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Polarizability Effects on the Aqueous Solution Basicity of Substituted Pyridines

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was performed on Merck silica gel 60 (type 9385). Petroleum ether refers to the fraction of bp 50–60 °C.

2-Hydroxy-5,10,15,20-tetraphenylporphyrin (2). 2-(Benzyloxy)-5,10,15,20-tetraphenylporphyrin⁴ (3) (240 mg, 0.33 mmol) was dissolved in tetrahydrofuran (6 mL) and ethanol (6 mL), protected from light, and heated to boiling. A saturated solution of sodium hydroxide in ethanol (2 mL) was added, and the solution was boiled under nitrogen for 45 min. The mixture was diluted with water and the product extracted into chloroform. The combined extracts were dried (Na₂SO₄), and the solvent was removed under reduced pressure to give a purple solid. Light was rigorously excluded in all workup procedures. Minor impurities were removed by flash chromatography on silica gel. The major band was eluted with CH₂Cl₂ and evaporated, and the product was washed successively with hot methanol and pentane to give 2 as purple crystals (170 mg, 83%): >300 °C; visible spectrum λ_{max} 419 (log ϵ 5.39), 517 (4.15), 556 (3.85), 592 (3.77), 648 nm (3.76); ¹H NMR (CD₂Cl₂) δ enol -2.94 (br s, NH), 1.53 (br s, OH), 8.62 and 8.85 (b AB q, J_{AB} = 5.03 Hz, H_{17,18}), 8.82 and 8.87 (b AB q, J_{AB} = 5.00 Hz, H_{7,8}), 8.83 (br s, H_{12,13}), keto -2.00, -2.06 (2 br s, NH), 4.62 (s, CH₂), 8.49 and 8.72 (b AB q, J_{AB} = 5.10 Hz, H_{17,18}), 8.53 and 8.78 (b AB q, J_{AB} = 5.10 Hz, H_{7,8}), 8.54 and 8.58 (AB q, J = 4.50 Hz, H_{12,13}), 7.65–7.80 (m, H_{m,p}), 7.87–8.25 (m, H_o); mass spectrum, m/z 630 (M⁺, 100). The deuteriated derivative was prepared by three successive equilibrations of a solution of the porphyrin 2 in toluene-*d*₈ with D₂O. The solution was dried over Na₂SO₄ prior to NMR analysis.

2-Amino-5,10,15,20-tetraphenylporphyrin (4). The crude aminoporphyrin 4 was prepared by the method of Baldwin et al.⁵ Purification was effected by chromatography over silica gel (dichloromethane/petroleum ether, 1:1) with careful exclusion of light. The major brown band was collected and the solvent removed under reduced pressure. The residue was boiled in methanol and filtered to give 4 as shiny fine purple crystals (30

mg, 64%): mp >300 °C; ¹H NMR (CD₂Cl₂) δ -2.78 (br s, NH), 4.52 (br s, NH₂), 7.70–7.86 (m, H_{m,p}), 8.11–8.22 (m, H_o), 8.74 and 8.52 (AB q, J_{AB} = 4.70 Hz, H_{17,18}), 8.78 and 8.69 (AB q, J_{AB} = 4.79 Hz, H_{7,8}), 8.79 and 8.81 (AB q, J_{AB} = 4.60 Hz, H_{12,13}).

(2-Hydroxy-5,10,15,20-tetraphenylporphinato)zinc(II) (5). Treatment of 2 with zinc(II) acetate according to the method of Fuhrhop and Smith⁷ gave the metalated porphyrin⁴ 5 in quantitative yield: visible spectrum λ_{max} 424 (log ϵ 5.45), 552 (4.15), 588 (3.70), 618 nm (3.34); ¹H NMR (CDCl₃) δ 5.95 (s, OH), 7.69–7.92 (m, H_{m,p}), 8.09 (s, H₃), 8.15–8.25 (m, H_o), 8.65 and 8.90 (AB q, J_{AB} = 4.65 Hz, H_{17,18}), 8.88 and 8.94 (AB q, J_{AB} = 4.71 Hz, H_{7,8}), 8.91 and 8.92 (AB q, J_{AB} = 4.66 Hz, H_{12,13}); mass spectrum, m/z 692 (M⁺, ⁶⁴Zn, 100), 694 (M⁺, ⁶⁶Zn, 70), 696 (M⁺, ⁶⁸Zn, 45).

(2-Hydroxy-5,10,15,20-tetraphenylporphinato)copper(II) (6). Porphyrin 2 (100 mg, 0.16 mmol) was treated with copper(II) acetate according to the method of Fuhrhop and Smith.⁷ The crude metalated porphyrin was chromatographed on silica gel (dichloromethane/petroleum ether, 1:1). The major red band was collected, and the solvent was removed under reduced pressure. Recrystallization of the resultant product from dichloromethane/pentane afforded pure 6 as fine purple crystals (86 mg, 78%): mp >300 °C; visible spectrum λ_{max} 416 (log ϵ 5.62), 539 (4.28), 579 (3.83), 601 nm (3.37); mass spectrum, m/z 691 (M⁺, 100), 675 (6).

Anal. Calcd for C₄₄H₂₈N₄OCu: C, 76.34; H, 4.08; N, 8.10. Found: C, 75.62; H, 4.00; N, 8.10.

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Polarizability Effects on the Aqueous Solution Basicity of Substituted Pyridines

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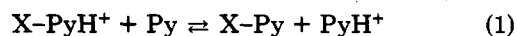
A quantitative dissection of polarizability (*P*), field (*F*) and resonance (*R*) substituent contributions to the relative gas-phase and aqueous solution basicities of 2-, 3-, and 4-substituted pyridines (XPy) is described in this work. The standard-free-energy changes for the reaction XPyH⁺ + Py \rightleftharpoons XPy + PyH⁺ (eq 1) in the gas-phase ($\delta\Delta G^\circ_g$) and in aqueous solution ($\delta\Delta G^\circ_{\text{aq}}$) have been analyzed. $\delta\Delta G^\circ_g$ has been found to be the sum of *F*, *R*, and *P* while $\delta\Delta G^\circ_{\text{aq}}$ only depends on *F* and *R*. $\delta\Delta G^\circ_g$ corrected for polarizability, ($\delta\Delta G^\circ_g - P$) is a linear function of $\delta\Delta G^\circ_{\text{aq}}$. This relationship holds for substituents in any of the three positions (ortho, meta, para), including 2-mono- and 2,6-disubstituted pyridines. These results show that the fundamental differences between gas-phase and solution basicities of pyridine are (i) the essentially complete disappearance of polarizability effects in solution and (ii) an attenuation (by a factor of ca. 2.3) of field and resonance contributions.

Studies of gas-phase acidities and basicities of organic compounds have led Taft and Topsom¹ to the quantitative dissection of substituent polarizability (σ_p), field-inductive (σ_F), and resonance (σ_R) effects. This scheme has successfully been applied to the analysis of structural effects on many kinds of proton-transfer reactions in the gas phase. A preliminary assessment also showed the applicability of this treatment to solution reactions wherein

substituent solvation effects are absent or are corrected for.

Here, we wish to report that this formalism has also allowed the analysis of the main factor governing the basicity of 2-, 3-, and 4-substituted pyridines in aqueous solution.

Consider the proton-exchange reaction 1, where Py stands for pyridine itself and X-Py is a 2-, 3-, or 4-substituted pyridine. The standard free-energy changes for



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Table I. Thermodynamic Data for Reaction 1 at 25 °C in the Gas-Phase and in Aqueous Solution

subst	$\delta\Delta G^\circ_g$, ^a kcal·mol ⁻¹	$\delta\Delta G^\circ_g - P$, ^d kcal·mol ⁻¹	$\delta\Delta G^\circ_{aq}$ kcal·mol ⁻¹
2-NMe ₂	8.8	6.0	2.4 ^e
2-n-C ₆ H ₁₃	6.9 ^b	3.1	1.0 ^d
2-t-Bu	6.6	1.8	0.7 ^{c,g}
2-i-Pr	6.4	3.3	0.8 ^g
2-NH ₂	4.8	3.8	2.0 ^h
2-Et	4.5	1.4	0.9 ⁱ
2-Me	3.8	1.6	1.0 ^j
2-SMe	1.6	-2.8	-2.2 ^k
2-OMe	0.6	-0.5	-2.9 ^l
none	0.0	0.0	0.0 ^m
2-Cl	-6.6	-9.5	-6.1 ⁿ
2-F	-10.2	-9.4	-7.7 ⁿ
2-CN	-13.2	-16.1	-7.5 ^o
2,6-t-Bu ₂	10.9	1.3	-0.3 ^c
2,6-i-Pr	9.1 ^c	1.2	1.4 ^c
2,6-Me ₂	6.7	2.2	2.0 ^j
2,4-t-Bu ₂	10.5 ^c	2.1	2.2 ^c
3-NMe ₂	9.5	7.7	1.7 ^e
3-Et	3.1	1.0	0.5 ⁱ
3-OMe	3.0	2.3	-0.6 ^m
3-Me	2.9	1.4	0.5 ^j
3-NH ₂	0.2	-0.5	1.1 ^h
3-CO ₂ Me	-2.8	-4.9	-2.9 ^m
3-MeCO	-3.9	-6.2	-2.7 ^p
3-Cl	-6.2	-8.0	-3.3 ^m
3-F	-7.0	-6.5	-3.0 ⁿ
3-CF ₃	-8.6	-9.7	-3.8 ^g
3-CN	-12.0	-13.9	-5.3 ^m
3-NO ₂	-13.5	-14.6	-6.0 ^h
4-NMe	15.6	13.5	6.0 ^e
4-NH ₂	11.4	10.6	5.3 ^h
4-OMe	7.1	6.3	1.9 ^m
4-t-Bu	5.7	2.1	0.6 ^c
4-SMe	5.4	2.1	1.0 ^q
4-Et	4.2	1.8	1.1 ^m
4-Me	3.5	1.8	1.1 ^j
4-CHCH ₂	2.4	0.0	0.6 ^c
4-CO ₂ Me	-2.3	-4.7	-2.4 ^m
4-Cl	-3.4	-5.5	-1.9 ^m
4-MeCO	-3.7	-6.3	-2.3 ^{m,p}
4-CF ₃	-8.3	-9.5	-3.4 ^a
4-CN	-11.1	-13.3	-4.6 ^m
4-NO ₂	-12.6	-13.8	-5.4 ^h

^a Unless stated otherwise, these data are taken from ref 1-3 and references cited therein. ^b Reference 4. ^c Reference 5. ^d Calculated with ρ_α and σ_α values from ref 1. ^e Reference 6a. ^f Reference 6b. ^g Reference 6c. ^h Reference 6d. ⁱ Reference 6e. ^j Reference 6f. ^k Reference 6g. ^l Reference 6h. ^m Reference 6i. ⁿ Reference 6j. ^o Reference 6k. ^p Reference 6l. ^q Reference 6m. ^r Reference 6n.

this reaction in the gas phase and in solution, respectively, noted $\delta\Delta G^\circ_g$ and $\delta\Delta G^\circ_{aq}$ are given in Table I.

Figure 1, a plot of $\delta\Delta G^\circ_g$ vs $\delta\Delta G^\circ_{aq}$ shows a crude linear relationship, a fact already noticed by Beauchamp,⁷ Taft,^{8a}

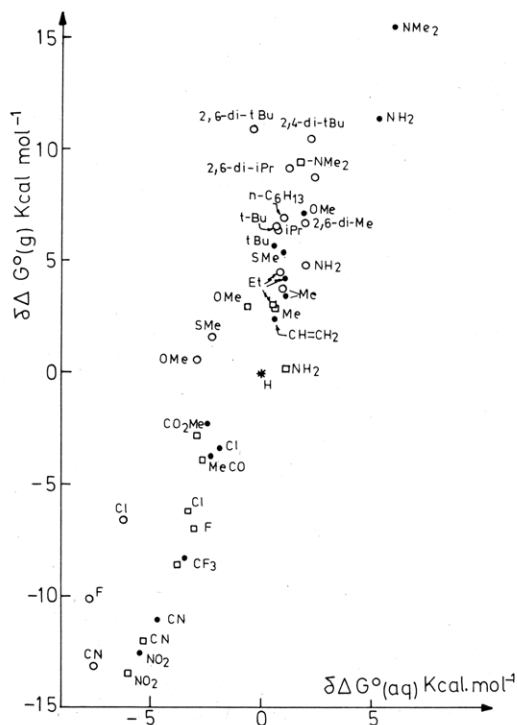


Figure 1. $\delta\Delta G_g$ vs $\delta\Delta G_{aq}$ for reaction 1: (○) ortho; (□) meta; (●) para.

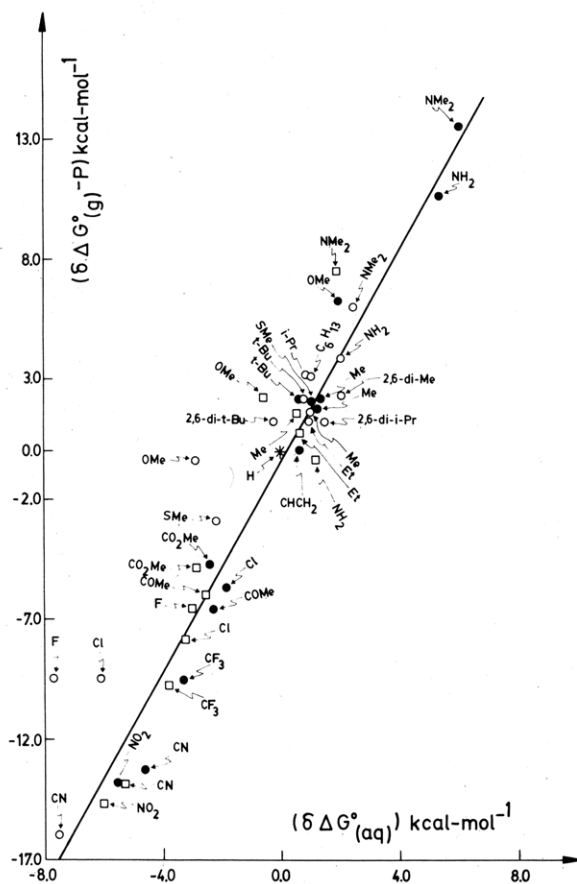


Figure 2. $\delta\Delta G_g - P$ vs $\delta\Delta G_{aq}$ for reaction 1: (○) ortho; (□) meta; (●) para.

and Aue, Liotta, and Hopkins.^{8b} It has recently been shown¹ that the differential standard free-energy changes,

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Table II. Quantitative Dissection^a of the Experimental $\delta\Delta G^\circ_g$ and $\delta\Delta G^\circ_{aq}$ Values

subst	$-\rho_\alpha(g)^c$	$-\rho_\alpha(aq)^c$	AF_α	$-\rho_F(g)^c$	$-\rho_F(aq)^c$	AF_F	$-\rho_R(g)^c$	$-\rho_R(aq)^c$	AF_R
2-X	6.4 ± 0.7	0.0	very large	27.0 ± 1.8	14.3 ± 2.0	1.9	14.3 ± 1.8	7.0 ± 2.1	2.0
3-X	4.2 ± 1.2	0.0	very large	22.8 ± 1.2	9.1 ± 1.0	2.5	16.3 ± 1.5	5.1 ± 1.0	3.2
4-X	4.8 ± 0.9	0.0	very large	21.5 ± 1.1	8.2 ± 0.6	2.6	25.9 ± 1.2	12.0 ± 0.7	2.2

^a Using equation 2. ^b Using the data from Table I. ^c All the ρ values are given with error limits of two standard deviations. The σ_α , σ_F , and σ_R are taken from ref 1, with the exception of σ_F for OMe (0.28) and N(CH₃)₂ (0.19). These values are those suggested by Charton¹⁷ as being more suitable for aqueous solution data.

$\delta\Delta G^\circ_g$ for a large number of gas-phase proton exchange processes, including reaction 1 are quite precisely described by eq 2.

$$\delta\Delta G^\circ_g = \rho_\alpha\sigma_\alpha + \rho_F\sigma_F + \rho_R\sigma_R \quad (2)$$

There is a large body of evidence suggesting that polarizability effects on proton-exchange reactions in aqueous solutions are very small, whenever efficient charge dispersal by the solvent can take place.^{19,10} Thus, $(\delta\Delta G^\circ_g - \rho_\alpha\sigma_\alpha)$ seems a more appropriate quantity for $\delta\Delta G^\circ_{aq}$ to be compared to (see Figure 2).

It is clear that with some exceptions, these quantities are linearly related. The correlation covers their full range of variation: 32 and 15 kcal·mol⁻¹. A statistical analysis of the separate regressions generated by the ortho, meta, and para derivatives, shows that they can be embodied into a single equation (eq 3), with n (number of data points) $(\delta\Delta G^\circ_g - \rho_\alpha\sigma_\alpha) = -(0.49 \pm 0.46) + (2.27 \pm 0.15)\delta\Delta G^\circ_{aq}$ (3)

$= 37$, r^2 (correlation coefficient) = 0.964, and a standard deviation of 1.3 kcal·mol⁻¹. (ρ_α values are given in Table II).

The departures from the correlation of the 2-OMe, 3-OMe, 4-OMe, and 3-NMe₂ derivatives can be understood in terms of differential (i.e., pertaining to both X-Py and X-PyH⁺) solvation effects involving the methoxy and the *N,N*-dimethylamino groups. These points, as well as those corresponding to the 2-fluoro- and 2-chloropyridines have been excluded from the data set leading to eq 3.

Two important conclusions can be drawn from this equation:

(1) The main difference between gas-phase and solution basicities of pyridines can be quantitatively described by the loss of polarizability stabilization in aqueous solution, as shown by the following analysis:

The $\delta\Delta G^\circ_g$ and $\delta\Delta G^\circ_{aq}$ data for 2-, 3-, and 4-substituted pyridines have been treated by means of eq 2. The corresponding ρ_α , ρ_F , and ρ_R values for $\delta\Delta G^\circ_g$ are given in Table II. The analysis of $\delta\Delta G^\circ_{aq}$ leads to

$$\delta\Delta G^\circ_{aq} = (0.6 \pm 0.8) + (0.7 \pm 1.0)\sigma_\alpha - (14.6 \pm 2.0)\sigma_F - (6.9 \pm 2.0)\sigma_R \quad (4)$$

with $n = 14$ (excluding 2-F and 2-OCH₃), $r^2 = 0.960$, and $sd = 0.7$ kcal·mol⁻¹ for 2-substituted pyridines,

$$\delta\Delta G^\circ_{aq} = -(0.1 \pm 0.5) + (0.06 \pm 0.86)\sigma_\alpha - (9.1 \pm 0.8)\sigma_F - (5.1 \pm 0.8)\sigma_R \quad (5)$$

with $n = 13$, $r^2 = 0.989$, and $sd = 0.4$ kcal·mol⁻¹ for 3-substituted pyridines, and

$$\delta\Delta G^\circ_{aq} = (0.18 \pm 0.56) + (0.49 \pm 0.68)\sigma_\alpha - (8.2 \pm 0.3)\sigma_F - (12.0 \pm 0.7)\sigma_R \quad (6)$$

with $n = 13$ (excluding 4-OMe), $r^2 = 0.996$, and $sd = 0.3$ kcal·mol⁻¹ for 4-substituted pyridines.

In all cases, the ρ_α 's are small and the corresponding uncertainties are comparatively quite large. A statistical study of eq 4-6 indicates that σ_α has indeed little statistical significance. Thus, it is possible to treat the corresponding data sets as functions of σ_F to σ_R only. This leads to eq 4'-6'. Also notice that in all cases the independent terms are essentially nil within the limits of error.

$$\delta\Delta G^\circ_{aq} = (0.18 \pm 0.56) - (14.3 \pm 2.0)\sigma_F - (7.0 \pm 2.1)\sigma_R \quad (4')$$

with $n = 14$, $r^2 = 0.952$, and $sd = 0.7$ kcal·mol⁻¹

$$\delta\Delta G^\circ_{aq} = -(0.13 \pm 0.40) - (9.1 \pm 1.0)\sigma_F - (5.1 \pm 1.0)\sigma_R \quad (5')$$

with $n = 13$, $r^2 = 0.988$, and $sd = 0.4$ kcal·mol⁻¹

$$\delta\Delta G^\circ_{aq} = -(0.0 \pm 0.4) - (8.2 \pm 0.6)\sigma_F - (12.0 \pm 0.7)\sigma_R \quad (6')$$

with $n = 13$, $r^2 = 0.996$, and $sd = 0.3$ kcal·mol⁻¹

These expressions are to be preferred to eq 4-6 for their goodness of fit is essentially the same but have one less adjustable parameter.

An attenuation factor, AF_Y , is defined as being equal to the ratio $\rho_Y(g)/\rho_Y(aq)$ for each of the electronic factors, Y ($Y = \alpha, F$, and R). The various AF_Y 's are collected in Table II.

We observe that AF_F and AF_R are largest in the meta and para positions, as it can be expected from essentially electrostatic effects. The slope of the line defined by eq 3, 2.3 is a measure of the average attenuation of field and resonance effects in aqueous solution.

In the case of anilines, the attenuation factor is 4.2¹¹ while for phenols, it reaches 6.8.^{12,13} This is reasonable, because anilinium ions can disperse charge through three hydrogens bonds, while only one is available to pyridinium ions. It is also known that bulk water is a strong hydrogen bonding acid,¹⁴ but it is a rather weak base,¹⁴ so that charge dispersal from phenoxides is more important.

(2) All 2-mono- and 2,6-dialkyl pyridines are close to the line defined by eq 3. This is remarkable because (a) polarizability effects for these compounds are often very large in the gas-phase, and (b) it implies the absence of major steric effects on solvation of the pyridinium ion center.

The essentially "normal" behavior of 2,6-di-*tert*-butylpyridine (DTBP) is important, for it indicates that charge dispersal through hydrogen-bonding is present in aqueous DTBPH⁺.

On the basis of other results, le Noble,¹⁵ Hopkins,^{5,16} Aue,⁵ and Meot-Ner⁴ and their co-workers have come to

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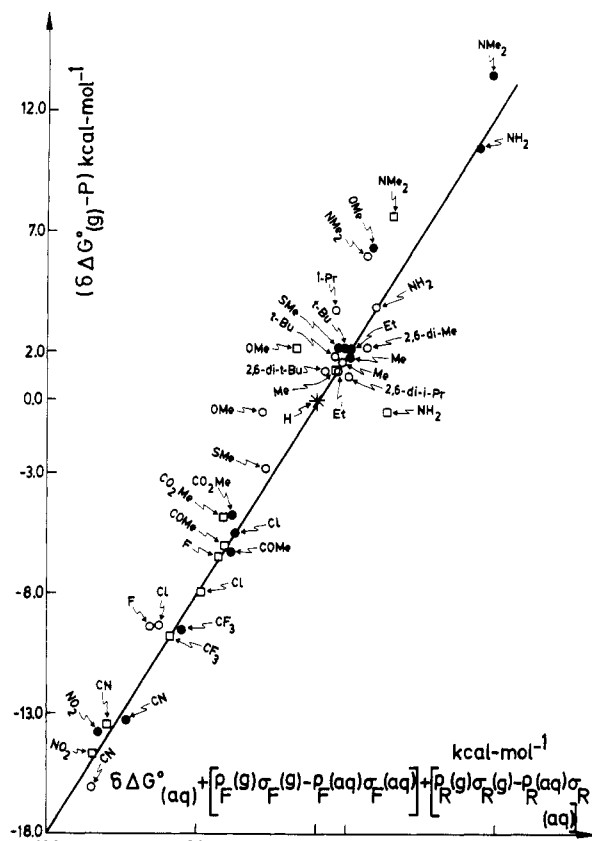


Figure 3. Plot of eq 7: (○) ortho; (□) meta; (●) para.

the same conclusions. Furthermore, should polarizability effects be the only difference between gas-phase and solution basicities of pyridines, then $\delta\Delta G^\circ_{\text{aq}}$ values for 2,6-DTBP and 2,6-diisopropylpyridine (2,6-DIPP) should be quite close. In fact, they differ by 1.7 kcal·mol⁻¹, the latter being more basic. Hopkins and Aue⁵ have concluded that

gaseous 2,6-DTBP⁺ suffers a loss of entropy of ca. 6 cal·mol⁻¹·K⁻¹ because of hindered rotations of and within the *tert*-butyl groups, while Meot-Ner⁴ estimates the entropy loss of aqueous 2,6-DIPP⁺ to be small. Thus, a difference of free energy of 1.7 kcal·mol⁻¹ can be well accounted for by this entropic effect.

We last notice that eq 3 assumes a constant attenuation factor for resonance and field effects in the ortho, meta, and para positions. As shown in Table II, this is only an approximation. Using eq 2 and keeping in mind that $\rho_\alpha(\text{aq}) \approx 0$, eq 7 obtains.

$$\delta\Delta G^\circ_{\text{g}} - P = \delta\Delta G^\circ_{\text{aq}} + [\rho_{\text{F}}(\text{g})\sigma_{\text{F}}(\text{g}) - \rho_{\text{F}}(\text{aq})\sigma_{\text{F}}(\text{aq})] + [\rho_{\text{R}}(\text{g})\sigma_{\text{R}}(\text{g}) - \rho_{\text{R}}(\text{aq})\sigma_{\text{R}}(\text{aq})] \quad (7)$$

This equation is represented in Figure 3, wherein the line drawn is the theoretical one (zero intercept and unity slope).¹⁸ Notice that for all substituents with the exception of NMe₂ and OMe¹⁷ we have taken $\sigma_{\text{F}}(\text{g}) = \sigma_{\text{F}}(\text{aq})$ and $\sigma_{\text{R}}(\text{g}) = \sigma_{\text{R}}(\text{aq})$. It is of interest that the points corresponding to the 2-fluoro- and 2-chloropyridines are now close to the theoretical line. On the other hand the amino, *N,N*-dimethylamino, and methoxy derivatives often show significant departures from the behavior predicted by eq 7. This result strongly supports the concept that these departures originate in specific solvent-solute interactions involving the substituents.

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Registry No. Pyridine, 110-86-1; pyridinium ion, 16969-45-2.

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(18) The actual correlation equation has an intercept of 0.41 ± 0.57 kcal·mol⁻¹ and a slope of 1.01 ± 0.07 , with $n = 39$ (all the available data), $r^2 = 0.955$, and $\text{sd} = 1.6$ kcal·mol⁻¹. Excluding the data for the 2-OMe, 3-OMe, and 3-NH₂ derivatives, the intercept and slope become, respectively, equal to 0.45 ± 0.36 kcal·mol⁻¹ and 1.03 ± 0.05 , with $n = 36$, $r^2 = 0.987$, $\text{sd} = 1.0$ kcal·mol⁻¹.

Alkylation of Allylic Derivatives. 13. Cross-Coupling Reactions of the Isomeric 2,3,4,4a,5,6-Hexahydro-2-naphthalenyl Carboxylates with Organocopper and Grignard Reagents

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The regio- and stereochemistry of cross-coupling of *cis*- and *trans*-2,3,4,4a,5,6-hexahydro-2-naphthalenyl pivalate (1-OPiv) with organocopper and Grignard reagents has been investigated. Alkylation of *cis*- and *trans*-1-OPiv with LiCuMe₂ and LiCuBu₂ gives the conjugated product 2,3,4,4a,5,6-hexahydro-2-alkylnaphthalene (2) primarily via α -anti-alkylation. Alkylation of *cis*- and *trans*-1-OPiv with LiCu(CN)Me and LiCu(CN)Bu gives both 2 and 3,4,4a,5,6,8a-hexahydro-8a-alkylnaphthalene (3). In this case, 2 arises nearly equally from α - and ϵ -alkylation. Alkylation of *cis*- and *trans*-1-OPiv with LiCuPh₂ and LiCu(CN)Ph gives only 2 as a result of α -anti-alkylation. Cross-coupling of *cis*- and *trans*-1-OPiv with Grignard reagents occurs remarkably fast. Reaction of *cis*- and *trans*-1-OPiv with Grignard reagents gives identical product mixtures. Evidence for the intermediacy of radical intermediates and mechanistic implications are discussed.

We have extended our initial studies¹ of the regio- and stereochemistry of alkylation of the *cis*- and *trans*-2,3,4,4a,5,6-hexahydro-2-naphthalenyl system with organocopper reagents. This paper reports an investigation of

the regio- and stereochemistry of alkylation of the epimeric pivalates (*trans*-1-OPiv and *cis*-1-OPiv) with LiCuR₂ and LiCu(CN)R in which the alkyl groups are methyl and *n*-butyl and with LiCuPh₂ and LiCu(CN)Ph. The unexpected proclivity of this system to couple with Grignard reagents in the absence of cuprous salts precluded a study of the copper(I)-catalyzed cross-coupling of 1-OPiv with

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