56. Polar Substituent Effects on Rates and Equilibria of 4-Substituted Quinuclidines

Preliminary Communication

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In contrast to their strong effect on the basicity of quinuclidines (I) [1] substituents in the 4-position have a relatively weak influence on their rate of quaternization to methiodides (II).

Second order rate constants[a] *for quaternization of quinuclidines* **1–30** *in methanol*[b] (10.00°) *and* pK_a *values in water* (25.00°)

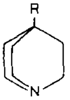
	R =	k × 10^3 l/mol · s	pK_a [1]
1	H	4.43 ± 0.068[c]	10.96
2	t-Bu	4.21 ± 0.110	11.07
3	i-Pr	4.05 ± 0.069	11.02
4	CH_2CH_3	3.95 ± 0.068	10.95
5	CH_3	3.85 ± 0.016	10.88
6	CH_2OCH_3	3.57 ± 0.025	10.50
7	CH_2OH	3.51 ± 0.016	10.45
8	C_6H_5	3.35 ± 0.019	10.20
9	$CH{=}CH_2$	3.25 ± 0.148	10.60
10	CH_2OAc	2.79 ± 0.109	10.27
11	CH_2Cl	2.70 ± 0.032	10.19
12	CH_2I	2.69 ± 0.067	10.12
13	CH_2Br	2.68 ± 0.043	10.13
14	NH_2	2.60 ± 0.115	10.10
15	$NHCH_3$	2.52 ± 0.043	10.28
16	CH_2OTs	2.39 ± 0.050	9.87
17	$C{\equiv}CH$	2.30 ± 0.011	9.53
18	$N(CH_3)_2$	2.25 ± 0.020	10.11
19	NHAc	2.22 ± 0.007	9.54
20	NHCOOEt	2.19 ± 0.023	9.57
21	OH	2.11 ± 0.012	9.44
22	$CONH_2$	2.11 ± 0.028	9.38
23	COOEt	2.02 ± 0.032	9.44
24	OCH_3	1.70 ± 0.010	9.31
25	OAc	1.51 ± 0.014	8.99
26	I	1.48 ± 0.024	8.70
27	Br	1.29 ± 0.014	8.49
28	Cl	1.23 ± 0.037	8.62
29	CN	1.00 ± 0.051[c]	8.07
30	NO_2	0.66 ± 0.011	7.65

[a] Calculated from five or more measurements.

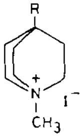
[b] *Ca.* 0.003 molar with a 120-fold excess of methyl iodide.

[c] The extrapolated value for 25.00° is *ca.* 1.3 times higher than the literature value [2].

I

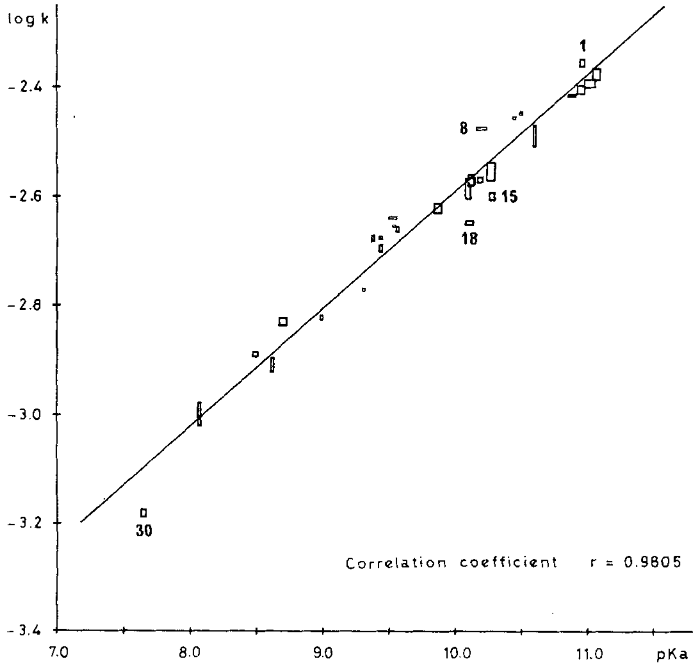


II



This follows from a comparison of the rate constants for N-methylation of the quinuclidines **1**–**30** with methyl iodide in methanol and from their pK_a values in water as shown in the Table[1]. Thus, the strongly electron withdrawing nitro group in **30** lowers the rate of quaternization of quinuclidine (**1**) by a factor of 6.7 whereas it reduces the pK_a of **1** by 3.31 units. The nitro group therefore increases the free energy of activation for N-methylation by 0.84 kcal, but raises the free energy difference between the base and its conjugate acid by 3.94 kcal. Evidently, only a partial positive charge on nitrogen has developed in the transition state for quaternization.

The rate constant for N-methylation of quinuclidine (**1**) exceeds those for the alkyl derivatives **2**–**5** in the order H > *t*-Bu > *i*-Pr > Et > Me. With the exception of the halomethyl derivatives **11**, **12** and **13**, and the hydroxy and amido derivatives **21** and **22** the rate constants differ significantly. The activation parameters for



Correlation of rate constants for N-methylation and pK_a values for the quinuclidines **1**–**30**. The sides of the rectangles indicate confidence limits of the mean for rate constants and confidence limits for pK_a values, calculated for 99% limits of inclusion in both cases.

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[1] Similar measurements of a smaller series of known 4-substituted quinuclidines have been published recently [2].

N-methylation of quinuclidine (**1**) ($H^{\neq}$ 12.55 kcal; $S^{\neq}$ -26.9 ± 1 cal/°) and 4-cyanoquinuclidine (**29**) ($H^{\neq}$ 13.97 kcal; $S^{\neq}$ -24.8 ± 2 cal/°) reveal that the substituent affects mainly the energy term.

When the logarithms of the rate constants for N-methylation are plotted against the pK_a values (s. Fig.) considerable scattering around the regression line (correlation coefficient 0.9805) results. This applies particularly to compounds **8**, **15**, **18** and, to a lesser degree, quinuclidine (**1**) itself. These deviations from linearity are not surprising since the log k values involve an irreversible reaction, the pK_a values a reversible process. These results illustrate a defect inherent in most linear free energy relationship, *i.e.* the assumption that polar substituents exert identical effects on reaction rates and equilibria. A full account of this work will follow.

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[3] *E. S. Swinbourne* 'Analysis of Kinetic Data', T. Nelson & Sons Ltd., London (1971).

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