Classical Carbonium Ions. Part 13.[1] Rearrangements from Secondary to Primary Alkyl Groups during Reactions involving Carbonium Ions

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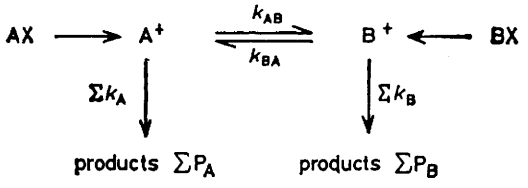
The rearrangement of cyclohexylamine to cyclopentylmethyl derivatives, earlier reported in brief, is confirmed. A similar reaction with 4-*trans*-t-butylcyclohexylamine is shown to give *trans*-3-t-butylcyclopentylmethyl derivatives, defining the conformational requirements and stereochemical course of the rearrangement. In similar reactions 2-butylamine and 3-pentylamine give, in small yield, derivatives of primary alcohols. Cyclohexyl toluenesulphonate probably gives a very small yield of cyclopentylmethyl acetate. All these reactions involve the formation of products formally derived from carbonium ions much less stable than those initially generated, and yields, though small, are much larger than can be accounted for by classical descriptions. It is proposed that corner-protonated cyclopropanes (' non-classical carbonium ions ') are ' intermediates ' of very short lifetime in these reactions; the extent to which it is possible to regard species of very short lifetime as intermediates is discussed.

In the classical theory of carbonium-ion rearrangements,[2] a precursor gives a cation which rearranges to an isomeric cation, products being formed from each by substitution and elimination. In one limiting case, the rearranged products are formed in small yield only, much less than would be expected if the two intermediates reached equilibrium. The majority of rearrangements by hydride shift studied in this Series, essentially thermoneutral, approach this limit. A second limit, approached in weakly nucleophilic solvents, involves nearly complete equilibration and, often, a statistically determined set of products. A third limiting situation is found where the rearrangement is exothermal, and products are largely derived from the rearranged cation; here accelerated formation of the intermediate suggests that the rearrangement is concerted with this process, leading to the concepts of ' synartesis ' [3a] or ' anchimeric assistance '.[3b] All cases within these limits fit Scheme 1.



Scheme 1

At the limit where equilibration between A and B precedes significant product formation, $\Sigma P_B/\Sigma P_A = k_{AB}\,\Sigma k_B/k_{BA}\,\Sigma k_A$, and if AX is the starting point, this is the maximum value of the product ratio. Normally that implies a predominance of products related to the more stable ion, because elimination and substitution processes are bimolecular, and therefore subject to a maximum value for the faster of the two rates (the encounter rate, in the case of an external nucleophile; some greater rate, less than the vibrational frequency of the covalent bond that results, in the case of the collapse of an encounter complex). Whereas equilibrium constants between isomeric carbonium ions can be very large indeed (see below), even relatively stable carbonium ions react so fast [*e.g.* 10^8 s^{-1} for PhMeC$^+$(OMe) in water at 25° [4]] that the term $\Sigma k_A/\Sigma k_B$ is necessarily much smaller than k_{AB}/k_{BA}, so long as the classical Whitmore theory remains a valid picture of the process. And indeed, a very large number of reactions involving rearrangements can be so formulated, within the three limits discussed above.

The formation of cyclopentylmethanol, along with cyclohexanol, when cyclohexylamine was treated with nitrous acid [5] cannot be fitted to the Whitmore scheme (see below), and is therefore crucial to any theory of reactions proceeding *via* carbonium ions. Here a precursor has given a secondary cation which has rearranged to a much less stable primary cation and this has collapsed to a primary alcohol in significant quantity. This reaction was described laconically, without yields, experimental details, or proof of identity, and in our view merited repetition under well defined conditions. Accordingly, *N*-nitroso-*N*-acetylaminocyclohexane was allowed to solvolyse in acetic acid, and gave two products of the right g.l.c. retention times for C_6 acetates. One was identical with cyclohexyl acetate, the other (0.95% of substitution product) was inseparable, on columns of 27 000 and 22 000 theoretical plates, from the acetate of cyclopentylmethanol; it was easily separable from 1-methylcyclopentyl and *cis*- and *trans*-2-methylcyclopentyl acetates. This result in a sense contradicts the report of Cogdell,[6] who treated cyclohexylamine and cyclopentylmethylamine with isoamyl nitrite in acetic acid at 80° and obtained from each a rather similar mixture of cyclohexyl acetate and cyclohexene, with some bicyclo[3.1.0]hexane in the former case, thus confirming only the exothermal direction of the interconversion. Yields were reported only to the nearest percent, so minor products could have been missed.

Maskill and Whiting reported that deamination of *trans*- (but not of *cis*-)t-butylcyclohexylamine, using either acetolysis of the *N*-nitroso-*N*-butyrylamino-compound or the butyrolysis of the corresponding acetyl compound, gave an acetate (' Z ') and a butyrate (' Y ') not identical with any of the acyloxy-t-butylcyclohexanes.[7] One of us proposed [8] that these compounds were the *trans*-3-butylcyclopentylmethyl esters, formed

by a reaction analogous to that reported by Reutov and Shatkina [5] and proceeding with inversion of configuration, as in conventional exothermal or thermoneutral 1,2-alkyl shifts in cationic intermediates. This hypothesis, however, required confirmation.

Oxidation of 4-t-butylcyclohexanone with hydrogen peroxide and selenium dioxide has been reported [9] to give *cis*-3-t-butylcyclopentanecarboxylic acid, and similarly 3-t-butylcyclohexanone was said to give the corresponding *trans*-3-t-butylcyclopentanecarboxylic acid. We have repeated both experiments and confirm the former conclusion. In the second case, however, we obtained, in low yields that frustrated attempts at purification, a mixture of two acids, having two n.m.r. peaks for the t-butyl group. Other 3-substituted cyclohexanones are known [9] to give mixtures of 2- and 3-substituted ring-contracted acids. Probably the t-butyl compound had behaved similarly, giving the reported 3-*trans*-compound as main component, but some 2-t-butylcyclopentanecarboxylic acid as well. Both the pure 3-*cis*-acid and, on a smaller scale, the impure 3-*trans*-acid were converted *via* methyl esters (methanol–sulphuric acid) into primary alcohols (lithium aluminium hydride, aqueous sodium hydroxide). These were not pure spectroscopically, and by g.l.c. contained small amounts of *cis*- and *trans*-4-t-butylcyclohexanol, which acted as convenient internal standards; presumably they were formed by unintentional acid-catalysed ring expansion. Each gave one main chromatographic peak, and was essentially free of the other, since at 10 000 plates on MBM they could just be distinguished (retention times 40.7 and 40.1 min; on Carbowax the retention times were even closer). The similarity in retention times of these 3-t-butylcyclopentyl derivatives is disconcerting. The corresponding aldehydes were almost certainly obtained by equilibration, but defeated all attempts at separation.[10]

Acetolysis of *trans*-4-t-butyl-*N*-nitroso-*N*-acetylcyclohexylamine gave a mixture of acetates, hydrolysed to a mixture of alcohols, in which ' compound Z ' [7] and the related alcohol were readily identified by yield, larger than the hydride-shifted products but smaller than the unrearranged 4-t-butylcyclohexyl derivatives. Co-injection of the two 3-t-butylcyclopentylmethanols proved that the rearrangement product could be distinguished from the *cis*-isomer, but not from the *trans*-compound.

Careful measurements of peak width rendered the comparison more reliable than most such proofs of identity, but it is not, of course, a rigorous method. These results should be taken in parallel with the confirmation of Reutov's work,[5] where no problems arise with the preparation of authentic cyclopentylmethanol or with the chromatographic comparison, and with such degradative work as it was possible to do on the total deamination product from 4-t-butylcyclohexylamine. This involved partial hydrolysis of the ester mixture with aqueous ethylamine, which proved the unknown compound ' Z ' to be much more reactive than the accompanying secondary acetates and therefore probably the acetate of a primary alcohol. Indeed, a liquid acid was formed on oxidation of a concentrate of the alcohol.[8]

We conclude that Reutov's report [5] is correct, and applies to deamination in carboxylic acid solvents *via* nitrosoamides; that the reaction proceeds *via* the equatorial conformer only; that the product ' Z ' from *trans*-4-t-butylcyclohexylamine is almost certainly *trans*-3-t-butylcyclopentylmethyl acetate (and certainly is not the *cis*-3-isomer); and that it is formed by an alkyl shift with inversion of configuration, stereoelectronically just like the exothermal or thermoneutral 1,2-alkyl shifts in intermediate cations that the Whitmore scheme is intended to rationalise. The ' contrathermodynamic ' rearrangement follows either the concerted decomposition of a secondary alkyldiazo-ester to carbocation, nitrogen, and anion, or a two-stage decomposition *via* a diazonium ion of extremely short lifetime.[1] It seemed unlikely that any special property of a six-membered ring could have led to this reaction. More probably it could be considered a consequence of the (B) local conformation,[1] or perhaps specifically of the (BB) conformation, present in an equatorial cyclohexylamine, having one or two C–C bonds antiparallel to the breaking C–N linkage. In that case, a similar secondary ⟶ primary rearrangement should be observable in the deamination of a straight-chain compound. No such result has been reported, to our knowledge, in any of the many such reactions investigated,[11] including the work of Part 12; [1] however, a minor product from a minor conformer would be formed only in small yield and safe identification would require use of pure intermediates and of refined analytical techniques not available at the time of our earlier work.

We chose to look for this process by converting pentan-3-one (presumably made from propionic acid and free from isomers) into 3-*N*-acetylaminopentane, which had m.p. 66—67° and could be thoroughly purified. Nitrosation and acetolysis gave a mixture of acetates, of which the main components were undoubtedly 2- and 3-acetoxypentanes; they were hard to separate, but we did not need to do this. With a large loading and high detector sensitivity another acetate was well separated from the main peaks, observed in yields of *ca.* 0.27% of the total acetates, *i.e.* 0.06% overall. It was shown to be inseparable from, and gave unbroadened peaks on co-injection with, the acetate of 2-methylbutan-1-ol, when two columns working at 6 000 and 22 000 plates were used. This is the acetate we were expecting, the result of migration of a methyl group to the site of charge. In a blank experiment, in which every component except the *N*-nitrosoamide was added, no sign of a peak in this position was seen. In the acetolysis of the nitrosoamide no other C_5 acetate was observed in anything like this yield, although a very small peak at long retention time (*ca.* 0.05% of acetate fraction) may have been 1-pentyl acetate; this was not investigated further, but we note that it could have been formed by a 1 ⟶ 2 shift of hydride in the 2-pentyl cation. In particular, the acetate of 3-methylbutan-1-ol was absent. The

olefinic fraction of the deamination product, probably also containing cyclopropanes, was not examined.

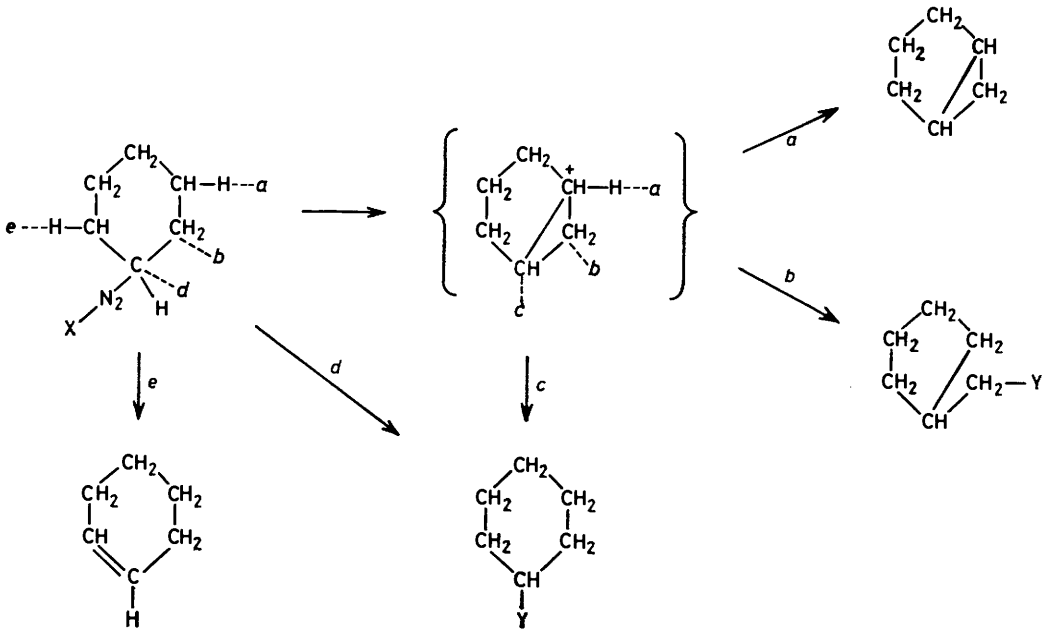
One may ask whether one C–C linkage antiparallel to the leaving group [local conformation (B)] suffices to induce secondary ⟶ primary rearrangement in acyclic carbonium ions, or whether two, as in equatorial cyclohexylamine or (potentially, in an energy-rich conformer) in 3-pentylamine, are needed. We therefore subjected 2-butylamine to the same set of reactions, with the difference that as its acetyl derivative was a liquid, we purified the amine *via* its crystalline benzoyl derivative, hydrolysed with potassium hydroxide solution. The 2-methylpropyl acetate sought was obtained as 0.24% of the acetate fraction, inseparable from an authentic specimen on two columns of 6 000 and 20 000 plates. Evidently one (B) conformation does suffice, and a C–H group antiparallel to the departing nitrogen molecule, and necessarily present in the adjacent methyl group, does not inhibit alkyl shift. Again, a very small yield of 1-butyl acetate was probably present.

All these deamination reactions involve 'hot carbonium ions'; would similar secondary ⟶ primary rearrangements be observed, albeit in smaller yield, in arenesulphonate solvolysis? In the 'contrathermodynamic' rearrangement of 2-adamantyl to protoadamantyl derivatives this is the case.[12] Furthermore, cyclopentylmethyl toluenesulphonate has been shown to give *ca.* 37% of ring-expanded products.[13] Bartlett *et al.* had shown that substantial amounts of primary solvolysis products are not formed from cyclohexyl precursors, but did not rule out small yields.[13b] Accordingly, recrystallised cyclohexyl toluenesulphonate (50 g) was acetolysed in the presence of potassium acetate for 16 half-lives. The main product was cyclohexene, but the acetate fraction (11.5%) was isolated and found, in careful g.l.c., to give a shoulder on the cyclohexyl acetate peak which agreed in position with that of cyclopentylmethyl acetate, using three different stationary phases at 10 000—34 000 plates, and corresponded to 0.03% of the substitution product (0.0035% yield). Cyclopentylmethyl toluenesulphonate is unreactive [13] and might have been formed by ion-pair return: we therefore isolated the unreacted toluenesulphonate, presumably containing <1 mg of starting material, and examined its acetolysis kinetically. The content of primary toluenesulphonate was estimated at <0.003% of the starting material, and quite possibly zero. The minute yield of primary acetate was probably real, but this cannot be asserted with the same confidence justified by the relatively large yields observed in the deamination reactions.

We turn now to the significance of these results in the general theory of rearrangements *via* electron-deficient intermediates, first showing that the Whitmore scheme is inapplicable. In the *trans*-4-t-butylcyclohexyl cases, all yields are known; in one example the cyclohexane-skeleton products (ΣA) sum to 95.3%, the primary esters (ΣB) sum to 2.4%, and the bicyclo[3.1.0]hexane to 1.95% (this may or may not be added to ΣB). Thus $\Sigma A/\Sigma B = 20$ or 38. If we know k_A and k_{AB}/k_{BA} we can calculate a minimum value for k_B. Lifetimes of carbonium ions are hard to measure, but Winstein,[14] aiming at a maximum value for the sake of his argument, deduced 10^{-10}—10^{-9} s for 2-norbornyl$^+$ (which he considered unusually stable) in typical solvents. For the equilibrium constant between primary and secondary cations we use the 73.5 kJ mol^{-1} activation energy (n.m.r. kinetics) for proton scrambling in 2-propyl$^+$, interpreted [15] as the 1-propyl$^+$/2-propyl$^+$ enthalpy difference plus the small activation energy for the exothermal 1-propyl$^+$ ⟶ 2-propyl$^+$ reaction. The latter must be smaller than that for the thermoneutral 2-butyl$^+$ ⇌ 3-butyl$^+$ rearrangement. For this, a maximal estimate of 3.5 ± 3.0 kJ mol^{-1} can be deduced from the 68.5 ± 0.8 kJ mol^{-1} activation energy (n.m.r. kinetics) [16] for the 2-methyl-2-butyl$^+$ ⇌ 3-methyl-3-butyl$^+$ scrambling process (secondary—tertiary enthalpy difference plus secondary$^+$—secondary$^+$ methyl shift activation energy, likely to exceed that of the hydride shift) and the calorimetric measurement [17] of the 2-butyl$^+$ ⟶ 2-methyl-2-propyl$^+$ rearrangement, 65.0 ± 2.2 kJ mol^{-1}. As a further check, the interconversion by 1,2-hydride shift of tertiary carbonium ions, surely the slowest type of symmetrical interconversions, has an activation energy of <17 kJ mol^{-1}.[18] From all these figures, we take a minimum enthalpy difference between secondary and primary cations to be 54 kJ mol^{-1}, and, although higher estimates can be defended,[18] a maximum of 69 kJ mol^{-1}. Neglecting an unimportant entropy term, these values lead to $10^{9.5}$ and $10^{11.7}$ for the equilibrium constant at room temperature, and 10^{-17}—$10^{-19.4}$ s as the lifetime of the cyclopentylmethyl$^+$ cation, when fitting our product ratio to the Whitmore scheme. The vibrational period of a C–O bond, 1 000 cm^{-1}, is 3×10^{-13} s; to force our data into the Whitmore scheme, assuming the collapse of a pre-formed encounter-complex at this rate, one would have to raise the assumed lifetime of a secondary carbonium ion to *ca.* 10^{-4} s, a quite impossible value. This argument was advanced before,[12] but there we used a rate of collapse based on the assumption that reaction between the hypothetical less stable cation (B)$^+$ and solvent occurs at encounter rate, a contention that could be disputed if it were a preformed encounter complex that collapsed. It can, of course, also be applied to the familiar cyclobutyl$^+$ ⇌ cyclopropylmethyl$^+$ system. However, there might be reservations about the lifetime of such species as cyclopropylmethyl$^+$ or protoadamantyl$^+$, which for electronic or steric reasons might be atypical. No such evasions of the argument are possible for the simple cations which are now shown to behave in the same way.

A convincing framework for discussions of the behaviour of simple secondary carbonium ions in common solvents emerges from the recent work of Kirby *et al.*[19] and of Knier and Jencks [20] on methoxymethyl$^+$ in water. This species should have a lifetime of *ca.* 10^{-15} s. It therefore cannot be formed in a process cleanly separable from its subsequent reaction; instead 'pre-association'

with a nucleophile is needed. With modifications this picture could well be applicable to secondary alkyl cations, whose lifetime in alcohol or acetic acid might well be nearer 10^{-15} s than to Winstein's conservative 10^{-9}—10^{-10} s (see following paper). As well as substitution, β-elimination of a proton must now be considered, presumably a bimolecular process involving a syn- or anti-coplanar nucleophile. But migration of an anticoplanar proton or alkyl group, giving a similarly incipient isomeric carbonium ion with which a nucleophile is in a proper ' pre-association ', is also possible. Much



SCHEME 2

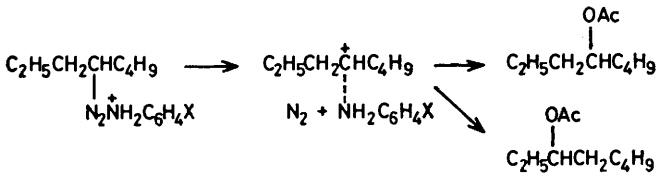
of this picture has been outlined long ago, *inter alia* by Gregoriou [21] and by one of us,[22] and necessarily follows once it is agreed that an Ingoldian S_N1 reaction *via* progressively less stable intermediates must lose the clear separation of rate-determining and product-determining stages. What is new is the demonstration [19,20] of second-order kinetics with extremely small sensitivity of rate to nucleophilic power. After all, the alkyl group that migrates in, *e.g.*, cyclohexyl$^+$ is permanently preassociated with the leaving group. Sophisticated *ab initio* calculations [23] show that propyl$^+$ is unstable with respect to corner-protonated cyclopropane. Experimentally, corner-protonated methylcyclopropane has been implicated [14] in the proton-scrambling of 2-butyl$^+$. We may thus reasonably picture the deamination of equatorial cyclohexylamine by Scheme 2.

Here the precursor reacts only when a nucleophile Y^- in one of the positions *a*—*e* satisfies the geometrical requirements of ' pre-association ', the reaction proceeding through an intermediate having considerable cationic character (for simplicity we omit the similar processes of β-hydride shift, leading to rearranged substitution and elimination products). If, of processes *c* and *d*, only *d* is allowed, it must be permissible in both retention and inversion modes. Indeed, preferred substitution with retention of configuration in non-classical 2-adamantyl$^+$ has been proposed,[24] and is found in the solvolysis of glucose derivatives.[25] We have argued [26] that near-zero entropies of activation in the acetolysis of secondary substrates, combined with evidence of nucleophilic assistance, imply a spatially undemanding form of interaction between nucleophilic and electrophilic centres, which is insensitive to steric hindrance. Plainly, Kirby–Jencks ' pre-association ' may differ considerably from the tight association typical of true S_N2 and E_2 transition states. What remains to be decided is whether the differences are of kind or merely of degree.

We are now in a position to explain the extraordinary ability of the *para*-substituent in an arylamine present in the transition state for the formation of octyl acetates and octenes from N^1-4-octyl-N^3-*p*-substituted aryltriazenes to influence in a rational manner the ratio of rearranged to unrearranged products (Scheme 3).[1,22] Evidently the electron pair of the arylamine, the availability of which is modulated by its *para*-substituent, diminishes to a variable extent the electron deficiency at the cationic centre, and therefore its likelihood of undergoing thermoneutral hydride shift before collapse. This is true for substitution both with retention and inversion.[7]

The addition of acetic acid to bicyclo[3.1.0]hexane, catalysed by toluenesulphonic acid, has been reported by LaLonde and Forney [27] to give *cis*- (11%) and *trans*-2-methylcyclopentyl acetate (68%), plus 1% 1-methylcyclopentyl acetate and 20% cyclohexyl acetate. Repetition and analysis by g.l.c. confirmed these results and the absence of cyclopentylmethyl acetate.

Similarly, compound ' Z ' was absent from the ring-opening products of the t-butyl analogue. Thus, protonation of a bicyclo[3.1.0]hexane involved the methylene, not the methine, groups of the cyclopropane ring, and collapse to products is faster than isomerisation *via* edge-protonated cyclopropanes, a result in good accord with calculations.[23]



SCHEME 3

The ratios of the rearranged and unrearranged substitution products in deamination and toluenesulphonate acetolysis are 0.95 and 0.02—0.03 in the cyclohexane series, a ratio of *ca.* 40. In the corresponding reactions in the 2-adamantyl system they were 9.4% and 0.4—0.5%, a ratio of *ca.* 20. Secondary alkylamine derivatives give *ca.* 0.25% of rearrangement products on deamination; we might therefore expect that secondary alkyl arenesulphonates would give *ca.* 0.25/30 = *ca.* 0.01% of primary acetate on hydrolysis, a quantity not easily identified. Variations in the ratio from one system to another are to be expected, notably on conformational grounds; 4-*trans*-t-butylcyclohexylamine derivatives presumably react mainly *via* the equatorial chair conformers, whereas the arenesulphonates probably react mainly *via* non-chair forms.[28] In all these cases, however, what is being observed is, in its essence, the same phenomenon as in allylic systems or in the cyclobutyl–cyclopropylcarbinyl system; the formation of a product mixture nearer to statistical expectations than to predictions based on prior equilibration of separate intermediates. Such results have been adduced as supporting the intervention of ' non-classical carbonium ions '. We have suggested that, just as in one set of metaphors [21] reacting systems avoid ever forming carbonium ions, and in another [22] intermediates whose lifetimes are measured in picoseconds have unfamiliar properties (but can be considered to exist), so we may regard almost all simple secondary carbonium ions, insofar as they exist at all, as sharing in much reduced degree the peculiarities of norbornyl, *etc.* This only reinforces the need to explain any unusual behaviour of norbornyl systems (stereochemistry of substitution, *etc.*) on other grounds, such as steric peculiarities; σ-delocalisation is the norm, and not the exception, during the fraction of a nano-second such intermediates exist in alcohol or acetic acid. In ' limiting ' solvents such as hexfluoroisopropanol, one could of course expect a more perfect degree of formation, and a lifetime allowing definable properties. It is only in these solvents that the familiar sequence of covalent molecule, intimate ion-pair, solvent-separated ion-pair, and separate ions can be applied to simple systems with some chance of accuracy; in alcohol, acetic acid, *etc.* the Kirby–Jencks description is surely more appropriate. For tertiary ions, phenonium ions, *etc.*, Winstein's descriptions may well apply to the common solvents.

The work now reported has been published in brief.[29]

EXPERIMENTAL

Acetic acid was purified by refluxing with tetra-acetyldiborate, followed by distillation. In all experiments with nitrosoamides, precautions were taken against accidental ingestion.

trans-3-t-*Butylcyclopentylmethyl Acetate* (*Compound* '*Z*').[7]—When *trans*-4-t-butyl-*N*-nitroso-*N*-acetylcyclohexylamine was added to glacial acetic acid containing 0.15M-potassium acetate at 25° and the mixture allowed to stand for 24 h, isolation of the reaction products gave a product containing t-butylcyclohexenes, a mixture of t-butylcyclohexyl acetates, and compound ' Z ' (4% of total acetates). By g.l.c.–mass spectrometry this was shown to be another isomer $C_{12}H_{22}O_2$. Partial hydrolysis with aqueous ethylamine showed this peak to be more rapidly reduced in area than those of the t-butylcyclohexyl acetates, but the alcohol formed had a retention time too near to those of the *cis*- and *trans*-4-t-butylcyclohexanols for preparative separation. Attempts to separate the mixture by column chromatography gave only a 10% concentrate, oxidised by chromic acid to a product containing an impure liquid acid fraction. Attempts to prepare a trityl ether were also unsuccessful.

cis-3-t-Butylcyclopentanecarboxylic acid was prepared (2.3 g, 53%) by the method of Granger *et al.*[9] from 4-t-butylcyclohexanone (4 g) and had the expected i.r. and n.m.r. spectra.

trans-3-t-Butylcyclopentanecarboxylic acid was prepared from 3-t-butylcyclohexanone (2.93 g) by the same method; yield 710 mg (21%) before, 460 mg (13.5%) after distillation at 9 mmHg. It had the expected i.r. spectrum, but its n.m.r. spectrum showed two signals, δ 0.93 and 1.00, for the t-butyl group.

Each of the above acids was converted into the methyl ester; the *cis*-isomer had the expected i.r. and n.m.r. spectra (t-butyl at δ 0.90) and gave a single peak, retention time R_t 51.2 min, on a SCOT MBM column at 120°. The *trans*-isomer showed the expected i.r. spectrum but again two signals, δ 0.86, 0.89 for t-butyl in the n.m.r. (ratio *ca.* 2 : 1). On g.l.c. it gave a main peak at R_t 50.9 min, just perceptibly broadened on co-injection with the *cis*-isomer, and minor peaks (10% of the total). Each ester was reduced with lithium aluminium hydride in ether, excess being destroyed with ethyl acetate, followed by sodium hydroxide solution. Notwithstanding these precautions against acid-catalysed rearrangement, the *cis*-alcohol contained, by g.l.c., small amounts of *cis*- and *trans*-4-t-butylcyclohexanols when subjected to g.l.c., plus a sharp main peak; the *trans*-isomer gave >90% a single compound on g.l.c. Clearly neither was pure, but each was free from the other, and g.l.c. comparison with ' Z alcohol ' was satisfactory.

The alcohols obtained from a deamination reaction followed by hydrolysis (NaOH–MeOH) gave peaks for *cis*-4-t-butylcyclohexanol (38 min; half-height peak-width 5 mm at the recorder chart speed used), Z-alcohol (40.7 min, 6 mm), and (much larger) *trans*-4-t-butylcyclohexanol (46.2 min, 6.5 mm). Successive additions of *trans*-3-t-butylcyclopentylmethanol increased the height of the

central peak, all three peak widths remaining constant. Successive additions of *cis*-3-t-butylcyclopentylmethanol increased the width of the central peak to 8.5 and 7.5 mm, its shape being visibly unsymmetrical: initially a shoulder appeared at the short-time side of the 40.7 min peak, then became the main maximum, with a shoulder on the long-time side, finally obscuring the original ' Z-alcohol ' peak, the retention time moving to 40.1 min. All this time, the two reference peaks remained constant in time (±0.2 min) and width (±0.25 mm.). Admixture of the rationally synthesised *cis*- and *trans*-3-t-butylcyclopentylmethanol specimens similarly increased the half-height peak-width from 6 mm to 8 mm. These experiments were carried out in unbroken succession, after the apparatus had stabilised and without touching controls.

Cyclopentanecarboxylic acid was prepared from cyclohexanone (4 g) and thallium nitrate trihydrate (18 g) in acetic acid.[29] Isolation of the acidic fraction gave the desired acid (2 g, 45%). The corresponding methyl ester (methanol and sulphuric acid) was reduced with lithium aluminium hydride in ether followed by saturated aqueous sodium sulphate, giving cyclopentylmethanol, converted by acetic anhydride and pyridine into its acetate. All these compounds had the expected i.r. and n.m.r. spectra, and the acetate gave a single g.l.c. peak.

Cyclohexylacetamide was prepared from commercial cyclohexylamine (excess) and acetic anhydride, and had m.p. 105.5—107° (lit.,[30] 107°). Nitrosation and solvolysis were carried out as described below for the 3-pentyl derivative; cyclohexyl and cyclopentylmethyl acetates were easily separated, and the latter proved to be identical with the specimen prepared as above, using both MBM and Apiezon L, at 125 and 70°, respectively (27 000 and 22 000 plates, capable of resolving compounds with a 1% difference in retention time). The yield of the primary acetate was measured (two injections of one deamination mixture) as 0.94 and 0.96%.

3-Pentylamine hydrochloride was prepared by reduction of the steam-distilled oxime of pentan-3-one [31] (22.5 g) in magnesium-dried methanol (250 cm³) with sodium (45 g), with cooling externally and by a reflux condenser. When the reaction ceased, methanol (100 cm³) was added to remove the remaining sodium, followed by water (100 cm³); the mixture was distilled, the distillate passing directly into a mixture of constant boiling hydrochloric acid (25 cm³) and water (25 cm³). Removal of water, methanol, and hydrochloric acid *in vacuo* gave the amine hydrochloride (7.6 g), evidently a hydrate since it had m.p. 125—160°.

3-N-*Acetylaminopentane*.—The above hydrated hydrochloride (2.5 g) was added to solid potassium hydroxide (3 g) in a stoppered test-tube, when an exothermal reaction occurred. The test-tube was connected to a second test-tube cooled to −70°, the pressure was reduced to 0.05 mmHg, and the first tube was warmed to 50°. Anhydrous potassium carbonate was added to the contents of the cooled tube, and the fairly pure amine (1.8 g) was removed by pipette and at once treated with acetic anhydride (2.0 g) and triethylamine (2.1 g; dried over 4 Å molecular sieve and redistilled). 10% Potassium carbonate solution was added, and the mixture was extracted continuously with ether for 24 h. Evaporation of the ether and sublimation gave the amide (2.0 g), which after three recrystallisations from light petroleum (b.p. 40—60°) had m.p. 66—67° (lit.,[30] 66°).

3-N-*Nitroso*-N-*acetylaminopentane and its Acetolysis*.—A solution of dinitrogen tetroxide (17 cm³) in methylene dichloride (85 cm³) was prepared at −25°. To fused sodium acetate (1 g) 10 cm³ of this solution was added at −70° with magnetic stirring, followed by the amide (250 mg), a nitrogen atmosphere being maintained. The temperature was allowed to rise to 0° during 1 h; after 30 min at 0° water (10 cm³) was added, the layers were separated and the aqueous phase was extracted with methylene dichloride (3 × 5 cm³). The combined extracts were washed with water, then potassium carbonate solution, dried ($MgSO_4$) and made up to 50 cm³ for spectroscopic assay, using the peaks of equal intensity with the assumption of ε 96.0, at 410 and 430 nm (determined in CH_2Cl_2 for *trans*-4-t-butyl-*N*-nitroso-*N*-acetylaminocyclohexane). Yields varied and were usually 50—65%. The methylene dichloride was removed *in vacuo* below room temperature, leaving a yellow oil which was at once treated with dry acetic acid (3.5 cm³). After 48 h at 25°, the solvolysis was >99.97% complete. Cyclohexane (3.5 cm³), purified by passage through silica gel, was added, followed by a solution (25 cm³) prepared from dipotassium hydrogenphosphate (400 g), potassium hydroxide (134 g), and water (400 cm³). After shaking, the cyclohexane layer was washed with 10 cm³ portions of water, sulphuric acid (1M) and water, dried over $MgSO_4$, and stored at 0°. G.l.c. (Carbowax 1540; 80°; 6 000 plates; MBM, 100°; 20 000 plates) showed it to contain a major fraction, partly separated, of 2- and 3-pentyl acetates, plus a minor component inseparable on both phases from 2-methylbutyl acetate. The deamination was carried out twice, and each deamination product was injected twice on the MBM column. Peaks were measured planimetrically several times, after recording with appropriate changes in signal attenuation, and the minor isomer was found to constitute in area (0.258 ± 0.009)% and (0.269 ± 0.010)% (first deamination), (0.277 ± 0.033)% and (0.279 ± 0.023)% (second deamination) of the main, double peak. Molar response factors were assumed to be the same for isomeric compounds, and the yield is quoted as 0.27% of the acetate fraction, believed (on the basis of work described earlier [1]) to be a *ca.* 25—30% yield. The only other, minor, peak, at long retention time, corresponded to 1-pentyl acetate (>0.05% of acetate fraction); the acetates of 3-methylbutan-1-ol, 3-methylbutan-2-ol, 2-methylbutan-2-ol, and 2,2-dimethylpropan-1-ol were all shown to be present, if at all, in much less than this amount.

A blank deamination, carried out with the omission of the amide from the nitrosation step but otherwise similar to the above experiment, gave no observable peaks in the relevant region of the chromatogram.

N-2-Butylbenzamide was prepared from redistilled 2-butylamine (10 g) and benzoyl chloride (9.6 g) in ether (100 cm³). The neutral fraction was isolated and recrystallised from aqueous ethanol, giving the *amide* (9.5 g), m.p. 84.5—85° (Found: C, 74.05; H, 8.7; N, 7.55. $C_{11}H_{15}NO$ requires C, 74.55; H, 8.55; N, 7.9%), with the expected i.r. and n.m.r. spectra. An early report [32] gives m.p. 75—76°, possibly a misprint or a lower-melting polymorph.

The amide was added to glycerol (50 cm³) and potassium hydroxide (3.2 g) and heated to 230° in a slow stream of nitrogen, which was passed into a cold trap (below 0°); only 0.3 g of amine was recovered, possibly through inadequate cooling. Acetic anhydride and triethylamine were added, and the neutral amide (305 mg) was isolated, as described for the higher homologue. Nitrosation gave

the *N*-nitroso-derivative (42%), which was immediately added to acetic acid. G.l.c. on MBM (90°) and Carbowax 1540 (60°) gave a main peak for 2-butyl acetate and a minor peak, inseparable on both columns from 2-methyl-1-propyl acetate (0.206 ± 0.002)% and (0.273 ± 0.003)% of the main peak. 1-Butyl acetate was also probably present (<0.04%), but 2-methyl-2-propyl acetate was absent; however, there were unidentified peaks of about the same size as the 2-methylpropyl acetate peak.

*Solvolysis of Cyclohexyl Toluene-*p*-sulphonate.*—The ester, m.p. 43—44° after recrystallisation (50 g), acetic acid (500 cm^3) and potassium acetate (20 g) were heated to 68.5° for 65 h (16 half-lives, neglecting the catalytic effect of potassium toluenesulphonate). Isolation of the neutral fraction and distillation gave the acetate fraction (3 g, *ca.* 11%), b.p. 63° at 12 mmHg. G.l.c. on squalane and on diethylene glycol succinate gave symmetrical peaks, but on Carbowax 1 540 at 110° (24 000 plates), MBM at 140° (34 000 plates), and Apiezon L at 70° (10 000 plates) a minute shoulder could be seen (retention times of main peak and shoulder 17.5, 19.0; 9.0, 9.4; and 44.0, 48.0 min). In every case, authentic cyclopentylmethyl acetate gave a peak at the same retention time as the shoulder, but this was so small (0.02—0.03% of the main peak) that the precise measurements of peak width on admixture possible in other cases described above could not be attempted, hence the use of three phases at high resolution.

Any cyclopentylmethyl toluene-*p*-sulphonate that might have been formed by ion-pair return would have largely survived the solvolysis, in view of the published rate constant.[13] The distillation residue was therefore extracted with light petroleum and ether. Evaporation gave a residue, the n.m.r. spectrum of which agreed neither with cyclohexyl nor cyclopentylmethyl toluenesulphonate, but which did give a typical toluenesulphonate-like u.v. spectrum. It was passed down a short alumina column to remove coloured material, then subjected to acetolysis at 75° for 120 h, one half-life for the primary toluenesulphonate; from a plot of the optical density against time, a maximum yield of 0.003% was calculated (minimum zero). Most of the absorption was unchanged, and is attributed to phenyl toluenesulphonate, from a trace of phenol in the original cyclohexanol.

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