J_{BP}, which adds credence to the analysis based on the latter coupling constants.

The possibility occurs that *intermolecular* hydrogen bonding of endo- or exocyclic NH with the basic P=O could perturb or be in part responsible for the substituent effects seen. All spectra were taken on dilute solutions (1%, w/v) to preclude intramolecular effects. In addition, the coupling constants for **3b** were measured in acetone-d_6 at both 1% and 0.1% and seen to be unchanged. Hydrogen bonding (NH···O=P) absorption[3i,9] in the region about 3200–3250 cm^{-1} was not observed in the IR spectrum of **3b** in acetone-d_6 solution at either of these concentrations. Most probably intermolecular hydrogen bonding is minimal in all three solvents. Most of the compounds were insoluble in benzene, which hydrogen bonds poorly.

Discussion

Figure 1 shows plots of log [K_X/K_H] for equilibrium **5/4** as a function of the Hammett σ parameter[10] in the three

(9) White, D. W.; Gibbs, D. E.; Verkade, J. G. *J. Am. Chem. Soc.* **1979**, *101*, 1937. Emsley, J.; Hall, D. *The Chemistry of Phosphorus*; Wiley: New York, 1976.

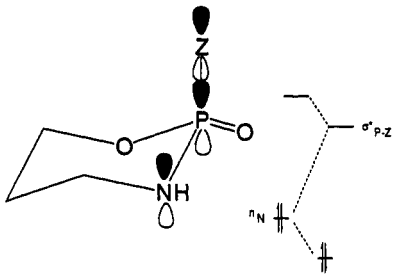


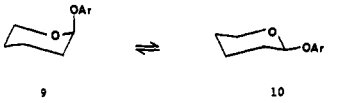
Figure 2. The endo anomeric effect in 1,3,2-oxazaphosphorinanes.

solvents. The correlations are reasonably good (r = 0.969, CD_3CN; 0.903, CD_3NO_2; 0.936, acetone-d_6). The response of K to substituent change is, however, relatively small, i.e., ρ = 0.35 in CD_3CN, 0.36 in CD_3NO_2, and 0.28 in acetone-d_6. The error in measurement of each coupling constant is about 0.2 Hz, based on the digital resolution of the instrument. Therefore, strictly speaking, K values for certain pairs of adjacent substituents with negative σ values in these plots are the same within experimental error, as shown by the approximate error bars given in Figure 1. However, taken together the effects are no doubt real, especially since exactly the same ordering of J_{AP} and J_{BP} values (and hence K) is found for all three solvents. The slight maximization of the effect in the more polar solvents, CD_3CN and CD_3NO_2, may not be outside the experimental error. Nonetheless, polar solvents should minimize intramolecular dipole–dipole interactions and allow orbital interactions to be more evident.[11] Quite likely all of the solvents are polar enough to exclude overiding contributions from dipole–dipole interactions. The similarity of solvent interactions in this system is also seen by the fact that the equilibrium constants, Table II, in the two most polar solvents are nearly the same, and there is no strong shift in the equilibrium constant on transfer to acetone-d_6.

In Figure 2 is illustrated for N(3) the sort of n/σ^* overlap which should lead to stabilization of the conformation with the P-Z bond axial. The hybridization about oxygen and nitrogen in these rings is likely close to sp^2 as indicated by measured P-O-C and P-N-C bond angles which typically run 115-121°.[3a-d,f,g,i,l,11] The stabilization shown in Figure 2 involves the p orbital and is only available to N(3) when the P–Z bond is axial. For O(1) a *lower* energy, more nearly sp^2 orbital is available for overlap with the σ^*_{P-Z} orbital when the latter is equatorial. However, as has been pointed out,[12] the resulting stabilization will be less than that involving the p orbital on oxygen and the axial σ^*_{P-Z} orbital. This determination of configuration by the higher energy neighboring orbital has been termed[13] superjacent orbital control. The most reasonable interpretation of the effect of substituent X on the equilibrium 5/4 is that replacement of p-H by an electron-withdrawing substituent, NO_2, lowers the energy of the σ^*_{P-Z} orbital and increases the n/σ^*_{P-Z} stabilization. Electron-donor p-Me_2N and p-MeO substituents have the opposite effect. Strangely, p-F does not have the effect predicted by its σ_p value and instead acts as though it were overall slightly electron donating. Indeed, if p-F is excluded from the graphs, excellent correlations result: acetone-d_6 (r = 0.985); CD_3CN (r = 1.00) CD_3NO_2 (r = 0.947) with ρ = 0.30, 0.37, and 0.39, respectively.

The σ^+ value for p-F is −0.07, a number which would move the point for that substituent much closer to the line. However, it is unreasonable to assume that these equilibria invoke a greater electron donation from p-F than for electron-ring substituents such as p-Me_2N and p-MeO. Use of σ^+ instead of σ for all substituents gives poorer correlations for acetone-d_6 (r = 0.878) and $CDNO_3$ (r = 0.885) and a similar one for CD_3CN (r = 0.930), all with smaller ρ values (ρ = 0.16, acetone-d_6; 0.20, CD_3CN; 0.22, CD_3NO_2.

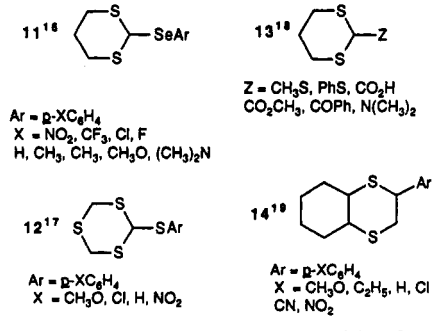
A related chair–chair equilibrium studied previously[14] is that for a series of 2-(aryloxy)tetrahydropyrans, **9** ⇌ **10**, Ar = p-XC_6H_4. The equilibrium, however, is slightly less



perturbed by substituent change. For the series, p-X = NO_2, CN, Cl, H, Me, MeO in $CDCl_3$, the maximum variation in ratio **9**/**10** was from 78/22 to 68/32. This corresponds to $\Delta\Delta G°$ of 0.3 kcal/mol compared to $\Delta\Delta G°$ for **5**/**4** over the range of substituents p-X = NO_2, H, R, and OMe of 0.4 kcal/mol (Table II). In cyclohexane the **9**/**10** ratio did not vary with p-X, but was increased to about 84/16, a phenomenum interpreted[14] as suggesting that anomeric effects are greatly reduced in such a nonpolar solvent while intramolecular dipole interactions are simultaneously increased.

Studies of a series of 2-substituted- and 2-substituted-4-methyltetrahydropyrans in different solvents and various temperatures gave strong evidence for the operation of n–σ^* anomeric effects for 2-substituents Cl, MeO, HO, and MeNH.[15] Competitive endo and exo anomeric effects were suggested.

Several related studies of substituent effects on chair–chair and/or axial–equatorial conformational equilibria have been carried out on six-membered-ring thianes (11–14). Thus, for 11 over the series of substituents Me_2N



to NO_2, $\Delta G°$ covered a range of 0.43 kcal/mol at 210 K.[16] For 12[17] the range of $\Delta G°$ over the range CH_3O to NO_2 was only 0.22 kcal/mol. At 57 °C $\Delta G°$ for 14[19] (trans ring

(10) σ values were taken from Table 4 of March, J. *Advanced Organic Chemistry*, 3rd ed.; John Wiley and Sons: New York, 1985; Chapter 9.
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fusion) varied from 2.63 to 1.75 kcal/mol. Rationalization of these variations was made in terms of anomeric effects and, in some cases, intramolecular dipole repulsions. For **14**, a good correlation of log K with σ_P[19] was obtained.

It must also be recognized that for the equilibrium **4** ⇌ **5** there are *two exo anomeric* interactions which are perturbed by substituent change. When the anilino group on phosphorus is axial (**5**), the lone-pair electrons on the anilino nitrogen potentially can interact with the antibonding, endocyclic, $\sigma^*_{P-N(3)}$, and/or $\sigma^*_{P-O(1)}$ orbital. The effects of *p*-X on the strength of this interaction in **3a–3e** will be *opposite* to those experienced by the N(3)/σ^*_{P-N} and O(1)/σ^*_{P-N} *endo anomeric* stabilization and tend to *offset* the effects of *p*-X variation on the latter. Indeed, X-ray structures of **3c** and **3d** reveal that the axial anilino groups are close to ideally oriented for such an N(1)/$\sigma^*_{P-N(3)}$ overlap.[3b] Most likely in solution overlap of the anilino lone pair with the $\sigma^*_{P-N(3)}$ or $\sigma^*_{P-O(1)}$ occurs.

In addition, an *equatorial* anilino substituent in conformer **4** will be involved with a *second exo anomeric* stabilization involving the equatorial anilino lone-pair electrons and the *endocyclic* σ^*_{P-O} and σ^*_{P-N} orbitals. The effects of *p*-X variation in **3a–3e** on this interaction will be opposite to those on the *first* exo anomeric described just described. To the degree that these exo anomeric interaction offset one another, the net effect on **5**/**4** observed will be the perturbation of the *endo* n/σ^*_{P-Z} stabilization operative when Z is axial. The balance of these three interactions controls the size of the net substituent observed (ρ = 0.28–0.35).

Finally, it should be noted that the above plots would be benefited by more points involving X with positive values of σ. Also, it is easy to show that if the equilibrium were more closely balanced, e.g., 75/25, there would be a greater variation in the observed equilibrium ratios for a commensurate change in free energy. The corresponding J_{HP} values would cover a greater range allowing a more accurate determination of the change in equilibrium constant with substituent. A study on such a system is in progress, and its results will be reported subsequently.

Conclusions

The variation of substituents on the anilino group in the series **3a–3e** led to a small but real perturbation of the equilibrium constant **5**/**4**. The variation is fairly well correlated by the Hammett equation by the use of σ_p values. A reasonable interpretation of these results is that the effect observed stems from the dominant influence on these equilibria of an n/σ^* stabilization involving the N(3) and O(1) p-orbital lone-pair electrons and the σ^*_{PN} for the anilino group when it is axial (Figure 1). This stabilization varies directly with the relative energies of the axial σ^*_{P-N} orbitals. Electron donors lower this energy while donor groups have the opposite effect. The overall net effect over the entire range of substituents amounts to about 0.7 kcal/mol. In data taken in three solvents, the role of the *p*-fluoro substituent is that of a net *donor* rather than an acceptor. These results are certainly consistent with the view that the sort of endo anomeric effect described here plays an important role in determining the axial or equatorial preferences of substituents on phosphorus of 2-oxo-1,3,2-oxazaphosphorinanes.

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Experimental Section

Methods and Materials. ^{1}H NMR spectra were taken on a Varian XL 300 NMR spectrometer operated at 300 MHz in the FT mode. Digital resolution is estimated to be 0.2 Hz. NMR solvents were used as received. ^{31}P NMR spectra were obtained by use of the same spectrometer at 121 MHz under proton decoupling conditions. Positive ^{31}P chemical shifts are in ppm downfield from external 85% H_3PO_4. Quantitative elemental analyses were carried out by Atlantic Microlabs Inc., Atlanta, GA, and Galbraith Laboratories Inc., Knoxville, TN. Melting points are uncorrected. Phosphorus oxychloride was purchased from EM Science. Substituted anilines from Aldrich Chemical were used as obtained. Ethyl acetate and triethylamine were freshly distilled from CaH_2 before use. The preparations of **3a**, **3c**, and **3d** were reported earlier.[6]

Preparation of 2-(*p*-Nitroanilino)-2-oxo-5,5-dimethyl-1,3,2-oxazaphosphorinane (3e). A solution of phosphorus oxychloride (3.07 g, 20 mmol), *p*-nitroaniline (2.76 g, 20 mmol), and triethylamine (2.02 g, 20 mmol) in 600 mL of ethyl acetate was stirred under argon for 3 days. The ^{31}P NMR spectrum of an aliquot of the resulting products confirmed the formation of the phosphoramidic dichloride as the primary product, δ^{31}P ($CDCl_3$) 7.39. Subsequently, triethylamine (4.84 mL, 4.04 g, 40 mmol) and 2-(hydroxymethyl)-2-methylpropylamine (20 mmol) were added, and the mixture was heated at gentle reflux for five days. The product mixture at room temperature was filtered to remove the triethylamine hydrochloride. Evaporation of the solvent from the filtrate gave 5.34 g of a yellow semisolid which showed in $CDCl_3$ a major ^{31}P peak at 3.37 ppm. Flash column chromatography (230–425-mesh SiO_2, 25 × 250 mm column) eluting first with CH_2Cl_2 and then with 5% MeOH in CH_2Cl_2 gave 2.86 g (41%, based on *p*-nitroaniline) of pure **3e**: mp 242–243 °C; ^{31}P NMR ($CDCl_3$) δ 3.37; ^{1}H NMR (acetone-d_6) Tables I and II plus peaks at δ 0.83 (3 H, s, Me), 1.21 (3 H, s, Me), 7.29 (2 H, d, J = 9.3 Hz, *p*-$NO_2C_6H_4$), 8.11 (2 H, d, J = 9.3 Hz, *p*-$NO_2C_6H_4$). Anal. Calcd for $C_{11}H_{16}N_3O_4P$: C, 46.31; H, 5.65; P, 10.55. Found: C, 46.34; H, 5.69; P, 10.85.

Preparation of 2-(*p*-Methoxyanilino)-2-oxo-5,5-dimethyl-1,3,2-oxazaphosphorinane (3b). In similar fashion a stirred solution of *p*-methoxyaniline (2.15 g, 19.4 mmol), triethylamine (2.72 mL, 1.96 g, 19.4 mmol), and $POCl_3$ (2.97 g, 19.4 mmol) in 600 mL of ethyl acetate underwent reaction for three days after which more triethylamine (5.14 mL, 3.93 g, 38.8 mmol) and 2-(hydroxymethyl)-2-methylpropylamine (19.4 mmol) were added. After a gentle, 5-day reflux, the triethylamine hydrochloride was filtered off. Removal of solvent from the filtrate yielded 4.22 g of a brownish solid. Recrystallization from ethyl acetate gave 1.48 g (28%) of a colorless crystalline solid: mp 167–168 °C; δ^{31}P NMR ($CDCl_3$) δ 4.32; ^{1}H NMR (acetone-d_6) Tables I and II plus peaks at δ 0.81 (3 H, s, Me), 1.16 (3 H, s, Me) 6.77 (2 H, d, J = 8.9 Hz, *p*-$MeOC_6H_4$), 7.09 (2 H, d, J = 8.9 Hz, *p*-$MeOC_6H_4$). Anal. Calcd for $C_{12}H_{19}N_2O_3P$: C, 53.32; H, 7.09; P, 11.46. Found: C, 53,26; H, 7.08; P, 11.17.

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