

6. A Reexamination of Inductive Substituent Constants Derived from pK_a Values of 4-Substituted Quinuclidines. Polar Effects. Part VIII

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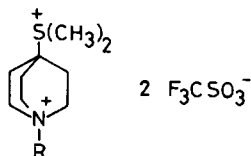
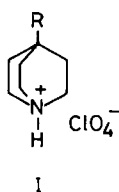
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Summary

pK_a Values of 42 quinuclidinium perchlorates I have been measured in 0.1 M aqueous KCl-solution. In a few cases small corrections of earlier thermodynamic pK_a values are indicated. These measurements, in conjunction with recent X-ray structure determinations, confirm the reliability of the inductive substituent constants σ_I^q derived from them.

The first paper in this series [1] described the derivation of inductive substituent constants (σ_I^q) from thermodynamic pK_a values of 42 quinuclidinium perchlorates I. These constants were defined by the pK_a difference between the standard unsubstituted salt 1 (Table 1) and the 4-substituted derivatives 2-42, i.e. by the equation $pK_a^H - pK_a^R = \rho \sigma_I^q$, the reaction constant ρ being taken as unity.



43 R = C₆H₅CH₂

44 R = H

However, some uncertainty remained concerning the accuracy of σ_I^q values and could have lessened their usefulness in the study of substituent effects in organic reactions¹⁾. Thus, it has been frequently questioned whether the distance between the N-atom and C(4) in I is constant regardless of the nature of R. If this were not the case pK_a values might well be influenced by effects of R other than their inductive effect²⁾.

¹⁾ See [2] and earlier papers in this series.

²⁾ E.g. steric effects, i.e. the bulk of the substituent could alter bond angles and hence the N-C(4) distance.

Table 1. pK_a -Values for 4-R-quinuclidinium perchlorates in water (pK_a^T) and with 0.1M KCl (pK_a^{KCl}) at 25° and derived inductive substituent constants σ_f

Nr.	R	pK_a^{KCl}	pK_a^T	$\sigma_f(KCl)$	$\sigma_f(T)$	$\Delta\sigma$
1	H	11.29	11.12	0	0	0
2	CH ₃	11.18	11.01	0.11	0.11	0
3	C ₂ H ₅	11.27	11.09	0.02	0.03	-0.01
4	<i>i</i> -C ₃ H ₇	11.39	11.20	-0.10	-0.08	-0.02
5	<i>t</i> -C ₄ H ₉	11.49	11.30 ^{a)}	-0.20	-0.18	-0.02
6	CH ₂ OH	10.67	10.46	0.62	0.66	-0.04
7	CH ₂ OCH ₃	10.57	10.44 ^{a)}	0.72	0.68	0.04
8	CH ₂ OCOCH ₃	10.39	10.24	0.90	0.88	0.02
9	CH ₂ OSO ₂ C ₆ H ₄ CH ₃	10.01	9.84	1.28	1.28	0
10	CH ₂ NH ₂	10.81	10.60	0.48	0.52	-0.04
11	CH ₂ Cl	10.27	10.10 ^{a)}	1.02	1.02	0
12	CH ₂ Br	10.22	10.05	1.07	1.07	0
13	CH ₂ I	10.19	10.07	1.10	1.05	0.05
14	CH(OH) ₂	10.07	9.89	1.22	1.23	-0.01
15	CH=CH ₂	10.67	10.51 ^{a)}	0.62	0.61	0.01
16	C(CH ₃)=CH ₂	10.70	10.52	0.59	0.60	-0.01
17	C≡CH	9.64	9.48	1.65	1.64	0.01
18	C ₆ H ₅	10.42	10.27 ^{a)}	0.87	0.85	0.02
19	COO ⁻	10.57	10.51	0.72	0.61	0.11
20	COOCH ₃	9.60	9.42	1.69	1.70	-0.01
21	COOC ₂ H ₅	9.59	9.42	1.70	1.70	0
22	COCH ₃	9.60	9.43	1.69	1.69	0
23	CONH ₂	9.47	9.30	1.82	1.82	0
24	CN	8.23	8.08	3.06	3.04	0.02
25	NH ₂	10.21	10.06 ^{a)}	1.08	1.06	0.02
26	CH ₃ NH	10.34	10.25 ^{a)}	0.95	0.87	0.08
27	(CH ₃) ₂ N	10.17	10.07 ^{a)}	1.12	1.05	0.07
28	(CH ₃) ₃ N ⁺	7.17	6.97	4.12	4.15	-0.03
29	NHCOCH ₃	9.63	9.47 ^{a)}	1.66	1.65	0.01
30	NHCOOC ₂ H ₅	9.70	9.56	1.59	1.56	0.03
31	NO ₂	7.75	7.60 ^{a)}	3.54	3.52	0.02
32	HO	9.53	9.38	1.76	1.74	0.02
33	CH ₃ O	9.40	9.26 ^{a)}	1.89	1.86	0.03
34	CH ₃ COO	9.13	9.00	2.16	2.12	0.04
35	CH ₃ S	9.60	9.46	1.69	1.66	0.03
36	CH ₃ SO ₂	7.94	7.86 ^{a)}	3.35	3.26	0.09
37	(CH ₃) ₂ S ⁺	6.83	6.62	4.46	4.50	-0.04
38	F	8.72	8.55	2.57	2.57	0
39	Cl	8.78	8.61	2.51	2.51	0
40	Br	8.60	8.47	2.69	2.65	-0.04
41	I	8.95	8.78	2.34	2.34	0
42	(CH ₃) ₃ Sn	11.52	11.38	-0.23	-0.26	0.03

a) Revised value.

Meanwhile, the crystal structures of 4-R-quinuclidinium chlorides (R=H, F, Cl and Br) and of R=(CH₃)₃Sn have been determined by *Nowacki et al.* [3] and *Zehnder* [4]. These studies have revealed changes in the N-C(4) distances of less than 0.05 Å as R is varied from the small and electron withdrawing F-atom to the

Table 2. N-C(4) distances in 4-R-quinuclidinium chlorides determined by X-ray crystallography

R	N-C(4) distances [Å]	Lit.
H	2.534	[3]
F	2.502	[3]
Cl	2.501	[3]
Br	2.506	[3]
(CH ₃) ₃ Sn	2.550	[4]

bulky and electronreleasing trimethyltin group (Table 2). It is therefore unlikely that a geometrical factor is superposed on the polar effect of R.

A further error is possibly introduced by the potentiometric titration method employed in the determination of thermodynamic pK_a values [1]. At low salt concentrations the glass electrode reacted sluggishly to changes in pH. Furthermore, the latter value tended to drift markedly with time, thus rendering the final reading somewhat arbitrary.

These defects can be avoided by measuring at a higher electrolyte concentration³⁾ which, at the same time, causes a shift of the pK_a to higher values. Since only the differences $pK_a^H - pK_a^R$ are relevant these shifts should not affect the magnitude of σ_f^q .

In the present study pK_a values for the 42 quinuclidinium perchlorates listed in Table 1 were measured in 0.1 M aqueous KCl at 25.0°, the results being far more reliable and reproducible under these conditions. Improvements in the syntheses of some of the quinuclidines I are described in the experimental part.

Discussion. - Table 1 shows that the pK_a^{KCl} values measured in 0.1 M aqueous KCl-solution (column 3) are mostly 0.1-0.2 units higher than those measured in water (pK_a^T , column 4)⁴⁾. The protonated form of the quinuclidines is thus favored at higher ionic strength. Notable exceptions are the pK_a^{KCl} values of **19**, **26**, **27** and **36** with R = COO⁻, CH₃NH, (CH₃)₂N and CH₃SO₂, respectively, which increase by only 0.06-0.1 units. These groups contain basic centers and would be expected to form hydrogen bonds with water. This ability is particularly pronounced when R = COO⁻ ($\Delta pK_a = 0.06$) and is apparently reduced in the presence of KCl in favor of shielding by K⁺-ions. It is noteworthy that the positively charged substituents (CH₃)₃N⁺ and (CH₃)₂S⁺, which do not form hydrogen bonds, show about the same ΔpK_a (0.20 and 0.21, respectively) as the neutral and dipolar groups.

These findings are reflected in the derived inductive substituent constants σ_f^q (KCl) and σ_f^q (T) (Table 1, columns 5 and 6), respectively. Except in the case of the four compounds mentioned above these constants are practically identical within the limits of error, i.e. a standard deviation of $\pm 0.02 pK_a$ units. Therefore, either set of σ_f^q values can be used, except for R = COO⁻, CH₃NH, (CH₃)₂N and CH₃SO₂, when one or the other value is indicated depending on the reaction conditions⁵⁾.

3) The procedure is described in [5] and in the experimental part.

4) Control measurements indicated that in 0.2 M aqueous KCl pK_a^{KCl} increased further.

5) As pointed out by Professor R. W. Taft (personal communication) the reaction type studied should also be considered.

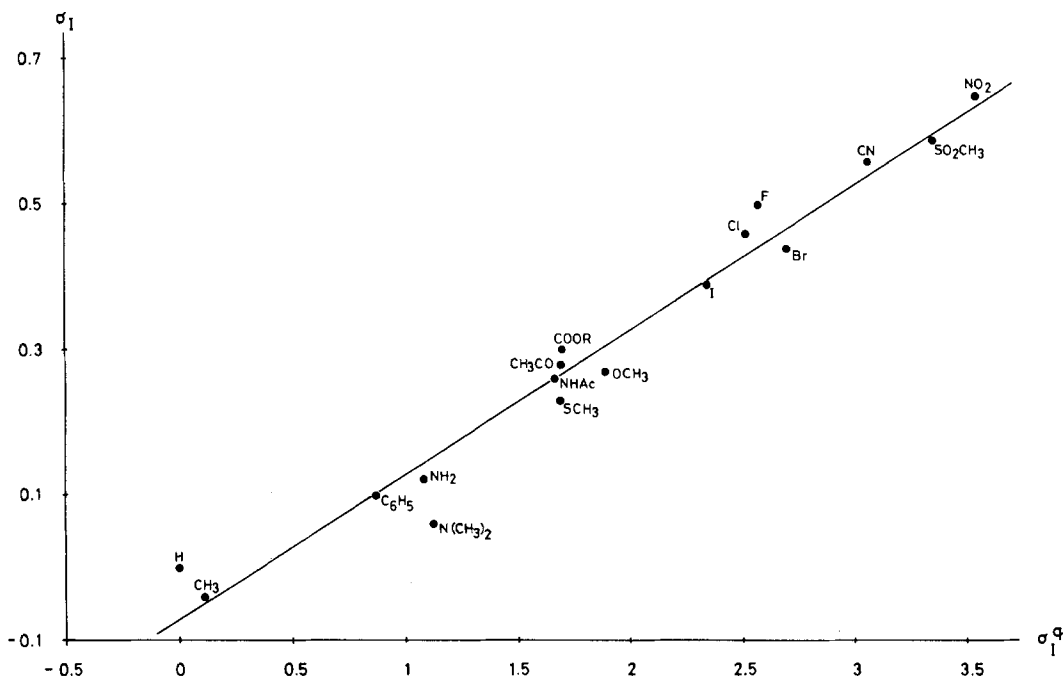


Fig. 1. Plot of $\sigma_I^q(KCl)$ against Taft's σ_I values [8].

It is interesting to compare these revised σ_I^q constants with inductive constants σ_I derived by other experimental methods, especially those of *Taft* [6] and *Charton* [7] which are based on acid- and base-catalyzed hydrolysis of substituted acetates [6] and on the pK_a values of substituted acetic acids [7], respectively. In fact the alleged shortcomings of these methods⁶⁾ were the cause of the present studies.

When $\sigma_I^q(KCl)$ values are plotted against *Taft's* σ_I values [8] some scattering of points around the regression line is observed (*Fig. 1*). When the point for $R = COO^-$, which is most sensitive to salt concentration, is omitted the fit can be regarded as fairly good (correlation coefficient $r = 0.9831$ (slope 0.200))⁷⁾. A better correlation is obtained with *Charton's* σ_I values [7] (*Fig. 2*) with $r = 0.9898$ (slope 0.192) and also with the recent values of *Fischer et al.* [9b] derived from the pK_a of α -substituted 3-methylpyridinium salts ($r = 0.9913$). It is probably inevitable that inductive substituent constants will vary somewhat with the nature of the model and the reaction employed in their determination.

We thank Dr. *H. G. Seiler* for his valuable assistance with the pK_a measurements. Our thanks are also due to Prof. *T. Kaden* and Prof. *A. Zuberbühler* for their assistance with the computations.

⁶⁾ For references see [1].

⁷⁾ Any such assessment is necessarily a matter of discretion. Thus, *Fischer et al.* [9a] recently stated that the correlation of σ_I^q and the σ_I values of *Taft* is excellent and concluded that the introduction of the former set of constants was unnecessary and undesirable. In our opinion σ_I^q values provide a more straightforward gauge of the inductive effect in saturated molecules since they do not involve ester and carboxyl groups as reaction sites.

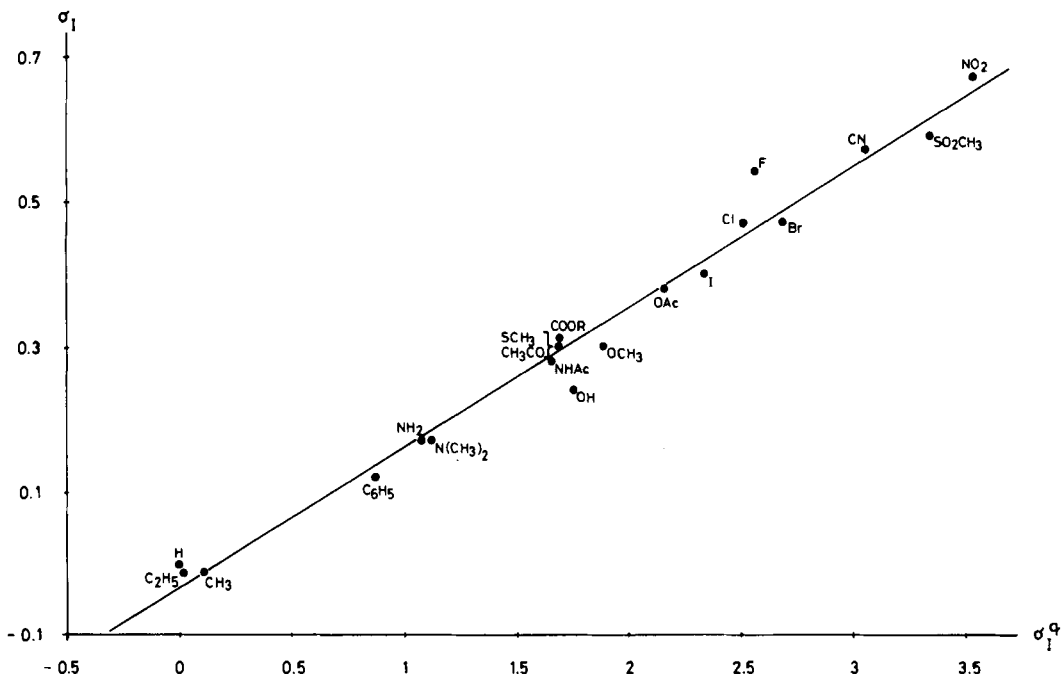


Fig. 2. Plot of $\sigma^{\phi}(\text{KCl})$ against Charton's σ_1 values [7].

Experimental Part

pK_a Measurements. Quinuclidinium perchlorate (15 to 30 mg) was dissolved in 20 ml of twice distilled water or in 0.1M aqueous KCl contained in the titration cell, which was held constantly at 25.00° with the aid of a thermostated water jacket. The titrand, 0.125N NaOH, was introduced in 20 μ l portions with a digital burette (*Metrohm*), the point of which was submerged in the solution through which argon was bubbled. The pH was registered with a Potentiograph E536 (*Metrohm*) connected to the combined glass electrode type EA121 (*Metrohm*). The apparatus was repeatedly calibrated with *Bureau of Standards* buffers in the pH range 6–10 at 25.0°. pK_a -Values were computed according to published procedures [10].

Syntheses. - 4-Methylthioquinuclidinium perchlorate (35). The following procedure gave more reproducible yields than the one previously published [11]: *p*-toluenesulfonyl chloride (3.8 g, 20.1 mmol) was added in small portions with stirring to a mixture of 1-benzyl-4-(2-hydroxyethyl)-4-methylthio-piperidine hydrochloride (5.5 g, 18.2 mmol) [11] and 10 ml of ice-cooled pyridine. After stirring for 2 days at 3° 1 ml of water was added to the light red suspension. After standing for 1 h at 20° the solvent was evaporated to dryness at 35° *in vacuo*. The viscous residue was taken up in 100 ml of ice-cold 2N aqueous Na_2CO_3 and the mixture repeatedly extracted with ether/benzene. The combined extracts were dried (K_2CO_3) and heated until the ether had distilled. Upon refluxing the benzene solution for 2 h crystallization of 1-benzyl-4-methylthioquinuclidinium *p*-toluenesulfonate began and was completed by addition of dry ether; yield 4.5 g (59%). From 2-propanol platelets m.p. 212–214°. - NMR. (D_2O): 1.85–2.26 (*m*, 6 H); 2.04 (*s*, 3 H, SCH_3); 2.36 (*s*, 3 H, CH_3 -aryl); 3.27–3.68 (*m*, 6 H); 4.32 (*s*, 2 H, $\text{C}_6\text{H}_5\text{CH}_2\text{N}$); 7.16–7.80 (*m*, 9 H, ar.).

$\text{C}_{22}\text{H}_{29}\text{NO}_3\text{S}_2$ (419.61) Calc. C 62.99 H 6.97 N 3.34% Found C 62.89 H 7.12 N 3.20%

The compound was converted to 4-methylthioquinuclidinium perchlorate (35) as described [11]; m.p. 155–156° ([11] 156–157°).

(1-Benzylquinuclidinyl-4)-dimethylsulfonium bis-trifluoromethylsulfonate (43). A mixture of 1-benzyl-4-methylthioquinuclidinium *p*-toluenesulfonate (600 mg, 1.44 mmol) and methyl trifluoromethyl-

sulfonate (4.0 ml *ca.* 45 mmol) was shaken for 5 h. After removal of the excess solvent *in vacuo* the residue was dissolved in 5 ml of water and extracted with ether. The aqueous solution was evaporated to dryness *in vacuo* and the crystalline residue debenzylated without further purification.

(*Quinuclidinyl-4*)-dimethylsulfonium bis-trifluoromethylsulfonate (**44**). A solution of **43** (760 mg, 1.3 mmol) in 15 ml methanol was hydrogenated over 0.20 g of 10% Pd/C. After addition of a further amount of catalyst (0.15 g) the theoretical amount of H₂ was taken up. Filtration through *Hyflo* and evaporation *in vacuo* yielded 520 mg of a crystalline residue. From 2-propanol/pentane 450 mg of hygroscopic needles, m.p. 222–225°. - NMR. ((CD₃)₂SO): 2.07–2.48 (*m*, 6 H); 2.90 (*s*, 6 H, +S(CH₃)₂); 3.25–3.68 (*m*, 6 H).

C₁₁H₁₉F₆NO₆S₃ (471.47) Calc. C 28.02 H 4.06 N 2.97% Found C 28.19 H 4.25 N 2.96%

Quinuclidine-4-carbaldehyde (**14**) from **6**. The following procedure gave more reproducible results than the previously one [12]. Silver carbonate supported on Celite was prepared as described [13] and dried for 4–6 h at 11 Torr at 35° with exclusion of light⁸). To a solution of 4-hydroxymethylquinuclidine (**6**) (4.1 g, 29.0 mmol) [12] in 850 ml of boiling toluene 190 g of freshly prepared Ag₂CO₃ on *Celite* (containing 1.75 mmol Ag₂CO₃ per gram of reagent) were added in small portions over a period of 5 h with constant stirring. The dark suspension was refluxed for a further 4 h and then filtered under N₂. The solvent was then removed at 50–60° at 60 Torr using a 30 cm *Vigreux* column. The residue was distilled and yielded 3.8 g (85%) of aldehyde, b.p. 61–63°/12 Torr, containing *ca.* 10% toluene. - IR. (CHCl₃): 2820, 2720, 1720 (CHO). - NMR. (CCl₄): 1.35–1.73 (*m*, 6 H); 2.55–2.95 (*m*, 6 H); 9.03 (*s*, 1 H, CHO). When exposed to air the aldehyde takes up water to form the hydrate.

14-Hydrop perchlorate. When water (0.5 ml) was added to the aldehyde **14** (460 mg, 330 mmol) the crystalline hydrate was formed with evolution of heat; m.p. 60–62°. To a solution of the hydrate in 10 ml of water 70% perchloric acid (465 mg, 3.24 mmol) was slowly added with cooling. The solution was concentrated *in vacuo* until 710 mg (83%) of the hydrop perchlorate crystallized; needles m.p. 293–296° (dec.) ([12] m.p. 293–295°). Drying at 60°/0.03 Torr yields the hydrop perchlorate of 4-quinuclidine carbaldehyde.

C₈H₁₄ClNO₅ (239.67) Calc. C 40.08 H 5.89 N 5.84% Found C 39.99 H 5.87 N 5.78%

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⁸) Drying for longer periods of time and at temperatures exceeding 40° lead to a less active oxidant and to lower yields of **14**.