Effect of 4-t-Butyl and Other 4-Substituents on Rate Constants for Reactions of 1,1-Disubstituted Cyclohexanes and Piperidines. 4-t-Butyl Derivatives as Valid Reactivity Models in the Kinetic Method of Conformational Analysis of Cyclohexanes

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A 4-t-butyl group (or a 4-methyl group) has no effect on the rate constant for ethoxy-exchange in diethyl cyclohexane-1,1-dicarboxylates; a 4-phenyl group, however, increases the rate constant by more than 50%. By contrast, both 4-alkyl and 4-phenyl groups increase the overall rate constants for nucleophilic displacement by thiopholate anion at the benzyl methylene groups in 1-benzylpiperidine benzobromides, a 4-t-butyl group approximately doubling the value. The significance of these results in relation to the validity of the usual kinetic method for conformational analysis of cyclohexanes is discussed.

In conformational analysis of cyclohexanes,[1] 4-t-butyl derivatives (1) and (2) have often been used as models for individual conformers (3) and (4) of the monosubstituted cyclohexane. A reaction rate constant or suitable physical property of the monosubstituted compound is expressed (usually) as a weighted average of known values from (1) and (2) and the equilibrium ratio of (3) : (4) is then readily derived by simple analysis. Otherwise, this ratio may more simply be equated to that for (1) : (2) at equilibrium, provided that these diastereoisomers are experimentally readily interconvertible, or the conformer ratio may be obtained directly without the use of models by low temperature n.m.r. or by other spectroscopic methods. Since rate constants for the individual conformers (3) and (4) cannot readily be determined directly for comparison with those for the models (1) and (2), the validity of the kinetic method has rested on the correspondence of conformer ratios obtained by this method and by other procedures. We have sought somewhat more direct evidence on the point for several reasons, including various criticisms[2] of the kinetic method that have been made from time to time, and the increasingly detailed interest in charac-

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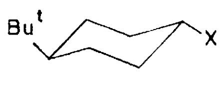
[1] E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, 'Conformational Analysis,' Wiley, New York, 1965, chs. 2 and 3.

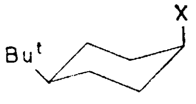
[2] See, *e.g.* H. Kwart and T. Takeshita, *J. Amer. Chem. Soc.*, 1964, **86**, 1161; J. L. Mateos, C. Perez, and H. Kwart, *Chem. Comm.*, 1967, 125; *cf.* ref. 1, p. 188.

teristics of good models for conformational analysis in a variety of systems.[3]

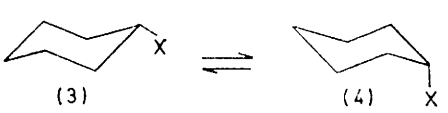
The approach adopted [4] was measurement of the combined rate constants for reaction at geminal positions in 1,1-disubstituted cyclohexanes, ethoxy-exchange in ethanolic sodium ethoxide with the esters (5; R = H and Bu^t) being the reaction selected; for additional comparison the esters (5; R = Me and Ph) were also examined. Technically, we found that rate constants for this exchange process were easier to measure than those for the more familiar hydrolysis. The required esters were readily prepared by suitable cyclisations with diethyl malonate, and then uniformly exchange-labelled with ^{14}C in both ethoxy-groups. The course of the chosen reactions was followed by measurement of the loss of radioactivity from the labelled esters in ethanolic sodium ethoxide in what amounted to a reversal of the preparative labelling procedure. In our preliminary quantitative work [4] we measured the initial rates of loss of activity as a guide to the effects of the 4-substituents. Subsequently, however, we have obtained good first-order plots (for exchange in a large excess of unlabelled ethanol) representing the combined rate constants for exchange at axial and equatorial positions; the low specific activity of the radioactive esters employed ensured that virtually no ester molecules would be doubly labelled.



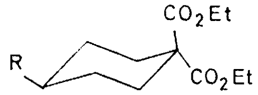
(1)



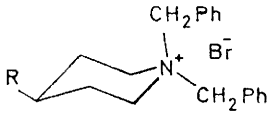
(2)



(3) (4)



(5)



(6)

Within experimental error there was no kinetic differentiation between the 4-unsubstituted, the 4-methyl, and the 4-t-butyl esters, a single first-order plot accommodating all three. The rate constant for the 4-phenyl ester, however, was 1.57 times larger than that for the others.

The clearcut result for the most important comparison of the 4-unsubsituted and the 4-t-butyl esters provides direct evidence only that the 4-t-butyl group does not affect the summed rate constants for reaction of the *gem*-diester system. This finding is of considerable interest in itself and it also leads to the strongly permissive if not essential conclusion that the 4-t-butyl group does not affect the reactivities of the individual ethoxycarbonyl groups in the diester (5; R = Bu^t) and in the diastereoisomers (1 and 2; X = CO_2Et). Equal effects from the 4-t-butyl group in opposite directions on the equatorial and axial ethoxycarbonyl groups in the diester (5; R = Bu^t) are not impossible but seem unlikely.

We hardly expected the more polarisable 4-phenyl group to be without effect on the combined exchange rate constant. 4-Phenyl derivatives have not been used as models for conformational analysis of cyclohexanes. In piperidine systems 4-aryl models have been employed,[5] but not usually for kinetically based methods, and separate evaluations are required of models for conformational analysis by other methods based on measurements of equilibria or physical properties.

The exchange reaction does not affect the ring C-1 atom directly. It has been recognised [6] that reactions which do so affect ring atoms are likely to be less satisfactory for application of the kinetic method of conformational analysis, although perhaps the most notorious such reaction,[2] solvolysis of cyclohexyl tosylates, also affects the adjacent methylene groups at C-2 and -6 by hyperconjugation with the developing carbonium ion centre at C-1, thus moving the reaction area still nearer to the 4-t-butyl conformation-holding group. We wished to study the effect of a 4-t-butyl substituent on a reaction of a saturated six-membered ring system which would affect atom-1 directly but not the adjacent ring methylene groups to the degree associated with the solvolysis reaction, and again our approach was based on the use of geminal 1-substituents. Difficulties in the choice of a suitable cyclohexane system coupled with our interest in piperidine stereochemistry led us to select the reaction of 1,1-dibenzylpiperidinium bromides (6; R = H, Me, Bu^t, and Ph) with thiophenolate anion, a substitution process yielding the tertiary 1-benzyl bases and benzyl phenyl sulphide.

We again employed a radiochemical procedure [7] for following the kinetics, the benzyl groups in the quaternary salts being ^{14}C-labelled either at methylene or randomly in the benzene ring; the radioactivity was thus transferred to the toluene-extractable products during reaction. An isotope effect for $^{12}k/^{14}k$ in the probable range 1.05—1.15 caused no problems with nonlinearity of the first-order (large excess of thiophenolate) plots in the ranges studies (2—3 half lives) for reactions of the methylene-labelled salts. The rate constants were sensitive to the water content of the solvent diethylene glycol, or to saturation of the glycol with

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[3] *Inter alia* J. McKenna, *Tetrahedron*, 1974, **30**, 1555; M. J. T. Robinson, *ibid.*, p. 1971.

[4] Preliminary communication, J. McKenna, J. M. McKenna, and B. G. Hutley, *J.C.S. Chem. Comm.*, 1974, 522.

[5] *Cf.* R. A. Y. Jones, A. R. Katritzky, A. C. Richards, and R. J. Wyatt, *J. Chem. Soc.* (*B*), 1970, 122; R. A. Y. Jones, A. R. Katritzky, A. C. Richards, R. J. Wyatt, R. J. Bishop, and L. E. Sutton, *ibid.*, p. 127.

[6] *Cf.* E. L. Eliel, *Pure Appl. Chem.*, 1971, Special Supplement 7, 219.

[7] Preliminary communication, P. G. Leviston, J. McKenna, J. M. McKenna, R. A. Melia, and J. C. Pratt, *Chem. Comm.*, 1970, 587.

toluene (as part of the technical procedure) in the directions expected for a reaction between oppositely charged ions.

It was found that rate constants for series of reactions run under any one of several sets of standard conditions on the quaternary salts (6) increased in the 4-substituent order H < Me < Bu^t < Ph, relative values being 1.00 : 1.30 : 2.15 : 2.80 and under different conditions 1.00 : 1.20 : 1.85 : 3.00 from the results detailed in the Experimental section. The comparison of 4-H and 4-Bu^t substituents is again of particular interest, and, following the same line of reasoning as that given above in discussion of the ester exchange, we conclude that the results support the view[6] already quoted that the standard kinetic method of conformational analysis using 4-t-butyl derivatives is unreliable when atom-1 (normally C-1 in cyclohexanes) is directly involved in the reaction.

Elemental analyses of esters and quaternary salts[a]

Compound	M.p. (°C) (recryst. solvent) or b.p. (°C) [p/mmHg]	Found (%)			Formula	Calc. (%)		
		C	H	N		C	H	N
Diethyl cyclohexane-1,1-dicarboxylate[b]	136 [16]	63.3	8.7		$C_{12}H_{20}O_4$	63.1	8.8	
Diethyl 4-methylcyclohexane-1,1-*dicarboxylate*	120 [12]	64.1	9.05		$C_{13}H_{22}O_4$	64.45	9.15	
Diethyl 4-t-butylcyclohexane-1,1-*dicarboxylate*	132 [2.5]	67.8	9.9		$C_{16}H_{28}O_4$	67.6	9.9	
Diethyl 4-phenylcyclohexane-1,1-dicarboxylate[c]	170 [2]	70.7	7.85		$C_{18}H_{24}O_4$	71.0	7.95	
1,1-Dibenzylpiperidinium bromide[d]	160—162 (MeOH–MeOAc)	66.1	6.9	4.2	$C_{19}H_{24}NBr$	65.9	6.95	4.05
1,1-*Dibenzyl*-4-*methylpiperidinium bromide*[e]	194—196 (MeOH–MeOAc)	65.4	7.2	3.5	$C_{20}H_{26}NBr,0.5CH_3OH$	65.4	7.5	3.7
1,1-*Dibenzyl*-4-*t-butypiperidinium bromide*[e]	174—175 (MeOH–MeOAc)	66.8	8.3	2.9	$C_{23}H_{32}NBr,CH_3OH$	66.35	8.35	3.2
1,1-*Dibenzyl*-4-*phenylpiperidinium bromide*	196—197 (MeOH–MeOAc)	70.9	6.7	3.1	$C_{25}H_{28}NBr$	71.1	6.7	3.3

[a] New compounds italicised. [b] Lit.,[8] b.p. 130—145° at 16 mmHg. [c] H. E. Zimmerman and H. J. Giallombardo, *J. Amer. Chem. Soc.*, 1956, **78**, 6259. B.p. 177—182° at 16 mmHg. [d] M. Schlotz and R. Wolfrum, *Ber.*, 1910, **43**, 2304. M.p. (from EtOH–Et_2O) 253° (N analysis given). We can offer no explanation for the unusually large discrepancy. [e] These salts retained the solvent tenaciously; a similar result was obtained on recrystallisation from ethanol or acetone. Retention of methanol in the proportion indicated was confirmed by the n.m.r. spectra. The very small concentration of methanol in the diethylene glycol solutions for the kinetic experiments is unlikely to have any noticeable effect on the rate constant.

EXPERIMENTAL

^{14}C Counts were measured on a Packard 'Tricarb' scintillation spectrometer, with a conventional PPO–POPOP–toluene scintillator solution. Counting efficiencies were determined by internal standardisation, using $[^{14}C]$-toluene.

Preparation of Esters.—All esters (5) were obtained from the appropriate 1,5-dibromopentane and diethyl malonate in sodium ethoxide–ethanol using a procedure already described[8] for the 4-unsubstituted ester (5; R = H). 1,5-Dibromopentane and its 3-methyl and 3-t-butyl derivatives were prepared from the corresponding piperidines (with 4-H, -Me, or -Bu^t) by Schotten–Baumann benzoylation followed by von Braun ring-fission; each dihalide has previously[9] been made in this way. 1,5-Dibromo-3-phenylpentane[10] was prepared from 3-phenylglutaric anhydride[11] by reduction to 3-phenylpentane-1,5-diol[10] with lithium aluminium hydride in tetrahydrofuran and treatment of the diol with hydrobromic acid–sulphuric acid.

$[^{14}C]$Ethanol was diluted to an activity of *ca.* 20 μCi mol^{-1}, distilled from sodium borohydride to remove aldehydes, and dried by treatment with magnesium and iodine and redistillation according to the method described by Vogel.[12] A 0.25M solution of sodium ethoxide prepared from this dry ethanol was employed for preparation of radioactive esters by ethoxy-exchange. Ethoxide solutions (10 ml) of each inactive ester (3×10^{-3} mol) were kept at 35° for 48 h, and then at room temperature for up to 7 days until checks on recovered esters indicated that >97% of the expected radioactivity had been introduced. The ethoxide solutions were worked up by dilution with water and extraction with ether; the ether extracts were dried (Na_2SO_4) and evaporated and the recovered esters were distilled *in vacuo*, the middle cuts being used for elemental analyses (see Table), spectroscopic checks, and kinetic measurements.

Preparation of Quaternary Salts.—The ^{14}C-labelled salts (6; R = H, Me, and Ph) were obtained from the corresponding 4-substituted piperidines with $[^{14}C]$benzyl bromide (activity *ca.* 40 μCi mol^{-1}) in methanol in the presence of excess of finely ground solid potassium carbonate, while the salt (6; R = Bu^t) was similarly prepared from 1-benzyl-4-t-butylpiperidine. This base was made by reduction of 1-benzyl-4-t-butylpyridinium chloride with sodium borohydride[13] to 1-benzyl-4-t-butyl-1,2,5,6-tetrahydropyridine which was then catalytically hydrogenated in ethanol over platinum oxide. Elemental analyses of salts similarly prepared with inactive benzyl bromide are given in the Table. All samples were also checked spectroscopically.

The required $[^{14}C]$benzyl bromide was prepared from

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[8] A. I. Vogel, *J. Chem. Soc.*, 1929, 1487.

[9] (*a*) A. I. Vogel, 'A Textbook of Practical Organic Chemistry,' Longman, London, 1957, 3rd edn., p. 492; (*b*) N. J. Leonard and Z. W. Wicks, *J. Amer. Chem. Soc.*, 1946, **68**, 2402; (*c*) C. R. Johnson and D. McCants, jun., *ibid.*, 1965, **87**, 1109.

[10] R. H. Manske, *J. Amer. Chem. Soc.*, 1931, **53**, 1104.

[11] R. Antschul, P. Bernstein, and S. G. Cohen, *J. Amer. Chem. Soc.*, 1956, **78**, 5091.

[12] Ref. 9*a*, p. 167.

[13] *Cf.* M. Ferles, *Coll. Czech. Chem. Comm.*, 1958, **23**, 479; D. R. Brown and J. McKenna, *J. Chem. Soc.* (*B*), 1969, 570.

[^{14}C]benzyl alcohol (labelled in the methylene group) by treatment with constant boiling aqueous hydrobromic acid for 1 h at 50°. Alternatively, [^{14}C]benzoic acid (randomly labelled in the benzene ring) was reduced to benzyl alcohol with lithium aluminium hydride in ether, and this was then converted into the correspondingly labelled benzyl bromide.

Kinetics of Ethoxide Exchange.—Several solutions of each radioactive ester (5; R = H, Me, Bu^t, and Ph) ($1-2 \times 10^{-4}$ mol) in dry ethanolic sodium ethoxide (11 ml; 0.091M; dry inactive ethanol prepared by procedure described above) were kept at 9.0°. At zero time and at appropriate intervals thereafter duplicate 1 ml portions were measured into centrifuge tubes each containing water (15 ml) and toluene (5 ml). Each tube was stoppered and vigorously shaken, the layers were separated in the centrifuge, the water layer was removed, and the toluene solution of ester was washed twice again with water (2 × 15 ml); this procedure was more than sufficient to ensure constant radioactivity in the toluene solution, duplicate 1 ml portions of which were taken for radiochemical assay.

Under the conditions employed (large excess of inactive ethanol) the loss of radioactivity from each of the four esters followed a first-order plot. Within experimental error, results for the esters (5; R = H, Me, and Bu^t) fitted the same line, giving $10^6k_{\text{uni}} = 4.50\ \text{s}^{-1}$. However, the ester (5; R = Ph) reacted faster, with $10^6k_{\text{uni}} = 7.05\ \text{s}^{-1}$. The standard deviation of these rate constants is *ca.* 5%.

Kinetics of Reaction of Quaternary Salts with Thiophenolate.—Sodium thiophenolate was prepared from redistilled thiophenol and recrystallised from acetone. Stock solutions of each quaternary salt (0.025M) and of sodium thiophenolate (0.3M) were prepared in diethylene glycol to which had been added either 0.5% (benzyl methylene-labelled salts) or 1% (ring-labelled salts) of water by volume.

Stoppered tubes each containing quaternary salt solution (2 ml) and sodium thiophenolate solution (2 ml) were kept at 60.5° for varying times and then cooled to room temperature and opened; the contents were shaken with toluene (10 ml) and aqueous potassium hydroxide (1N; 4.5 ml), and the mixture was centrifuged. Weighed portions (2—3 ml) of the toluene solution (containing tertiary base and sulphide) were taken for radiochemical assay. Further washing of the toluene solution was unnecessary. The procedure is based on one previously described [14] dealing with the reaction of some related radioactive *N*-methyl methiodides with sodium thiophenolate. Infinity values were conveniently determined using sealed tubes at higher temperatures.

Excellent first-order plots (12-fold excess of nucleophile) were obtained for decomposition of the quaternary salts. The derived rate constants were as follows (4-substituent, 10^6k_{uni} for solvent containing 0.5% water, 10^6k_{uni} for solvent containing 1% water): 4-H, 18.4, 6.8 s^{-1}; 4-Me, 23.9, 8.2 s^{-1}; 4-Bu^t, 39.6, 12.6 s^{-1}; 4-Ph, 51.5, 20.4 s^{-1}. All standard deviations were *ca.* 5%. In earlier experiments the toluene was introduced (for intended subsequent convenience) into the tubes containing the reaction mixtures before heating. The rate constants were increased as a result of this procedure (reaction in slightly aqueous diethylene glycol saturated with toluene) and were rather less precise, but fell in the same order (4-H < 4-Me < 4-Bu^t < 4-Ph).

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[14] B. G. Hutley, J. McKenna, and J. M. Stuart, *J. Chem. Soc.* (*B*), 1967, 1199.