184. Nucleophilicity and Basicity in the Quaternization of 4-Substituted Quinuclidines. Polar effects. Part III.

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Summary

The second order rate constants (k) for quaternization of thirty 4-substituted quinuclidines (**1**) by methyl iodide in methanol have been measured. The effects of the substituents on rate are relatively small and indicate an early transition state with little charge separation. They also indicate less involvement of the nitrogen atom, *i.e.* a looser transition state, for quaternization by allyl halides than for the less reactive propyl halides. The log k values of 4-substituted quinuclidines correlate moderately well with their pK_a values, the main reason being the imperfect correlation between nucleophilicity and basicity. The assumption that substituents exert equal effects on rates and equilibria is therefore only partly justified. Certain irregularities in the correlation can be attributed to a reduction of the nucleophilicity of nitrogen in **1** due to hydrogen bonding to the solvent methanol. Furthermore, quaternization is faster and responds more strongly to substituent effects in the aprotic solvent acetonitrile.

For reasons set forth in Part I [1] the pK_a values of 4-substituted quinuclidines (**1**) provide a reasonably accurate measure of polar substituent effects. In fact, a new set of polar substituent constants σ_I^q was defined by equation *(1)*,

$$pK_a^H - pK_a^R = \rho\,\sigma_I^q \qquad (1)$$

pK_a^H and pK_a^R being thermodynamic values for quinuclidine itself and for its 4-substituted derivatives. ρ is a reaction constant arbitrarily taken as unity.

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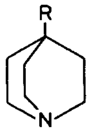

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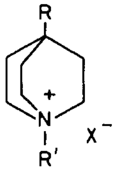

1a R=H
1b R=N(CH$_3$)$_2$
1c R=CN
1d R=*t*-Butyl
1e R=C$_6$H$_5$

1f R=COOC$_2$H$_5$
1g R=Br
1h R=OH
1i R=F
1j R=NO$_2$

The alkylation of quinuclidines (**1**), the *Menshutkin* reaction, to form quaternary salts **2** (R' = alkyl) is closely related to protonation, since positive charge is acquired by the nitrogen atom in both cases. However, contrary to reversible protonation, as measured by pK_a, quaternization is an irreversible nucleophilic substitution of the S_N2 type. It was therefore of considerable interest to determine whether the logarithms of the rate constants for quaternization (log k) of a series of 4-substituted quinuclidines (**1**) would show a linear correlation with the respective pK_a or σ_I^q values. If this were the case it would indicate that polar substituents indeed affect rate and equilibrium constants in the same way. Free activation enthalpies ΔG^{+} would then be linearly related to free reaction enthalpies ΔG_0, as is tacitly assumed in many so-called linear free energy relationships1).

To our knowledge no systematic study of the effect of polar substituents on the rate of quaternization of *saturated* tertiary amines has been reported2). The rates of reaction of a series of 4-substituted quinuclidines (**1**) (Table 1) with methyl iodide in methanol were therefore determined3)4). Because of the distance of the substituents at C(4) from the reaction site, steric effects, so important in other cases5), should be negligible.

Quaternization rates of amines are strongly influenced by the solvent. Thus, protic solvents tend to form hydrogen bonds to nitrogen thereby reducing its

Table 1. *4-Substituted quinuclidines* (**1**). σ_I^q values and second order rate constants for reaction with methyl iodide in methanol at 10.00°, mean deviation 1%.

R	σ_I^q a)	$k \times 10^3$	k_{rel}	R	σ_I^q a)	$k \times 10^3$	k_{rel}
H	0	4.39b)	1	$C \equiv CH$	1.64	2.29	0.522
$t\text{-}C_4H_9$	−0.15	4.18	0.952	$N(CH_3)_2$	0.97	2.25	0.513
$i\text{-}C_3H_7$	−0.08	4.06	0.925	$NHCOCH_3$	1.58	2.22	0.506
CH_2CH_3	0.03	3.95	0.900	$NHCOOC_2H_5$	1.56	2.19	0.499
CH_3	0.11	3.85	0.877	OH	1.68	2.11	0.481
CH_2OCH_3	0.66	3.57	0.813	$CONH_2$	1.78	2.11	0.481
CH_2OH	0.66	3.51	0.800	$COOC_2H_5$	1.70	2.02	0.460
C_6H_5	0.94	3.35	0.763	OCH_3	1.81	1.70	0.387
$CH{=}CH_2$	0.56	3.26	0.743	$OCOCH_3$	2.12	1.51	0.344
CH_2OCOCH_3	0.88	2.79	0.636	I	2.34	1.48	0.337
CH_2Cl	0.97	2.70	0.615	Br	2.65	1.29	0.294
CH_2I	1.04	2.69	0.613	Cl	2.51	1.23	0.280
CH_2Br	1.02	2.68	0.610	F	2.57	1.06	0.241
NH_2	0.98	2.60	0.592	CNc)	3.04	1.00	0.228
$NHCH_3$	0.80	2.52	0.547	NO_2	3.48	0.66	0.150
CH_2OTsd)	1.28	2.39	0.544				

a) Defined by equation (*1*) [1].

b) $\Delta H^{\neq} = 12.05$ kcal/mol; $\Delta S^{\neq} = -26.6$ cal/mol °C.

c) $\Delta H^{\neq} = 13.40$ kcal/mol; $\Delta S^{\neq} = -24.8$ cal/mol °C.

d) $Ts = p\text{-}CH_3C_6H_4SO_2$.

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1) For reviews see [2-4].

2) The reaction of 3- and 4-substituted pyridines with ethyl iodide, as described by *Fischer et al.* [5], is not comparable owing to the incursion of conjugative effects in these compounds.

3) A smaller number of such measurements have been reported [6].

4) Preliminary communications [7].

5) See *e.g.* [8-11].

nucleophilicity [12–14]. Solvents also affect the energy of the transition state leading to quaternary salts [13–17]. The net solvent effect is therefore complex. In the present investigation the effect of the protic solvent methanol and the aprotic dipolar solvent acetonitrile on the magnitude of polar substituent effects was studied. Finally, the sensitivity of the rate of quaternization by different electrophiles, namely alkyl and allyl halides, towards substituent polarity was determined in order to obtain a better insight into the structure of the transition state.

Results. - References to the preparation of the required 4-substituted quinuclidines **(1)** are given in Part 1 [1]. Their second order rate constants with methyl iodide in methanol were measured conductometrically and are listed in *Table 1* together with the respective polar substituent constants σ_I^q. A number of representative methiodides formed during the reaction was isolated and characterized by combustion and instrumental analysis. In the case of 4-dimethylaminoquinuclidine **(1b)** it was important to ascertain whether quaternization occurred exclusively at N(1). The logarithms of the second order rate constants are plotted against σ_I^q values in the *Figure.*

Table 2 shows the rate constants for the reaction of six quinuclidines **(1)** with methyl iodide in acetonitrile and a comparison of these rate constants with those determined in methanol. *Table 3* summarizes the rate constants for the reaction of four alkyl halides and two allyl halides with quinuclidine and its 4-cyano derivative. The reaction constants ρ derived from these measurements are listed in column 4.

Discussion. - The k_{rel} values in *Table 1* show that polar substituents at C(4) have a relatively weak influence on the rate of quaternization by methyl iodide in methanol. The nitro group, which lowers the basicity of quinuclidine by 3.48 pK_a units, decreases the rate by a factor of only 6.7. Hence, it increases the free energy of activation by 0.84 kcal/mol whereas it raises the free energy difference between the base and its conjugate acid by 4.51 kcal/mol. It follows that the nitrogen atom has acquired only a small positive charge in the transition state[7]. The rate constants (*Table 1*) follow the order of σ_I^q, *i.e.* pK_a, with some notable exceptions. Thus quinuclidine itself shows the highest methylation rate, although its pK_a ranks behind those of the strongest bases 4-*t*-butyl- and 4-isopropylquinuclidine. Furthermore, the C_6H_5, C≡CH and $CONH_2$ substituted quinuclidines react faster, whereas the F, $NHCH_3$ and $N(CH_3)_2$ substituted quinuclidines react more slowly than expected on the basis of their σ_I^q values.

These irregularities are more apparent in the plot of log k against σ_I^q (*Fig.*) which shows a fair amount of scattering around the regression line and a correlation coefficient of 0.975. The correlation is not as good as could be expected in view of the similarity of the reactions compared, *N*-methylation and *N*-protonation[8]. Aside from experimental errors, part of the deviations from linearity can be ascribed to hydrogen bonding of methanol to the nitrogen atom. This reduces its nucleophilicity

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[7] Relatively small polar substituent were also observed in the *Menshutkin* reaction of 3- and 4-substituted pyridines [5].

[8] The correlation is certainly not excellent as stated by *Palecek & Hlavaty* [6] employing a smaller series of compounds. Furthermore, the correlation is not improved if the substituent constants σ^* and σ_I of *Taft* and *Charton* [1] [3], respectively, are used instead of σ_I^q.

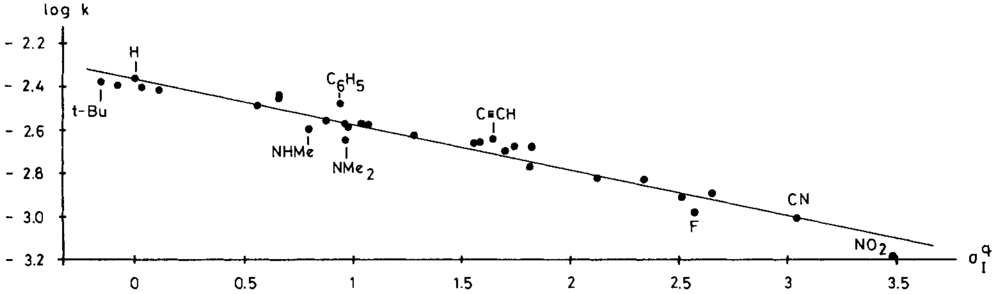

Fig. *Relationship between log* k *for the quaternization of 4-substituted quinuclidines with methyl iodide and their inductive substituent constants* σ_I^q

towards methyl iodide but not its basicity. Thus *t*-butylquinuclidine is a stronger base but a weaker nucleophile owing to stronger blocking of the nitrogen lone pair by hydrogen bonding. This is also borne out by the fact that quaternization rates are generally much higher in acetonitrile (*Table 2*), a solvent not forming hydrogen bonds.

Moreover, the rate ratios for methylation in acetonitrile and methanol, $k(CH_3CN)/k(CH_3OH)$ in *Table 2*, increase from 85 for the cyano (**1c**) to 385 for the *t*-butyl derivative (**1d**). The stronger the hydrogen bond to methanol the larger the rate difference compared to acetonitrile.

Hydrogen bonding alone, however, does not account satisfactorily for the observed deviations from the regression line (*e.g. ca.* 20% for **1e** ($R = C_6H_5$) in the plot (*Fig.*). Thus, the weaker bases, such as **1b**, **1i** and **1j** ($R = N(CH_3)_2$, F, and NO_2 respectively), which should form weaker hydrogen bonds, react more slowly than **1** with other substituents.

More likely, the main reason for these deviations is related to the basic assumptions inherent in many of the currently used linear free energy relationships. It is assumed that substituents affect equilibria and rates in the same way, *i.e.* that free reaction enthalpies are proportional to free activation enthalpies. The limited validity of this assumption is already apparent in the frequently observed poor

Table 2. *Rate constants for the reaction of* **1** with methyl iodide in acetonitrile at 10.00° (mean deviation 1%[a]))

R	k [l mol^{-1} s^{-1}]	k_{rel}	$k(CH_3CN)/k(CH_3OH)$
t-C_4H_9	1.61	1.10	385
H	1.47	1	335[b])
i-C_3H_7	1.42	0.97	350
CH_3CH_2	1.26	0.86	319
CH_3	1.10	0.75	286
CN	0.085	0.06	85[c])

[a]) Average of at least 5 measurements.
[b]) For *n*-propyl iodide this ratio is 343.
[c]) For *n*-propyl iodide this ratio is 103.

Table 3. *Rate constants* [l mol^{-1}*s*$^{-1}$] *for the reaction of alkyl and allyl halides* with **1**-*H* and **1**-*CN* in acetonitrile at 10.00° (mean deviation 1%)

electrophile	k(**1**-*H*)	k(**1**-*CN*)	ρ
CH_3I	1.47	8.51×10^{-2}	−0.41
$CH_2{=}CH{-}CH_2Br$	8.36×10^{-1}	5.06×10^{-2}	−0.40
$CH_2{=}CH{-}CH_2Cl$	4.22×10^{-3}	2.60×10^{-4}	−0.40
$CH_3CH_2CH_2I$	9.71×10^{-3}	5.20×10^{-4}	−0.42
$CH_3CH_2CH_2Br$	1.93×10^{-3}	9.98×10^{-5}	−0.42
$CH_3CH_2CH_2Cl$	1.39×10^{-5}	7.00×10^{-7}	−0.43

correspondence between basicity, a thermodynamic property, and nucleophilicity, a kinetic property [18].

The slope of the regression line (*Fig.*) leads to a reaction constant ρ of −0.21. This is approximately 20% of the ρ value for the standard reaction *(1)*, the dissociation of quinuclidinium perchlorates, the ρ value of which was arbitrarily set at 1. The diminished reaction constant for quaternization reflects its much smaller response to polar substituent effects.

Table 3 shows the rate constants for the reaction of various electrophiles with quinuclidine and its 4-cyano derivative in acetonitrile in decreasing order. As expected, allyl halides react 300 to 500 times faster than their saturated analogues. Also, rates decrease in the order I > Br > Cl for a given type of compound [18]. It is noteworthy, however, that quinuclidine reacts 16-19 times as fast as its 4-cyano derivative in acetonitrile. From these rate data and the substituent constant σ_I^q for the cyano group (3.04) the ρ values in column 4 were calculated. They vary from −0.40 for the most reactive compounds, allyl bromide and chloride, to −0.43 for the least reactive compound, *n*-propyl chloride. The trend of these ρ values shows that the nucleophile is more involved in the displacement of the halide atom in the less reactive compounds, the rate of which is consequently more affected by the cyano group. In contrast, the more reactive allyl halides are less affected, displacement being easier and the transition state looser.

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Experimental part

Rate measurements. - These were carried out with the free bases obtained from the corresponding quinuclidinium salts [1] as follows: the salt (*ca.* 100 mg) was dissolved in ice water (*ca.* 0.5 ml) in a 25 ml separatory funnel. K_2CO_3 was then added until a viscous paste was obtained which adhered to the side of the funnel. This was then repeatedly extracted with ether or pentane. After drying over Na_2SO_4 the combined extracts were slowly distilled through a *Vigreux* column, bath temperature <60° to avoid loss of the volatile bases. The latter were then purified by short-path distillation, employing a vacuum line where necessary. The base (*ca.* 0.01 mmol) was then dissolved in highly purified solvent, methanol or acetonitrile (8 ml), and placed in a conductivity cell (cell constant 1 cm^{-1}) thermostated at the desired temperature (±0.01°). Freshly distilled and thermostated alkyl or allyl halide (250-fold excess) was then added with a 0.5 ml mechanical micro burette (*Metrohm* E 457-0.5). The increase in conductivity was recorded and evaluated by the equation $\ln \lambda_\infty - \lambda_o/\lambda_\infty - \lambda_t = k't$ where k' is the pseudo first order rate constant and equals the second order constant k multiplied by the concentration of halide.

The best exponential function corresponding to the experimental curve was computed using a least square fit [19]. The rate constants listed in *Table 1* are the average of 5 to 10 runs[9]).

Characterization of the methiodides from **1**. The methanol solutions from the rate measurements were evaporated to dryness *in vacuo* and the crystalline methiodides taken up in D_2O. The NMR. spectra showed the characteristic singlet for the $\overset{+}{N}-CH_3$ group at 2.93 ppm for the methiodide from **1a**, which was shifted to somewhat lower field (*e.g.* 3.01 for the methiodides from **1f** and **1c** ($R = COOC_2H_5$ and CN respectively) when more electronegative substituents at C(4) were present. The *methiodide* of **1b** was recrystallized from methanol/ether. - NMR. ($(CH_3)_2SO$): 2.14 (*s*, 6H, $N(CH_3)_2$); 2.96 (*s*, 3H, $\overset{+}{N}-CH_3$).

$C_{10}H_{21}IN_2$ (296.19) Calc. C 40.36 H 7.43 N 9.68% Found C 40.55 H 7.15 N 9.46%

Methiodide of **1f**, from acetone m.p. 211-213°.

$C_{11}H_{20}INO_2$ (325.18) Calc. C 40.62 H 6.20 N 4.31% Found C 40.90 H 6.47 N 4.50%

Methiodide of **1g**, from methanol/ether, m.p. 269-270° (dec.)

$C_8H_{15}BrIN$ (332.02) Calc. C 28.93 H 4.55 N 4.21% Found C 28.90 H 4.65 N 4.23%

Methiodide of **1h**, from methanol/ether, m.p. > 300°.

$C_8H_{16}INO$ (269.12) Calc. C 35.70 H 5.99 N 5.20% Found C 35.63 H 6.09 N 5.27%

Methiodide of **1c**, from 2-propanol, m.p. > 300°.

$C_9H_{15}IN_2$ (278.13) Calc. C 38.86 H 5.43 N 10.07% Found C 38.62 H 5.44 N 9.99%

Combustion analyses by *Mr. E. Thommen;* NMR. spectra by *Mr. K. Aegerter.*

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[9]) For further details concerning rate measurements and computation see [20].