ISOTOPIC EXCHANGE IN HETEROCYCLIC QUATERNARY SALTS. II. (1) HYDROGEN-DEUTERIUM EXCHANGE IN ACTIVE C-METHYL GROUPS.

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SUMMARY

The non-catalysed H-D exchange in heterocyclic quaternary ammonium salts (1-3) was studied by ^{1}H-nmr. Exchange occurs only at the C-CH_3 group, at a rate decreasing in the order X = $C(CH_3)_2$, Se, CH=CH, S, NCH_3. In substituted benzothiazolium salts the exchange rates decrease in the series Y = NO_2, Cl, H, OCH_3. Chemical shifts (δ) of C-CH_3 and N-CH_3 groups decrease in the same sequence. Both exchange rate constants and chemical shifts can be related to Hammett σ_p values of the Y substituents. The mechanism of the exchange reaction is briefly discussed.

Keywords: ^{1}H-nmr chemical shifts, benzothiazolium, benzoselenazolium, benzimidazolium, quinolinium and pyridinium salts.

INTRODUCTION

The isotopic exchange of active methyl hydrogens was intensely investigated. A review of the literature up to 1970 was compiled by one of us (2). Hydrogen-deuterium exchange in heterocyclic compounds was extensively studied (3-5) and recently reviewed by Zatsepina and Tupitsyn (3). Methyl substituents in alpha position relatively to a nitrogen heteroatom in neutral compounds

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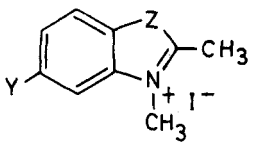
exchange their hydrogens very slowly in non-catalytic conditions. It was found, however, that the corresponding quaternary ammonium salts exchange significantly faster than the free bases (3,6). According to our knowledge no systematic study of the exchange rates in quaternary heterocyclic ammonium salts was published. In a previous paper (1), results on H-D exchange in 2,3-dimethyl-benzothiazolium iodide (1Ac) were reported, isotopic compositions being determined by a destructive method. In the present work, H-D exchange rates were determined for a series of heterocyclic quaternary ammonium salts (1-3), using ^{1}H-nmr measurements.



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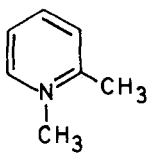

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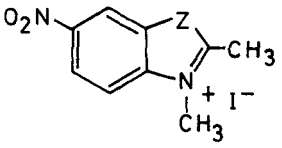

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1Aa; Y = H; Z = $C(CH_3)_2$;
1Ab; Y = H; Z = Se;
1Ac; Y = H; Z = S;
1Ad; Y = H; Z = NCH_3;

1Ae; Y = H; Z = -CH=CH-;
1Bc; Y = NO_2; Z = S;
1Cc; Y = Cl; Z = S;
1Dc; Y = OCH_3; Z = S;

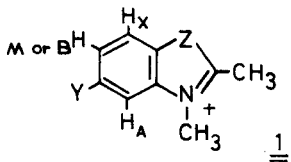
3c; Z = S;
3d; Z = NCH_3;

EXPERIMENTAL PART

Compounds (1-3) were synthetized using well-known methods. N-Methylation was performed with dimethyl sulphate, followed by metathesis, or directly with methyl iodide.

^{1}H-Nmr chemical shifts were measured in D_2O solution with sodium 4,4-dimethyl-4-silapentane sulphonate as internal reference, using a Bruker WP-60 FT-nmr instrument operating at 60 MHz. Results are given in Table I; as it may be seen, all compounds could be fully characterized. Chemical shifts are accurate within ±0.01 ppm and coupling constants within ±0.1 Hz. The parameters calculated for the ABX multiplet of the benzenic protons in compound 1Dc afforded a simulated spectrum with all transitions within ±0.1 Hz

Table I. ^{1}H-Nmr chemical shifts (δ, ppm) and coupling constants (J, Hz) of heterocyclic ammonium iodides.



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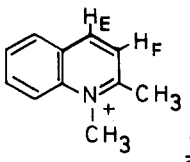
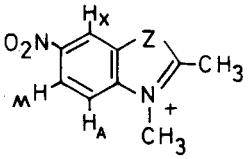


1Ae



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Compound	C-CH_3 δ	N-CH_3 δ	Aromatic protons δ	J
1Aa*	2.76	4.00	7.60 - 7.70 (m)	
1Ab	3.16	4.18	7.50 - 8.30 (m)	
1Ac	3.17	4.23	7.50 - 8.30 (m)	
1Ad	2.86	3.96	7.40 - 7.90 (m)	
1Ae	3.10	4.47	(E) 8.87; (F) 7.91	(EF) 8.5
			7.70 - 8.50 (m)	
1Bc	3.21	4.31	(A) 9.09	(AM) 1.9
			(M) 8.65	(AX) 0.7
			(X) 8.41	(MX) 9.0
1Cc	3.16	4.20	(A) 8.24	(AM) 1.8
			(M) 7.79	(AX) 0.5
			(X) 8.17	(MX) 8.7
1Dc**	3.10	4.17	(A) 7.55	(AB) 2.2
			(B) 7.41	(AX) 0.7
			(X) 8.04	(BX) 8.9
2	2.78	4.22	7.50 - 8.80 (m)	
3c	3.23	4.34	(A) 8.32	(AM) 9.3
			(M) 8.73	(AX) 0.5
			(X) 9.15	(MX) 2.2
3d	2.96	4.073	(A) 8.01	(AM) 9.0
		4.100	(M) 8.54	(AX) 0.5
			(X) 8.85	(MX) 2.1

(m) unassigned multiplet; * Z = $C(CH_3)_2$ at δ = 1.54 ppm;

** Y = OCH_3 at δ = 4.00 ppm;

from those of the experimental spectrum. Hydrogen-deuterium exchange rates were measured in 0.015-0.030 **M** solutions in D_2O, directly in the nmr tube. The pH-dependance of the exchange rates was not investigated; pH-values between 5.5-6.0 were measured both in the stock D_2O and in the sample solutions. Samples were kept in an ultrathermostat and periodically transferred into the spectrometer for measurement; zero-time exchange was measured for all samples immediately after dissolution. No exchange was noticed for the N-CH_3 group in any of the compounds and at any exchange time; therefore integrated signal intensities were taken for both N-CH_3 and C-CH_3 groups, the former being used as reference.

Exchange measurements for compounds 1Aa-1Ae, 2 and 3d were performed on a Varian A 60 A instrument. Results are shown in Table II. At least three scans of the spectrum integral were recorded for each data point. Exchange in compounds 1Ac-1Dc and compound 3c was measured on a Bruker WP-60 FT-nmr instrument, recording one spectrum integral per data point, as spectrum integration on this type of instrument involves only computation. Results are included in Table III. There is a systematic difference between mean k_1 values obtained for compound 1Ac on the two instruments; the respective activation energy, frequency factor and activation entropy values are however in fair agreement.

Exchange experiments were attempted on the similar benzoxazolium derivative (1, Z = O; Y = H). Although deuteration definitely takes place, no accurate results could be obtained owing to rapid decomposition of the sample.

In some preliminary experiments CD_3OD was used as exchange partner. Exchange proceeds at a somewhat lower rate than in D_2O.

RESULTS AND DISCUSSION

The general equation of isotopic exchange between a methyl group and D_2O being

$$2\ R\text{-}CH_3 + 3\ D_2O \rightleftharpoons 2\ R\text{-}CD_3 + 3\ H_2O\ ,$$

Table II. Isotopic exchange parameters for heterocyclic ammonium salts.

Compound	Temp. (°C)	$k_1.10^4$ (sec^{-1})	MSD	E (kcal/mol)	lg A	$\Delta S^{\neq 353°K}$ (cal/mol.°K)
	14	5.14				
1Aa	24	10.82	0.40	12.6 ± 0.3	6.3 ± 0.8	
	34	28.33				
	80	321.30*				-31.9
	70	2.01				
1Ab	80	5.44	0.08	23.9 ± 0.2	11.6 ± 0.5	-7.9
	90	13.93				
	70	1.66				
1Ac	80	3.94	0.12	20.8 ± 0.2	9.5 ± 0.7	-17.3
	90	8.93				
	70	1.91				
1Ae	80	5.20	0.13	24.3 ± 0.3	11.8 ± 0.7	-6.9
	90	13.60				
	70	0.63				
2	80	1.43	0.16	19.7 ± 0.3	8.4 ± 0.8	-22.5
	90	3.11				

* extrapolated;

Table III. Isotopic exchange parameters for 2,3-dimethyl-benzothiazolium iodides.

Compound	Temp. (°C)	$k_1 \cdot 10^4$ (sec^{-1})	MSD	E (kcal/mol)	lg A	$\Delta S^{\neq 353}$ °K (cal/mol.°K)
	70	0.78				
1Ac	80	1.88	0.27	21.1 ± 0.4	9.4 ± 1.0	-17.9
	90	4.31				
	70	34.40				
1Bc	80	71.60	0.16	17.6 ± 0.3	8.8 ± 0.9	-20.6
	90	143.10				
	70	2.94				
1Cc	80	9.17	0.24	27.3 ± 0.3	13.9 ± 0.9	2.7
	90	26.80				
	70	0.30				
1Dc	80	0.92	0.27	27.2 ± 0.3	12.8 ± 0.9	-2.1
	90	2.66				
	70	68.20				
3c	80	118.25	0.13	13.2 ± 0.5	6.3 ± 1.3	-32.1
	90	198.82				

the corresponding McKay relation can be written as:

$$r = -\frac{2.303}{t} \cdot \frac{3a \cdot 2b}{3a + 2b} \cdot \lg \frac{1 - f}{1 - f_o} \quad ,$$

where: a is the total concentration of the compound bearing the exchanging methyl group, in our case the quaternary ammonium iodide; b is the total concentration of water; f is the fraction of exchange, defined as $f = n/n_\infty$, n being the procentual D-content of the exchanging methyl group at a given exchange time t and n_∞ the equilibrum value ($t = \infty$).

Owing to the very low molar concentrations of the quaternary ammonium iodides used, we have b>>a. Thus the McKay relation may be approximated as

$$r = -\frac{2.303}{t} \cdot 3a \cdot \lg \frac{1 - f}{1 - f_o} \qquad \text{(eq. 1)}$$

and the exchange reaction will obey a pseudomonomolecular kinetics, as expressed by equation 2:

$$r = k_1 \cdot a \cdot \qquad \text{(eq. 2)}$$

Accordingly, equations 1 and 2 were used for evaluation of the exchange data.

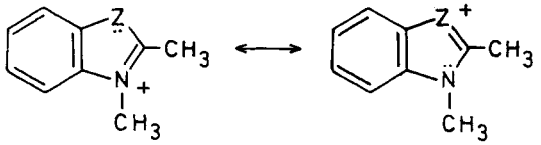
Rate constant values (k_1) were determined for each temperature on at least three duplicate samples, a minimum of five different exchange times being measured for each sample. These individual k_1 values were used in the Arrhenius relation

$$k_1 = A \cdot \exp(-E/RT),$$

to compute the activation energy (E) and frequency factor (A) values, averaged by the least squares procedure, which are included in Tables II and III. The k_1 values from Tables II and III are calculated using these averaged E and A values in the Arrhenius relation. Mean square deviation (MSD) values were computed and are given for each compound. Activation entropies were calculated by the following equation: $\Delta S^{\neq} = 4.576 \cdot \lg(A/T) - 49.206$.

According to the magnitude of the exchange rate constants (k_1) the compounds investigated (Y = H) may be roughly divided into three categories (Z-groups are given): $C(CH_3)_2 >$ S,Se,CH=CH>> NCH_3. This sequence exhibits a striking parallelism with the increase of delocalization in the rings bearing the exchanging methyl group. Thus compound 1Aa is the only one where no aromatic delocalization in the five-membered ring is possible, as the $C(CH_3)_2$ group is unable to contribute any orbital to the π-electronic system. Aromatic delocalization is possible in the five-membered rings of compounds 1Ab and 1Ac; the two possible canoni-

cal structures (4 and 5) are however energetically non-equivalent, a fact which according to the valence-bond theory implies low values of the delocalization energy.



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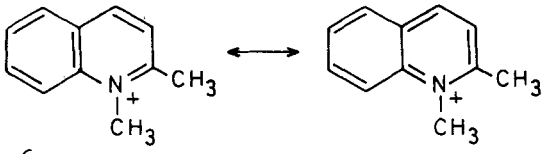
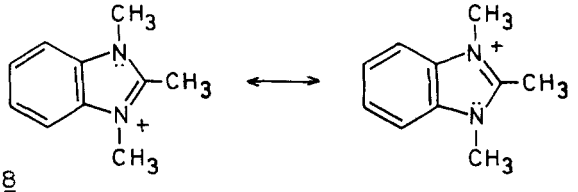
Similarly, compound 1Ae presents two energetically non-equivalent canonical structures 6 and 7, the latter having an orto-quinoid pattern of double bonds.



6 7

Compound 2, where the energetic difference between the two benzenoid canonical structures should be less important, exhibits a slower exchange than any of the compounds mentioned above. The exchange rate difference found between compounds 1Ae and 2 is not surprising as it is known (2) that a condensed benzenoid ring will generally enhance the exchange rates of the active methyl groups bound to heterocycles.

Finally, no exchange was detected in the benzimidazolium compounds 1Ad and 3d. These posess a symmetric π-electronic distribution in the five-membered ring, having two identical canonical structures 8 and 9, corresponding to high values of the delocalization energy, according to the terms of the valence bond theory.



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Even introduction of a nitro-group as in 3d does not result in measurable exchange rates, although this substituent greatly en-

hances the mobility of methyl hydrogens in 2,3-dimethylbenzothiazolium iodide, as it results from comparison of k_1 values for compound 1Ac with those for 1Bc and especially 3c.

Clearly, measured exchange rates depend on the energy content of the ground state of the exchanging molecule: the higher its delocalization energy, the larger will be the activation barrier necessary to reach the intermediate 10 of the exchange process.

For the series of the 2,3-dimethylbenzothiazolium iodides (Z = S), 1Ac-1Dc, the logarithms of the measured rate constants could be linearly related to the corresponding Hammett σ_p constants of the Y substituents, as shown in Fig. 1. From the slope of the linear plots in Fig. 1, a value $\rho = +1.96$ was obtained. Further, the measured rate constants k_1, are proportional to the chemical shifts of both N-CH_3 and C-CH_3 groups in the benzothiazolium compounds 1Ac-1Dc and 3c. The linear dependance between the Ham-

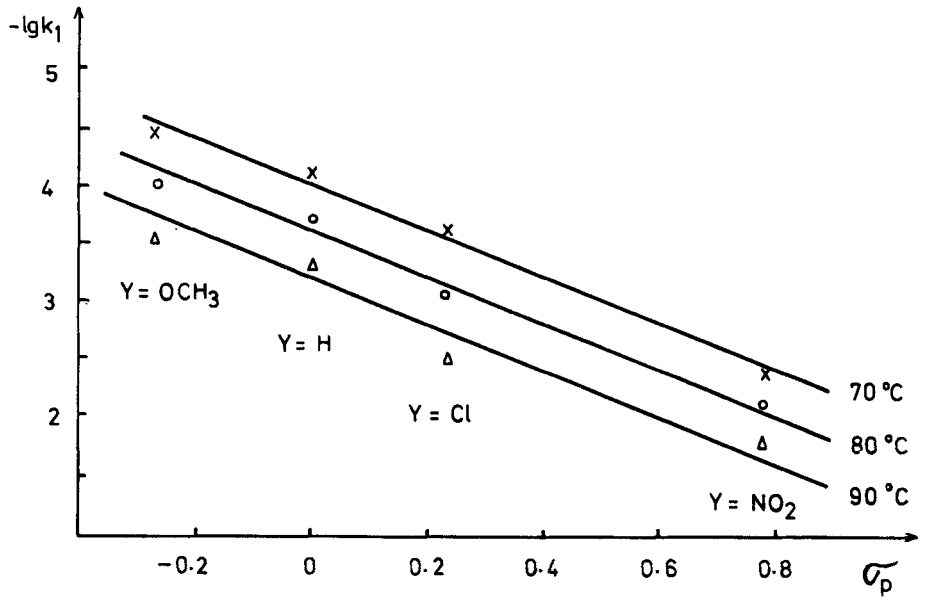


Fig. 1. Exchange rate constants k_1 vs. Hammett σ_p constants of the Y substituents.

mett σ_p constants of the Y substituents and the chemical shift of the exchanging C-CH_3 group is shown in Fig. 2. The chemical shifts being inversely proportional to the electron densities, we may conclude that the measured exchange rates are inversely proportional with the electron densities at the exchanging methyl group. Similar conclusions were drawn by other investigators (3). The existence of a linear relationship between the measured rate constants and the Hammett σ_p parameters of the Y substituents also proves that the exchange rate depends on the electron density at the reaction center and that these densities are determined by mesomeric electronic effects of the Y substituents. The positive ϱ value indicates that the electron density at the reaction center is greater in the transition state than in the initial reactant, a finding consistent with a proton donation as the rate-determining step for the exchange process.

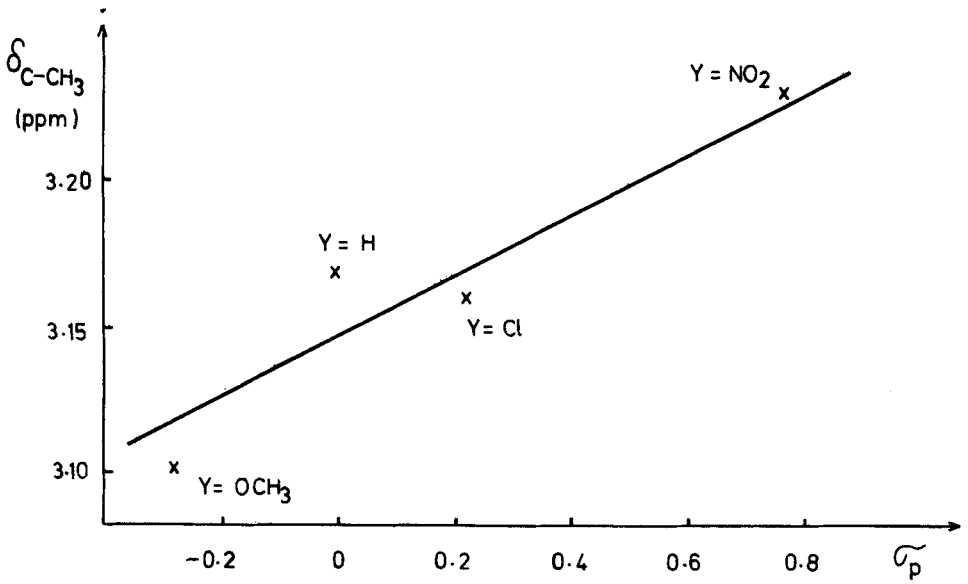
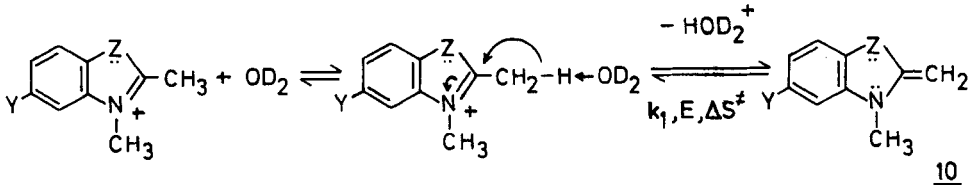


Fig. 2. Hammett σ_p constants of the Y substituents vs. ^{1}H-chemical shifts (δ) of the exchanging C-CH_3 group in benzothiazolium compounds, 1Ac-1Dc.

Thus our data mentioned so far support an exchange mechanism as outlined below, the formation of the methylene base 10 with a non-aromatic five-membered ring being the rate-determining step. Analogous exchange mechanisms were advocated for related active methyl-bearing cations such as pyrylium (2,7-9) and pyridinium (9,10) salts.



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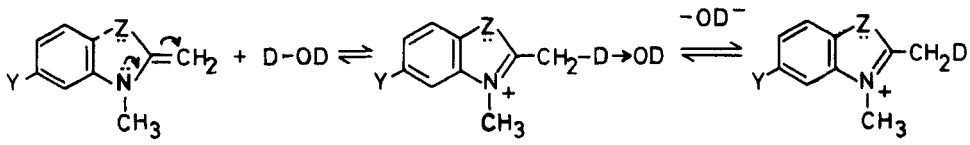
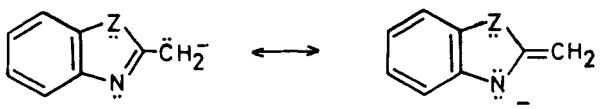


Activation entropy values ($\Delta S^{\neq}$) calculated from our kinetic data, although largely different from compound to compound, are throughout negative, with one notable exception (1Cc). Similar activation entropy values can be calculated from literature data (3) on the corresponding neutral non-quaternized heterocycles as well as for some alkylpyrylium (8,9) and alkylpyridinium (9,10) salts. Our tentative interpretation of these negative activation entropy values is that they are at least in part due to the hindered free rotation of the methylenic reaction center both in the neutral transition state 10 involved in the exchange of cationic compounds, as well in the anionic transition state 11↔12 involved (3) in the exchange of the neutral heterocycles.



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The important variations of the activation entropy measured for compounds of apparently similar structure reveal the in-

fluence of some unidentified factors on this kinetic parameter.

ACKNOWLEDGEMENTS

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