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ACIDITY OF CYCLOPROPANES WITH ELECTRON-WITHDRAWING SUBSTITUENTS

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Summary—The hydrogen isotope exchange rates of α-deuterio- and α-tritiocyclopropanes with electron-withdrawing substituents and the corresponding open 2-substituted propanes have been measured in solutions of sodium methoxide in methanol.

Substituents fall in two classes: CF_3, CN and ϕSO_2 make the α-hydrogen in cyclopropanes *more* acidic than in the open chain analogues. On the other hand acyl groups (t-C_4H_9CO, iso-C_3H_7CO, C_6H_5CO) make the cyclopropanes *less* acidic than the corresponding 2-substituted propanes. An explanation based on inductive and mesomeric stabilisation of carbanions is given.

A large isotope effect has been found for bulky isopropyl t-butyl ketone, suggesting rate limiting hydrogen abstraction by base. In most other cases (Table 2) isotope effects are small, presumably because anions remain strongly associated with methanol by hydrogen bonding (e.g. $R^- \ldots DOCH_3$) and consequently solvent exchange (with MeOH) becomes rate limiting for D/H (T/H) exchange.

INTRODUCTION

IN RECENT YEARS the acidity of the α-proton in cyclopropanes with electron-withdrawing substituents and the corresponding open chain isopropyl compounds has received much attention.[1-6] In order to evaluate such acidities more quantitatively, we have measured kinetic acidities by hydrogen isotope exchange in a solution of
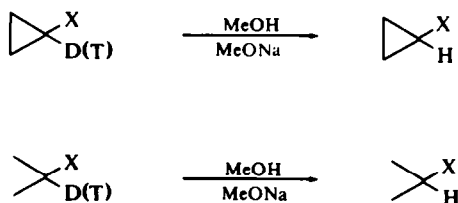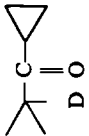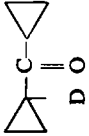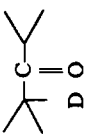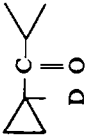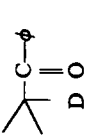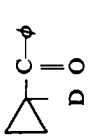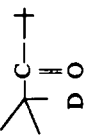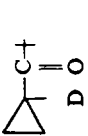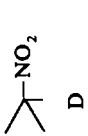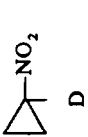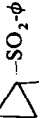
sodium methoxide in methanol. As mentioned previously[7,8] we performed most of the exchange reactions with α-deuterated and α-tritiated compounds in methanol (OH).

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TABLE 1. RELATIVE RATE CONSTANTS FOR THE EXCHANGE REACTION OF RD IN MeONa/MeOH AT 53.2°

Isopropyl		$k_{D\,rel.}$	note	cyclopropyl		$k_{D\,rel.}$	note	k_{iso}/k_{cyclo}
	IIa	1330 ± 100	b		I	1	a, e	1330 ± 100
	III	1550 ± 100	a, b, g		IIb	1.8 ± 0.2	b	850 ± 100
	V	4000 ± 400	b		IV	24 ± 2	b	170 ± 20
	VII	4.4 ± 0.3	c		VI	0.42 ± 0.65	c	10 ± 2
	IX	—	d		VIII	5500 ± 500	b	—

	Compound			Compound	
XI	$>$-CN, D	0.81 ± 0.06 [c]	X	$\triangleright$-CN, D	11.8 ± 0.7 [c]	0.067 ± 0.006
XIII	$>$-CF$_3$, H	$10^{-6} - 10^{-7}$ [e]	XII	$\triangleright$-CF$_3$, H	$(2.0 \pm 0.5)10^{-4}$ [e]	$5 \cdot 10^{-3} - 5 \cdot 10^{-4}$
XV	$>$-SO$_2$-ϕ, H	1.63 ± 0.05 [f]	XIV	$\triangleright$-SO$_2$-ϕ, H	55.0 ± 1.5 [f]	0.029 ± 0.001

[a] corrected for statistical factors.
[b] at [MeONa] = 0·05 M.
[c] at $H_{\infty-} = 17.75^7$.
[d] see text.
[e] $k_{H \, rel}$ for the exchange of 30% of RH in MeOD/MeONa (3·2 M) at 100°.
[f] $k_{H \, rel}$ for the exchange of 30% of RH in MeOD/MeONa (0·22 M) at 53·2°.
[g] the ratio of the exchange rate of α,α-dideuterio- and mono-α-deuterio-dicyclopropyl ketone and that of di- and mono-α-deuterated diisopropyl ketone are found to be 2·0 ± 0·1 and 2·01 ± 0·05 respectively.
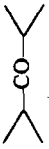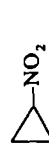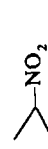
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TABLE 4. ISOTOPE EFFECTS AND ACTIVATION PARAMETERS ($\Delta H^\ddagger$ AND $\Delta S^\ddagger$) FOR THE ISOTOPIC EXCHANGE REACTION OF RD AND RT IN MeOH/MeONa AT 53·2°

compound	k_D/k_T	k_H/k_D^c	$\Delta H_D^\ddagger$ kcal/mol	$\Delta H_T^\ddagger$ kcal/mol	$\Delta S_D^\ddagger$ e.u.	$\Delta S_T^\ddagger$ e.u.
I (cyclopropyl–CO–)	1·6 ±0·1	2·9 ±0·5	20·2 ±0·8	22·0 ±1·5	−25 ±1	−20 ±2
III (isopropyl–CO–)	2·0 ±0·1	4·8 ±0·6	16·7 ±0·4	18·8 ±0·6	−22 ±2	−17 ±2
IV (cyclopropyl–CO–φ)	1·8 ±0·2	3·8 ±1·0	—	—	—	—
V (isopropyl–CO–φ)	2·0 ±0·2	4·8 ±1·1	—	—	—	—
VI (cyclopropyl–CO–)	1·70 ±0·05	3·4 ±0·3	22·2 ±0·2	22·8 ±0·6	—	—
VII (isopropyl–CO–)	2·34 ±0·05	6·8 ±0·3	22·5 ±0·5	22 ±1	−15 ±1	−18 ±3
VIII (cyclopropyl–NO₂)	1·5 ±0·1	2·5 ±0·4	21·7 ±0·6	22·7 ±0·6	−3·0 ±1·5	−1·0 ±1·5
IX (isopropyl–NO₂)	2·3 ±0·1ᵃ	7·0 ±0·5	15 ±1	—	−10 ±4	—
X (cyclopropyl–CN)	1·35 ±0·05	2·0 ±0·2	27·2 ±0·8ᵇ	—	+2 ±2ᶜ	—
XI (isopropyl–CN)	1·13 ±0·05	1·3 ±0·1	—	29ᵈ	—	+1ᵈ

ᵃ isotope effect of the hydrogen abstraction step only.
ᵇ $\Delta H_H^\ddagger$ (ref. 7)'
ᶜ $\Delta S_H^\ddagger$ (ref. 7).
ᵈ based on two measurements only.
ᵉ calculated from the Swain equation[14] $k_H/k_D = (k_D/k_T)^{2,26}$

RESULTS AND DISCUSSION

In all cases studied the exchange reaction was found to be first order in substrate and in base, provided that base concentrations were below 0·5 molar. For very weakly acidic substrates (e.g. with pivaloyl as a substituent) reactions had to be carried out at higher base concentrations and in those cases the logarithm of the pseudo-first order rate constant was found to be linearly related to the H_{m-} function[9, 10] (experimental). Monodeuterio dicyclopropyl ketone I was used as a standard to express relative kinetic acidities of other substrates, with appropriate extra- or inter-polation at [MeONa] = 0·05 molar or H_{m-} = 17·75 (Table 1), whenever necessary. No exchange rates for 2-nitropropane (IX) could be measured, because it forms à stable (aci)-anion. Its ionization rate (determ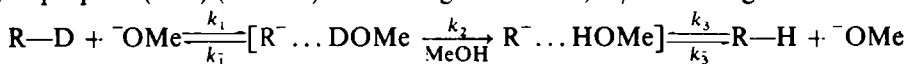ined by polarography[11] and by UV[12]) is ca. 10^6 times higher than the exchange rate of I and ca. 200 times faster than that of 1-deuterio-1-nitro-cyclopropane (VIII) (Table 1). According to Cram[13], D/H exchange in methanolic

$$R—D + {}^-OMe \underset{k_{\bar{1}}}{\overset{k_1}{\rightleftharpoons}} [R^- \ldots DOMe \xrightarrow[\text{MeOH}]{k_2} R^- \ldots HOMe] \underset{k_{\bar{3}}}{\overset{k_3}{\rightleftharpoons}} R—H + {}^-OMe$$

NaOMe involves abstraction of the α-proton (deuteron) from the substrate RD by MeO⁻ to give a hydrogen-bonded carbanion (k_1), followed by solvent exchange (k_2) and protonation of the carbanion by solvent (k_3). Using the steady-state condition, it can be derived that

$$k_{obs} = k_1 k_2 / (k_{\bar{1}} + k_2)$$

Which particular step(s) is (are) rate-limiting, can generally be deduced from the order of magnitude of the hydrogen-deuterium (deuterium–tritium) isotope effect. If $k_{\bar{1}} \ll k_2$, then $k_{obs} = k_1$ and we would expect a large isotope effect. With $k_{\bar{1}} \gg k_2$, we have $k_{obs} = k_1 k_2 / k_{\bar{1}}$ and a small(er) isotope effect will be found*. As can be seen from Table 2, the largest isotope effects (k_H / k_D = 6·8–7) are observed for isopropyl t-butyl ketone (VII) and for 2-nitropropane (IX), while the other compounds show smaller effects ($\leqslant$ 4·8). Furthermore it can be concluded that the cyclopropyl and the corresponding isopropyl compounds (e.g. I–III, IV–V, X–XI) have approximately the same isotope effect, so that k_{obs} for each pair presumably refers to similar steps in the mechanism.

The strongly negative entropies of activation for all the deuterated ($\Delta S_D^{\ddagger}$) and the tritiated ($\Delta S_T^{\ddagger}$) acyl-substituted substrates (Table 2) are consistent with a strongly solvated transition state (see exchange mechanism), and a rate-limiting first step because of the relatively large isotope effects. The higher (less negative) $\Delta S_D^{\ddagger}$ and $\Delta S_T^{\ddagger}$ values for the cyanides X and XI and for nitrocyclopropane (VIII) are probably the result of a compensation of the entropy term in the pre-equilibrium ($\Delta S_1^{\ddagger} - \Delta S_{\bar{1}}^{\ddagger}$) and that of the solvent exchange step ($\Delta S_2^{\ddagger}$).

The k_{iso}/k_{cyclo}-values (Table 1) show that:

(i) All cyclopropanes substituted with various acyl groups, are less acidic than their open chain analogues, factors ranging from 10 to 1300.

(ii) The CF_3-substituted cyclopropane[15] is about 10,000 times more acidic (in the kinetic sense) than its open chain analogue. The same but weaker tendency is found for cyanides and sulfones.

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* In our opinion the discrepancy between the calculated and the observed k_H/k_D values in Walborsky's work[1a] is probably due to solvent isotope effects.

The essential difference can be explained as follows:

Carbanions derived from compounds with a "mesomeric" substituent such as the acyl group derive their stability from an overlap between a p-type orbital on the atom in the α-position and the π-orbital of the carbonyl group. Normally a planar (enolate) structure is required for effective overlap, and because this is relatively difficult in cyclopropanes, the corresponding acyl carbanions are less stable than the analogous carbanions with an isopropyl group instead of cyclopropyl and consequently $k_{iso}/k_{cyclo} \gg 1$.

The relatively low k_{iso}/k_{cyclo}-value of 10 for the pivaloyl compounds (VI and VII) is presumably due to the bulky t-butyl group, which seriously hinders not only the approach of the MeO⁻ anion but also the coplanarity even of the enolate anion of the isopropyl derivative VII.

With an "inductive" substituent like CF_3, the acidifying power of the substituent is not affected by ring strain effects ($k_{iso}/k_{c\ clo} \approx 10^{-4}$, cf. Table 1). The greater acidity of the cyclopropyl protons is caused by the greater s-character of the C—H bond in cyclopropanes than in (substituted) propanes. The low k_{iso}/k_{cyclo} value (≈ 0.07) for the cyanide suggests that the electron withdrawing action of the cyano group—like that of the CF_3 group—is largely due to an inductive effect and much less so to a mesomeric effect.[16] This follows also from the H/D-exchange reaction of 2,2-diphenylcyclopropyl cyanide and its open-chain analogue.[1a–b] Because the k_{iso}/k_{cyclo} value for the sulfones (XV compared with XIV) is also small (≈ 0.03), a similar explanation involving the C—H bond s-character might hold for the sulfonyl group. Moreover, the sulfonyl group can stabilise a negative charge on an α-position by d-orbital overlap. This type of overlap requires a different geometry than p-orbital overlap. It is probable that the negative charge in the cyclopropyl phenyl sulfone carbanion can be delocalised in a nonplanar structure. So the electron-withdrawing power of the sulfonyl group is less suppressed than that of the carbonyl group when each is attached to a cyclopropyl ring.

Cram et al.[2a] and Zimmerman et al.[2b] state that the thermodynamic acidities of cyclopropyl phenyl sulfone (XIV) and isopropyl phenyl sulfone (XV) are about equal. If we assume that the rate of protonation of both sulfone anions is about equal, we calculate from our results indeed a relatively small difference in pK_a of about 1·5 units.

EXPERIMENTAL

Dicyclopropyl ketone (I), diisopropyl ketone (II), cyclopropyl phenyl ketone (IV), cyclopropyl cyanide (X), isopropyl cyanide (XI) and 2-nitropropane (IX) were commercially available and were purified by VPC before use. The following compounds were prepared according to the literature: nitrocyclopropane (VIII),[18] isopropyl phenyl sulfone (XV),[2a] cyclopropyl phenyl sulfone (XIV)[2b] and isopropyl phenyl ketone (V).[19]

Isopropyl cyclopropyl ketone (II) *and t-butyl cyclopropyl ketone* (VI). Ketones II and VI were prepared according to Bunce[17] by treatment of methyl cyclopropyl ketone with two and three equivalent of MeI respectively in a solution of $NaNH_2$ in benzene. Yield after purification by VPC of II: 40% and of VI: 50%.

t-Butyl isopropyl ketone (VII). To a stirred solution of 300 ml of water, 50 g of potassium bichromate and 25 ml of conc. H_2SO_4 was added 20 g of 2,2,4-trimethyl-3-pentanol. The mixture was refluxed for one hr and ether extracted. The ethereal layer was washed with saturated $NaHCO_3$ and saturated NaCl solution and dried $(MgSO)_4$. After ether evaporation, VII distilled at 134–135°, yield 10 g (50%).
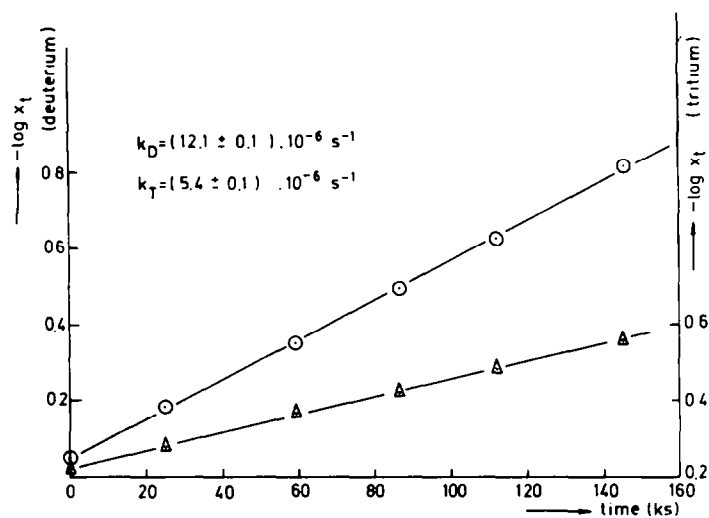
FIG. 1a. Pseudo-first order D/H and T/H exchange in α-deuterio (⊙)- and α-tritio isopropyl t-butyl ketone (Δ) (0·2 M) dissolved in MeOH/MeONa (0·52 M) at 70°. 0.
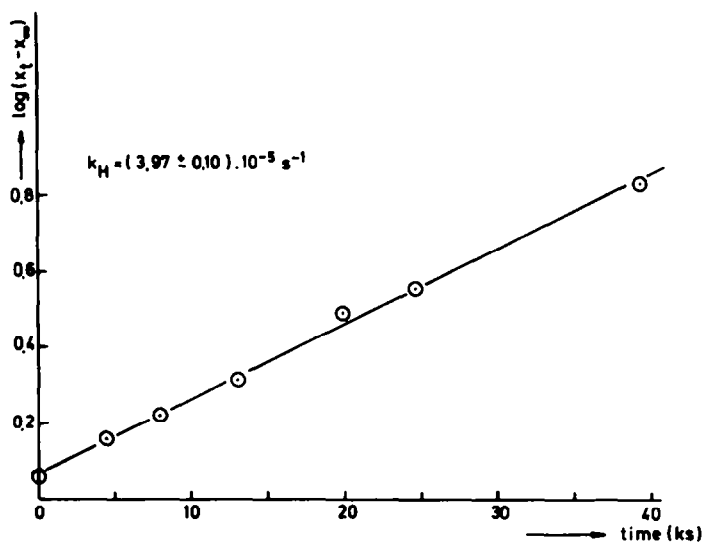
FIG. 1b. Pseudo-first order H/D exchange in cyclopropyl phenyl sulfone (1·5 M) dissolved in MeOD/MeONa (0·22 M) at 53°·2.
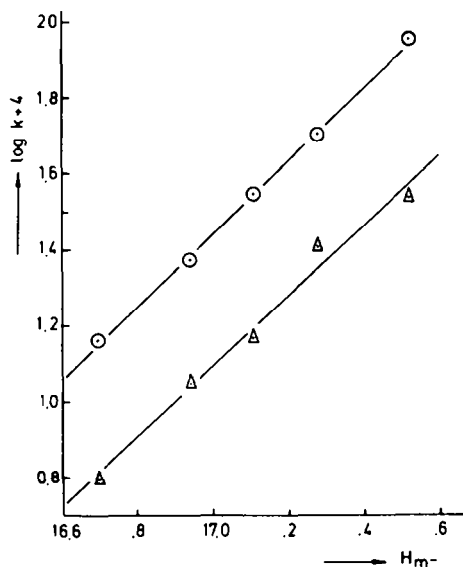
Fig. 2a. Second order D/H and T/H exchange rate constant k of α-deuterio ($\odot$-) and α-tritio isopropyl t-butyl ketone (Δ) (0·2 M) vs. H_m- at 53°.2.
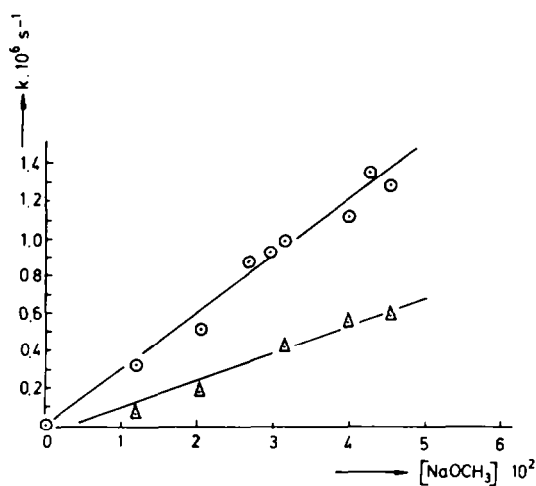
Fig. 2b. Second order D/H and T/H exchange rate constant k of α-deuterio ($\odot$)- and α-tritio isopropyl phenyl ketone (Δ) (0·2 M) vs. [MeONa] at 53°.2.

Trifluoromethylcyclopropane (XII). An ethereal solution of 2,2,2-trifluoropropene (Pierce and Co, U.S.A.) (10 g) and an equimolar amount of CH_2N_2 was irradiated with UV light, until the yellow colour had disappeared (about two hr). The ether was evaporated and the residue was distilled *in vacuo* at 60°/27 mm. Yield 10 g (70%) of 3-trifluoromethyl-1-pyrazoline.* The 1-pyrazoline was pyrolysed by passing it with N_2 as carrier through a heated tube (260°), filled with 2 g of KOH and 4 g of Pt on asbestos (10%). From the mixture, trapped at −80°, trifluoromethylcyclopropane (b.p. 20°) was isolated by VPC. Yield 50%.

1,1,1-Trifluoro-2-methylpropane (XIII). 3,3,3-Trifluoro-2-methylpropene (Pierce and Co, U.S.A.) (b.p. 6°) was hydrogenated at 70 atm. at room temp. Yield of XIII: 98%; b.p. 11°.

Deuteration and tritiation procedure. The cyclopropyl and isopropyl compounds were deuterated and tritiated simply by exchange of the tertiary proton in deuterated and tritiated MeOH with NaOMe as catalyst. 2-Nitropropane was labeled by exchange in D_2O (HTO) with NaOH (1%).

The deuterium content varied from 65 to 70% D (dicyclopropyl ketone I and diisopropyl ketone III 60% D); the specific activity of the products was 20 to 40 dps/mg (0·05–0·10 nCi/mg).

Deuterium analysis. The deuterium analyses of III–V, VIII, IX, XI–XV were carried out by NMR (Varian A-60D, HR-60 or HA-100 spectrometer) by comparing the integrated signals of the tertiary proton with other protons in the substrate, that cannot take part in the exchange (average of three measurements). The amount of protio-, monodeuterio- and dideuterio cyclopropylketone I and diisopropyl ketone II and the deuterium content of VI and VII were determined by mass spectrometry (AEI MS-902 mass spectrometer). The deuterium content of X was determined by IR (Perkin Elmer 125 spectrometer).[7]

Tritium analysis. The tritium analyses were performed on a Packard "Tri-Carb" liquid scintillation spectrometer model 314, or on an internal flow proportional counter, coupled to a gas chromatograph.[20]

Kinetic measurements. A mixture of 150 mg of the substrate and a given amount of NaOMe in 7·5 ml MeOH was heated in a soft-glass ampoule at fixed temperatures. The reaction was stopped by cooling the ampoules to −30°. The mixture was poured into water (40 ml) and ether extracted (4 × 2 ml). The combined ethereal fractions were washed with sat NaCl (20 ml) and dried ($MgSO_4$). Solvent was evaporated and the substrate isolated from the residue by VPC.

The reaction constants k_D and k_T were calculated from the pseudo-first order relation $kt = \ln x_0/x_t$, in which x_t and x_o are the deuterium (or tritium) content at time t and zero (Fig. 1).

A different procedure was used with the trifluoromethyl compounds XII and XIII and the phenylsulfones XIV and XV. A mixture of 100 mg of the unlabelled compound and 200 µl of a solution of NaOMe in MeOD was heated in a sealed NMR tube. At various times the D-incorporation in the substrate was determined indirectly from the increase of the solvent OH-signal with respect to an internal proton signal of the substrate. The reaction constant k_H (Table 1) was calculated from the relation

$$\frac{x_0}{x_0 - x_\infty} \cdot kt = \ln \frac{x_0 - x_\infty}{x_t - x_\infty},$$

in which x_∞, x_t and x_0 is the fraction of H incorporation in the substrate at time ∞, t and zero. Some typical examples of the kinetic procedures are given in Fig. 1 and 2.

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