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Substituent Effects. 8.[1] Basic Strength of Azatriptycene, Triphenylamine, and Some Related Amines

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The thermodynamic dissociation constants in water and 50% ethanol of quinuclidine and mono-, di-, and tribenzoquinuclidine (azatriptycene) yield 3.3 pK_a units as the base-weakening influence of the inductive effect of a phenyl group in aromatic amines. Triphenylamine is 15 pK units weaker than quinuclidine; only 5 pK units of this difference are due to resonance effects.

In previous papers we have discussed benzoquinuclidine (**2**)[2] and dibenzoquinuclidine (**3**)[3] as models of "aromatic" amines in which the aniline-type conjugation is completely or virtually absent. The present paper reports on the basic strength of the last member of the series, tribenzoquinuclidine or azatriptycene (**4**). For reasons of comparison we include some other tertiary amines and take occasion to replace earlier apparent pK_a values by thermodynamic ones. Table I gives the relevant dissociation constants along with supporting UV absorption intensity data expressed as oscillator strengths f.

The spectroscopic data confirm that the resonance interaction in **4** is practically zero, as expected on steric grounds.[2–4] As with **2** and **3**, the absorption intensity is low and does not change drastically upon protonation. By way of contrast we note that whereas triphenylamine (**7**) absorbs strongly ($f = 0.66$), the absorption intensity of its protonated form ($f = 0.014$) is 50 times weaker, resembling that of triphenylmethane ($f = 0.013$). Wittig and Steinhoff,[4] who were the first to obtain **4**, already emphasized the resemblance of its spectrum to that of triptycene.

The basic strengths of **1**–**4** decrease regularly, following eq 1 in which n is the number of benzene rings. For water

$$\mathrm{p}K_a = A - Bn \qquad (1)$$

the least-squares equation has $A = 11.10$, $B = 3.30 \pm 0.05$, SD = 0.11, and a correlation coefficient of 0.9998. For 50% ethanol, $A = 10.08$, $B = 3.24 \pm 0.04$, SD = 0.10, and a correlation coefficient of 0.9998. It follows that 3.3 pK units can be taken to represent the inductive effect of a phenyl group in aromatic amines. We recall that a similar value (3 pK units) was obtained[2] by an evaluation of the pK differences between $\mathrm{Ph(CH_2)}_n\mathit{NH}_3^+$ and $\mathrm{H(CH_2)}_n\mathit{NH}_3^+$ for n = 4–1.

As discussed earlier[2] this value for the inductive effect should be almost free from contributions by other factors. We can be more specific now as to steric inhibition to solvation caused by the presence of the "peri" CH group in **2**. First, it may be noted that **2** is (locally) homomorphous with that conformation of *N*,*N*-dimethylaniline (**5**) in which the axis of the lone pair of nitrogen is in the plane of the benzene ring. Considering that the steric inhibition to solvation for 2-methyl-*N*,*N*-dimethylaniline has been estimated at 1.6 pK_a units,[5] it must be very small when the *o*-methyl group is substituted by hydrogen. Of course, this is equivalent to saying that the solvation of **5** and its conjugate acid is little dependent on rotation around the $\mathrm{C_{ar}N}$ bond. Alternatively, **2** can be viewed as being (locally) homomorphous with 2-methylpyridine for which an analysis of the basic strengths of alkylpyridines has shown steric inhibition to solvation by the methyl group to be of little or no importance.[6,5] A similar argument can be given for **3** with reference to 2,6-dimethylpyridine.

Kreil and Sandel[7] recently reported pK_a = 2.1 for **4** in water at 25 °C from the half-neutralization point of a titration curve obtained in anhydrous acetic acid with anhydrous perchloric acid as the titrant, by application of a correlation established by Wegmann and Simon[8] between such half-neutralization data and aqueous pK_a values. Our value, pK_a = 1.12, would seem the more reliable one since it is based on spectroscopic and potentiometric measurements in highly aqueous solutions that need only small and reliable corrections and a short extrapolation. We note that the average value for the inductive effect of a phenyl group derived by Kreil and Sandel (2.8 pK units[9]) is smaller than our value also because they used a considerably lower pK_a value for **1**.

The determination of the basic strength of triphenylamine (**7**) by equilibrium measurements has not been reported previously. This is probably due to its low solubility and its instability in perchloric acid and sulfuric acid at the concentrations required for protonation. We found hydrochloric acid solutions satisfactory although not stable indefinitely. The present pK_a = −3.91, found by using Arnett and Mach's acidity function for tertiary amines,[10] is somewhat higher than the pK_a = −5 ± 0.7 estimated by Arnett et al.[11] from the enthalpy of protonation in pure fluorosulfonic acid. The latter value rests on a correlation between such enthalpies and aqueous pK_a values established for a set of some 30 amines, mostly primary aromatic amines and only one tertiary aromatic amine, *N*,*N*-dimethylaniline. Rather than stressing the difference between the two values, we would argue that their reasonable agreement shows that a tertiary aromatic amine which is 9 pK units weaker than *N*,*N*-dimethylaniline does not deviate largely from the correlation.

The resonance energies of **5**–**7** can be obtained by comparison with **2**–**4**, respectively. This gives, in water, 3.6 kcal/mol for **5** [$(7.79 - 5.16)2.3RT$], 5.1 kcal/mol for **6**, and

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[2] Wepster, B. M. *Recl. Trav. Chim. Pays-Bas* **1952**, *71*, 1159, 1171.

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[9] The pK_a values used by Kreil and Sandel give for eq 1: $A = 10.55$, $B = 2.88 \pm 0.13$, SD = 0.28, correlation coefficient 0.998.

[10] Arnett, E. M.; Mach, G. W. *J. Am. Chem. Soc.* **1966**, *88*, 1177.

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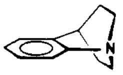
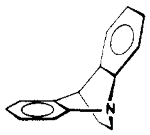
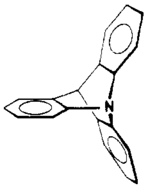
Table I.[a] Thermodynamic pK_a Values and Oscillator Strengths of Azatriptycene, Triphenylamine, and Some Related Amines at 25 °C

	 1	 2	 3	 4	$NPhMe_2$ 5	NPh_2Me 6	NPh_3 7
pK_a H_2O	11.06[b]	7.79	4.62[c]	1.12[d]	5.16	0.86[e]	−3.91[e]
50E	10.16	6.75	3.58	0.43[f]	4.16	−0.59[g]	
base		0.0052[h]	0.016[h]	0.035[i]	0.29[j]	0.40[k]	0.66[l]
baseH$^+$		0.0047[m]	0.011[n]	0.019[o]	0.0033[p]	0.0100[q]	0.0141[r]

[a] pK_a = thermodynamic dissociation constant of conjugate acid. Unless specified otherwise the potentiometric method was used (for this and other methods of determination, see the Experimental Section). 50E = 50 volumes of absolute ethanol in 100 volumes of final solution, etc. f = oscillator strength = $4.32 \times 10^{-9} \int \epsilon d\nu$ (ν in cm^{-1}); solvents are specified in the notes. For dielectric constants, D_s, see: Akerlöf, G. *J. Am. Chem. Soc.* **1932**, *54*, 4125. [b] Bayles, J. W.; Sankar, M. *J. Chem. Soc., Perkin Trans. 2* **1977**, 102. These authors give pK_a = 11.036 ± 0.010. Grob, C. A.; Schlageter, M. G. *Helv. Chim. Acta* **1976**, *59*, 264. These authors give pK_a = 11.12. [c] By linear extrapolation of pK_a values in 30E (4.07), 20E (4.30), and 10E (4.46) vs. $1/D_s$. [d] By linear extrapolation of pK_a values (SP method) in 30.7E (0.86) and 9.6E (1.05) vs. $1/D_s$. [e] In 2E–HCl, by using the H_0''' acidity function for aqueous HCl from ref 10. The SP method gives pK_a = 0.82 for **6**. [f] SP method. [g] By using an unpublished acidity function for tertiary aromatic amines without ortho substituents in 50E. [h] In 95E.[3] [i] In 50E. [j] In isooctane, C band; f = 0.036 for D band (see ref 5). [k] In 2E. [l] In 4E. [m] In 95E, 0.1 M HCl.[3] [n] In 95E, 0.4 M HCl.[3] [o] In 50E, 4.5 M H_2SO_4. [p] In 0.01 M HCl. [q] In 10E, 6.5 M HCl. [r] In 2E, 13 M HCl.

6.9 kcal/mol for **7**; in 50% ethanol 3.5 and 5.7 kcal/mol are obtained for **5** and **6**. Some comment may be pertinent.

The nonadditivity of these resonance energies is not surprising. First, HMO calculations on planar benzyl, diphenylmethyl, and triphenylmethyl anions give a similar pattern of resonance energies.[12] Second, the propeller form of **7**[13] implies a built-in steric inhibition of the resonance; **6** is most likely not all planar either.[3] Apart from this, it should be recalled that the derived values are composite, containing contributions from differences in van der Waals interactions in amine and ammonium ion,[14] and contributions from differences in nitrogen hybridization.[15]

In view of the complications in the interpretation of these resonance energies it is worth mentioning that two other approaches yield similar values for aniline and related compounds. The older of the two is based on extrapolation of the experimental acid strengths in water of $Ph(CH_2)_nNH_3^+$ with n = 4–1 to n = 0. Using the MacInnes relations and some variations thereof, Rumpf et al.[16,17] obtained calculated pK_a values for aniline which are 2.8–3.0 pK units higher than the observed value. This corresponds with 3.8–4.1 kcal/mol of resonance energy. An attractive point of this approach is that it provides a direct comparison of the real aniline with resonance-free aniline, and thus avoids the comparison of compounds of different composition like **2** and **5**. On the other hand, the latter comparison avoids the change of sp^{3}CN to sp^{2}CN involved in the extrapolation. Of course, the fact that two methods with a different blend of possible complications give compatible results is reassuring with respect to the credibility of either of them.

More recently, resonance energies were obtained by Taft et al. from gas-phase measurements. Comparison of **2** with *N*-phenylpiperidine gave 4.2 kcal/mol;[18] when *N*-phenylpyrrolidine was included, an average value of 4.8 kcal/mol was derived.[19,20] The correspondence with the values given above is pleasing and may be taken as evidence that the resonance energies in the gas phase and in water do not differ strongly; in our opinion the uncertainty in the values derived do not allow more quantitative conclusions.

Our last observation concerns the relative importance of resonance and inductive effects of the phenyl groups for the basic strengths of **5**–**7**. This paper confirms that these effects are approximately equal for **5**, and that the inductive effect is the more important one for **6**; the present analysis assigns 6.6 pK units to the inductive effect for **6** out of a total of ca. 10 pK units. Finally, the 15 pK units that separate **1** and **7** can be split up into 10 pK units from the inductive effect of the three phenyl groups and 5 pK units from the resonance effects.

Experimental Section

Materials and Electronic Spectra. Quinuclidine (**1**) hydrochloride (Aldrich) was recrystallized from absolute ethanol: mp 325 °C dec.

Azatriptycene, i.e., 9*H*-9,10-[1′,2′]benzenoacridine (**4**)[4] was recrystallized from ethyl acetate: mp 269–270 °C (lit.[4] mp 266–267 °C); UV (in 50E) λ_{max} 278 nm (ϵ 3970), 270 (3125); λ_{min} 274 (2340),

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[12] Heilbronner, E.; Bock, H. "Das HMO-Modell und seine Anwendung", Part 3; Verlag Chemie: Weinheim Bergstr, Germany, 1970. The extra resonance energies are calculated as 0.72β, 1.30β, and 1.80β, respectively.

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[14] For a separation in "electronic strain" and "steric strain" see: (a) Wepster, B. M. *Prog. Stereochem.* **1958**, *2*, 99 (in particular pp 104–106); (b) *Recl. Trav. Chim. Pays-Bas* **1957**, *76*, 335 (in particular pp 344–346). As to the acidity of triphenylmethane, see: Streitwieser, A.; Caldwell, R. A.; Granger, M. R. *J. Am. Chem. Soc.* **1964**, *86*, 3578.

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[19] Taft, R. W. In "Proton-Transfer Reactions"; Caldin, E. F., Gold, V., Eds.; Chapman and Hall: London, 1975; pp 51–53.

[20] There are good reasons to accept that the resonance energies of *N*-phenylpyrrolidine, *N*,*N*-dimethylaniline, and *N*-phenylpiperidine decrease in this order. The basic strengths in 50% ethanol[1] yield 4.7, 3.5, and 2.4 kcal/mol, respectively. The gas-phase basicities give 5.4 kcal/mol (corrected) for the first and 4.2 kcal/mol for the third compound. Probably the strongest argument stems from their dipole moments (benzene, 25 °C): 2.00, 1.60, and 1.39 D, respectively (unpublished, and in harmony with 2.04, 1.61, and 1.48 D, obtained and discussed along with other data by: Mazet, D.; Weringa, W. D.; Lumbroso, H. *C. R. Hebd. Seances Acad. Sci., Ser C* **1970**, *270*, 1537). Supporting evidence comes from the pK values of 4-substituted benzoic acids in 50% ethanol[1] with values for σ(*N*-pyrrolidino) = −0.69, $\sigma(NMe_2)$ = −0.61, and σ(*N*-piperidino) = −0.41 (cf.: Weringa, W. D.; Janssen, M. J. *Recl. Trav. Chim. Pays-Bas* **1968**, *87*, 1372).

256 (1130); $f = 0.035$ for 290–256 nm; UV (in 2E) λ_{max} 277 nm (ϵ 3900). Our spectrum in 96E differs rather strongly from that given in ref 4 [λ, nm (ϵ reference, ϵ present work): λ_{max} 278 (4900, 4090), 270 (3800, 3200); λ_{min} 255.5 (~1600, 1070)]. Our sample is probably less contaminated by more strongly absorbing impurities: UV max (50E, 4.5 M H_2SO_4) 274.5 nm (ϵ 1590), 266.5 (1320); min 270 (950), 256 (850); $f = 0.019$ for 290–250 nm.

N,*N*-Dimethylaniline (**5**):[5] UV max (in 0.01 M HCl) 264 nm (ϵ 102), 254 (205), 248.5 (169); min 262.5 (85), 250.5 (152), 222 (23); $f = 0.033$ for 290–222 nm. In 50E, 0.26 M HCl, $f = 0.0030$ nm. *N*-Methyldiphenylamine (**6**):[21] bp 124 °C (1.5 mm); UV max (in 2E) 286 nm (ϵ 8230), 243 (8160); min 258 (5970), 223 (6530); $f = 0.210$ for 350–258 nm, $f = 0.188$ for 258–223 nm; UV max (50E) 292 nm (ϵ 10600), 245 (8920); min 261 (4770), 224 (5570); $f = 0.232$ for 350–261 nm; $f = 0.184$ for 261–224 nm; UV max (10E, 6.5 M HCl) 265.5 nm (ϵ 344), 255.5 (546), 249.5 (479); min 264 (320), 252 (447), 233 (265); $f = 0.0100$ for 300–233 nm. In 50E, 4.5 M H_2SO_4, $f = 0.0073$ for 300–233 nm. Triphenylamine (**7**) was recrystallized from 96E: mp 128–129 °C; UV max (4E) 312 nm (ϵ 20200), min 265 (7800); $f = 0.66$ for 600–265 nm. The solutions are light-sensitive. In 2E, 13 M HCl (Merck GR): UV max 294 nm (ϵ 220), 261 (645), 256 (770), 251 (750); min 275 (150), 260 (640), 253 (680), 237 (530); $f = 0.0048$ for 350–275 nm, $f = 0.0141$ for 275–237 nm. In all probability the band around 300 nm (at $H_0''' \approx -5.9$) is due to free amine; the (light blue) solution in 10.5 M H_2SO_4 ($H_0''' \approx -6.9$[22]), is, initially, optically empty at this wavelength. Sulfuric acid and phosphoric acid give light blue solutions[23] the spectra of which change rapidly. Perchloric acid gives deep blue solutions instantaneously,[23] probably containing the radical cation [max at 710 nm (ϵ ~40000)]. One HCl bottle out of ten also gave a light blue solution.

Triphenylmethane was recrystallized from ethanol: mp 93–93.5 °C; UV max (50E) 270 nm (ϵ 628), 262 (891); min 268 (528), 241 (348); $f = 0.0134$ for 290–241 nm. The spectrum in 50E, 6 M HCl is almost identical.

Determination of pK_a Values. Three methods can be distinguished. Most values were obtained by the potentiometric method described earlier;[24] for **1** a Beckman Enduraglas electrode was used to avoid sodium ion corrections. As indicated in Table I, some of the lower pK_a values were determined on the basis of an acidity function. The third method, denoted as the SP method, gives $pK_a = R - \Delta + \log (BH^+/B) + \log y$, where R is the pH meter reading, Δ is the solvent correction of this reading,[24] BH^+/B is the spectrophotometrically determined ratio of conjugate acid and base, and log y is the Debye–Hückel correction.[24] For example, a 2×10^{-5} M solution of **4** in 50E, 0.194 M HCl with $R = 0.99$, $\Delta = 0.17$, $\log (BH^+/B) = -0.179$, and $-\log y = 0.213$, gives $pK_a = 0.428$. The value in Table I is the average (SD 0.02) of four measurements at 270 nm and four measurements at 278 nm, with $\log (BH^+/B)$ ranging from −0.53 to +0.69. In 30.7E and 9.6E the corrections are smaller; in 9.6E, $\Delta = 0.05$, and $-\log y$ of the four solutions ranges from 0.06 to 0.14. In our experience the SP method works well down to pH meter readings of about 0.5.

Registry No. 1, 100-76-5; **2**, 4363-25-1; **3**, 4378-82-9; **4**, 197-45-5; **5**, 121-69-7; **6**, 552-82-9; **7**, 603-34-9; triphenylmethane, 519-73-3.

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Kinetics and Mechanism of the Reaction of 5-Nitroisoquinolinium Cations with 1,4-Dihydronicotinamides

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The kinetics of the reduction of 2-methyl- (**7**) and 2-(Z-benzyl)-5-nitroisoquinolinium cations (**2**) by 1-(X-benzyl)-1,4-dihydronicotinamides (**1**) to give the corresponding 1,2-dihydro-5-nitroisoquinolines have been studied in 20% acetonitrile–80% water (v/v) at pH 7.0, 25 °C, and an ionic strength of 1.0. Deuterium labeling studies indicated direct hydrogen transfer from C-4 of **1** to C-1 of **2** or **7** without exchange with solvent protons. In the presence of large excesses of the 5-nitroisoquinolinium cations, the reactions are cleanly first order in **1**. The pseudo-first-order rate constants (k_{obsd}) were evaluated as a function of the concentrations of **2** and **7** and were found to display kinetic saturation consistent with the rapid preequilibrium formation of 1:1 complexes between **1** and **2** or **7**. Association constants for complex formation were evaluated from the kinetic data; these constants are independent of X in **1** but strongly dependent on Z in **2**. These data require the presence of at least two types of 1:1 complex, at least one of which is nonproductive, in the reaction between **1** and **2**. Rate constants for hydrogen transfer were also calculated and shown to be closely correlated by the Hammett σ constants for X and Z. For **1**, ρ_x is the same for the reduction of **7** and **2** (i.e., ρ_x is independent of Z), while for **2**, ρ_z is independent of X within experimental error. Comparison of these kinetic ρ_x and ρ_z parameters with ρ values for equilibria which involve generation (or neutralization) of a unit positive charge in closely related systems allows evaluation of $\delta = 0.82$ for the magnitude of the partial positive charge generated on the dihydronicotinamide moiety in the rate-determining transition state, and $\xi = 0.38$ for the fraction of positive charge neutralized on the isoquinolinium cation in this transition state. This discrepancy between δ and ξ indicates that the migrating hydrogen atom bears a −0.44 charge in the transition state and is thus clearly "hydridic" in character.

The nature of the detailed reaction mechanisms of enzymic reactions involving the nicotinamide coenzymes continues to be a major unsolved problem of bioorganic chemistry.[1-5] All such reactions formally involve the transfer of a hydride ion from the reduced form of the coenzyme (NADH or NADPH) to a suitable hydride-ac-

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