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CONFORMATIONAL ANALYSIS BY KINETIC METHODS: A CRITIQUE

THEORY AND EXPERIMENTAL DEVELOPMENT OF PROCEDURES BASED ON VERY FAST CHEMICAL REACTIONS

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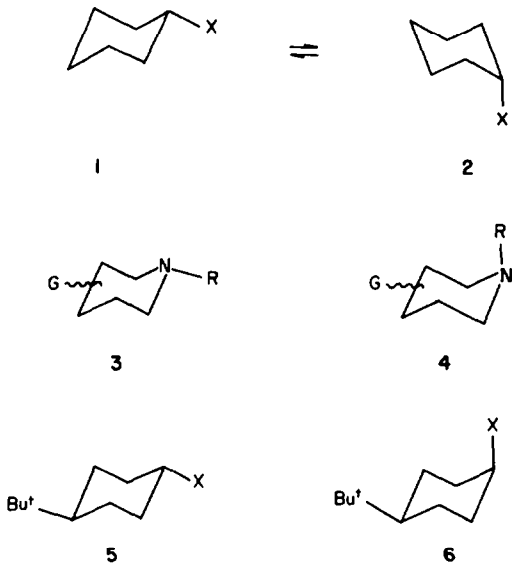
Abstract—Two general methods of conformational analysis by kinetic methods are distinguished, and some definitive experiments are described concerning the validity of the reactivity-model method as employed for cyclohexanes. The fast chemical reaction method is analysed in detail, and potential applications to conformational equilibria of N-alkylpiperidines are discussed. The selectivity of electrophilic addition of some photogenerated carbenes and nitrenes to organic sulphides is examined.

INTRODUCTION

Two variants may be distinguished for conformational analysis by kinetic methods. The first, employed for many years with cyclohexane derivatives,[1] is based on the use of reactivity models, which are relatively inflexible molecules with fuctional groups in well defined steric orientations. The rate-constants for reactions of these models are compared with the weighted-average rate constants for the conformationally mobile system, such as a monsubstituted cyclohexane $1 \rightleftharpoons 2$. Some criticisms[2] have been made regarding the use of this method for cyclohexanes, and we describe briefly two series of experiments designed to provide as direct a test as possible of its practical validity in this area.

The foregoing procedure is of little value for the conformational analysis of N-alkylpiperidines and related tertiary bases where the conformers are interconverted by stereochemical inversion at nitrogen, for example as in the system $3 \rightleftharpoons 4$, where G is a conformation-biasing group for the ring such as a 4-t-butyl group. We discuss the problems arising in such attempted applications.

An alternative variant of the kinetic method of conformational analysis may be termed[3] the method of fast chemical reactions. It has been little discussed or used so far, and indeed the basic principles have apparently not previously been set out in detail. We do so here, and outline earlier applications, including one[4] involving fast proton transfer which has been employed in the quantitative conformational analysis of piperidine systems such as $3 \rightleftharpoons 4$ and analogous secondary base equilibria. Use of highly active electrophiles other than strong proton acids as stereochemical probes



1 2 3 4 5 6

for the conformationally mobile amines may well have certain advantages, which are outlined. We analyse the required reaction characteristics of such probes, and describe progress in our evaluation of some photochemically generated carbonium ions, carbenes, and nitrenes (or equivalent reactive species). Very marked variations in the stereoselectivity of electrophilic additions of the carbenes and the nitrenes have been observed,[5] a result which has a considerable bearing on their relative potential utility for the intended purpose.

Conformational analysis of cyclohexane derivatives by the standard kinetic method. The funda-

mental equation underlying the standard procedure is

$$k_{overall} = k_1 N_1 + k_2 N_2 + \ldots \quad (1)$$

where $k_{overall}$ is the rate-constant for the chosen reaction of the conformationally mobile compound, k_1, $k_2 \ldots$ the rate constants for the individual conformers, and N_1, $N_2 \ldots$ the fractions of these at equilibrium; hence

$$N_1 + N_2 + \ldots = 1 \quad (2)$$

For the relatively slow reactions used in the standard procedure (case 1, p. 1557; Curtin–Hammett conditions) the conformer ratio is constant during the reaction and equal to the equilibrium value.

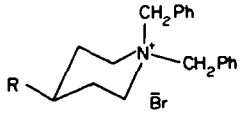
In work with cyclohexanes equilibria **1** ⇌ **2** are under investigation, and k_{eq}, k_{ax} are taken to correspond to the appropriate rate constants for the conformationally biased analogues **5** and **6**. The conformation-locking group in such compounds is significantly remote from the reaction centre X. From $k_{overall}$ (for the compound **1** ⇌ **2**), k_{eq}, and k_{ax} it is possible readily to drive N_{eq} and N_{ax}, and hence $K = N_{eq}/N_{ax}$.

This analysis has been widely applied,[1] and the results generally accord very well with those obtained by a variety of other physical methods. Furthermore, X-ray crystallographic and some NMR spectroscopic results[6] indicate that there is little molecular distortion in the neighbourhood of the reactive group X associated with introduction of the 4-t-butyl group in the models **5** and **6**. However, the theoretical basis and practical utility of this kinetic method have from time to time been queried,[2] particularly when the reaction involves the ring carbon atom to which X is attached. We may summarise our own views on the theoretical drawbacks as follows. The mobile system **1** ⇌ **2** can undergo chair ⇌ non-chair ⇌ alternative chair conformational inversions, while the models **5** and **6** can not. Hence the more remote areas of the reaction surfaces for a mobile conformer and its model, reached in higher vibrational states, are certain to be different in each case, and this result could lead to corresponding differences in activation entropies and in the thermal-energy content of the activation enthalpies, even if the potential-energy content of the activation enthalpies were the same. The effect (if observable) of a 4-t-butyl group on a rate constant for a reaction at X would thus be more marked at increased temperatures, and also for greater structural differences between reactants and corresponding transition states. The major problem in checking experimentally for such effects, or indeed in checking if **1** and **5** have the same rate-constant in the chosen reaction, likewise **2** and **6**, is of course that one can hardly perform kinetic experiments with the separate mobile conformers **1** and **2**, for comparison of the results with those obtained from corresponding experiments on the models.

We decided to circumvent this problem by the use of geminal pairs of reactive groups. We examined[7] the *combined* reactivities of the geminal 1-benzyl groups in the reaction of the piperidinium salts **7** with sodium thiophenoxide. This process leads of course, by nucleophilic displacement at the benzyl methylene groups, to the N-benzyl base and benzyl phenyl thioether, and it could be regarded as providing a model for reactions of cyclohexyl systems in which the ring atom carrying the reactive substituent becomes involved. For the more crucial analogous test of the validity of the kinetic method with reactions of cyclohexyl derivatives *not* involving the ring carbon we felt that it was necessary to use geminal substituted cyclohexanes rather than heterocyclic analogues. We accordingly studied[8] exchange of the ester ethoxy groups in the ^{14}C labelled (asterisked) cyclic malonic esters **8** with ethanolic sodium ethoxide. In the conformationally biased esters (R≠H) two separate reactions with (presumably) different rate constants are involved, and each ester molecule undergoes *both* reactions. To simplify the kinetic examination we therefore measured the *initial* rates of loss of radiocarbon for each diester as an indication of summed reactivity of the axial plus equatorial ester groups. To provide a more extended basis for comparisons, the effects of a range of 4-substituents (Me, Bu^t, Ph) were studied in the reactions of both geminate systems.

Of course, it could be argued that the device of using geminal substitution to provide a method of studying the effects of 4-substituents on summed axial plus equatorial reactivity of substituents at position 1 itself introduces a further perturbation of the reaction surface. Such a perturbation, however, is more evenly applied to both mobile conformer and model than is that associated with the 4-t-butyl group, which of course affects only the model.

The results of our experiments (Table 1) show



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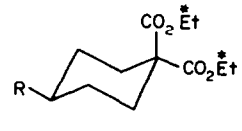

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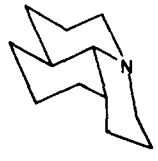

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Table 1. Relative rate-constants for decomposition of 4-substituted-1-benzylpiperidine benzobromides (7) with sodium thiophenate in diethylene glycol at 60·5°, and relative initial rates for ethoxy exchange with 4-substituted diethylcyclohexane-1,1-dicarboxylates (8) in 0·091-M ethanolic sodium ethoxide at 9°

4-Substituent	H	Me	Bu^t	Ph
Relative k (thiophenate displacement)	1·00	1·40	2·40	3·15
Relative initial rate (ester exchange)	1·0	1·0	1·0	1·6

marked effects from all the 4-substituents (but especially from t-butyl and phenyl) in the thiophenate displacement reactions. More significantly, within the precision limits of the technically quite difficult ester-exchange rate study, neither 4-alkyl group had a measurable effect on the combined initial reaction rates despite the theoretical possibilities discussed above), but the more polar 4-phenyl group did. *We believe that this work provides the most direct experimental evidence available to date on the lack of interference of a conformation-holding 4-t-butyl group on the rate constants of reactions at axial or equatorial 1-substituents in cyclohexane derivatives not involving the ring atom,* and our results hapilly confirm the similar conclusion[1] reached indirectly by the leading workers in this field during the past two decades.

Drawbacks of the standard kinetic method for the conformational analysis of N-*alkylpiperidines* (*e.g.*, 3 ⇌ 4) *and related systems.* In principle the method as used for cyclohexanes (*e.g.*, 1 ⇌ 2) might also be applied to the mobile tertiary base systems, if suitable reactivity models say for 3 and 4 could be devised. The reaction employed might involve the nitrogen atom, for example by alkylation to give a quaternary salt (mixture), or it might otherwise involve the exocyclic group as in the case of cyclohexane derivatives. The chief problem lies in devising suitable reactivity models for conformers such as 3 and 4 in which the exocyclic group is held in a definite equatorial or axial orientation but in which appropriate reactivities are not appreciably altered. A conformational lock for the exocyclic group *remote* from the reaction centre, such as the 4-t-butyl group for 1-substituted cyclohexanes, does not seem possible here (although such a group may *additionally* be employed in piperidines just as in cyclohexanes to bias the ring conformation).

Presumably for the above reason the standard kinetic method has not been used in full quantitative analyses for the piperidine conformers, but a relatively crude partial usage was once attempted.[9] The product ratio P (P > 1) in a tertiary piperidine quaternisation is given by

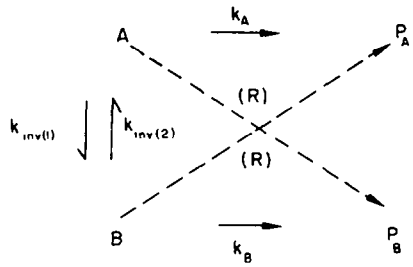
$$P = k_a N_e / k_e N_a \text{ or } k_a N_a / k_a N_e \qquad (3)$$

depending on whether there is a preference for axial or equatorial quaternisation. Combination of Eqs 3 and 1, with k_a and k_e for k_1 and k_2, gives two pairs of simultaneous equations which with an input of $k_{overall}$ (measured), N_a and N_e (considered known) can be solved for unknowns k_a and k_e, the rate constants for axial quaternisation of the N-equatorial conformer 3 and equatorial quaternisation of the N-axial conformer 4 respectively. Two sets of possible values for these rate constants were obtained, from which a choice had to be made partly on the basis of internal consistency and partly from comparison with rate constants for models such as 9 or 10. Hence the preferred direction of quaternisation could hopefully be deduced. This attempted method failed partly because, as we pointed out,[10] the relatively rigid models would be expected to give quite unsatisfactory representations of the reactivity of more flexible conformers such as 3 or 4. We suggested that the projected method be abandoned, and that, since the stereochemical preference for quaternisations in a large range of tertiary piperidines has in any case been well established by other methods, equations 1 and 3 should be used merely for cross-correlation work at a secondary level. Both suggestions have now been accepted.[11,12]

The fast chemical reaction method of measuring conformational equilibrium constants. We now turn to the alternative kinetic approach which does offer possibilities for analysis of mixtures of tertiary piperidine conformers. In the past it has been appreciated[3,4,13] that if a mixture of conformers reacted very rapidly to give a mixture of products separately related to the individual conformers, then the product ratio could equal the conformer ratio if the reaction rate-constants were greater than the conformer-inversion rate-constants. A more detailed analysis is desirable, and is now given for conformers A ⇌ B reacting with a reagent R or intramolecularly (no R) to give products P_A, P_B (see Scheme 1). We can distinguish five cases:

(1) Intermolecular reaction (with R); $k_{inv.\,(1)}$, $k_{inv\,(2)} \gg k_A[R]$, $k_B[R]$ primarily because of relatively small values of k_A, k_B. Conclusion: product ratio P = conformer ratio K only if adventitiously $k_A = k_B$; otherwise $P \neq K$ (usual result).

(2) Intermolecular reaction; excess of highly reactive R produced suddenly, e.g., in flash-photolysis experiment; total time for formation of



SCHEME 1

R and its (essentially complete) reaction with the conformer mixture $A \rightleftharpoons B \ll 1/k_{inv.\,(1)}, 1/k_{inv\,(2)}$. Conclusion: $P = K$ even if $k_A \neq k_B$.

(3) Intermolecular reaction; highly reactive R produced relatively slowly from appropriate precursor, e.g., in conventional photochemical reactor or thermally, or highly reactive R mixed relatively slowly with $A \rightleftharpoons B$; total period for essentially complete reaction in either case $\gg 1/k_{inv.(1)}, 1/k_{inv.(2)}$; $k_{inv.(1)}, k_{inv.(2)} > k_A[R], k_B[R]$ notwithstanding very high k_A, k_B because of low experimental ranges of [R] (*cf* case 1).
Conclusion: $P = K$ only if there is no kinetic discrimination between A and B. Usually this will imply $k_A = k_B$, but if each phenomenological rate-constant is at the diffusion-controlled limit in the liquid phase there could still be in-cage discrimination leading to $P \neq K$ if the average lifetime of the cage-pairs before reaction was greater than the average conformer lifetimes $1/k_{inv.\,(1)}, 1/k_{inv.\,(2)}$. This will not be the case for the tertiary-base conformers, with lifetimes $\sim 10^{-6}$ sec.

(4) Intramolecular reaction (no R); $k_{inv.\,(1)}, k_{inv\,(2)} \gg k_A, k_B$. Conclusion: as in case 1.

(5) Intramolecular reaction; $k_{inv.(1)}, k_{inv.\,(2)} \ll k_A, k_B$. Conclusion: as in case 2.

Of these five cases, 1 and 4 are well known and will not be discussed further; the remaining three cases involve very fast chemical reactions. Case 2 is an interesting possibility for the flash-photolysis technique particularly since this would permit monitoring the appearance and disappearance of the active reagent R. There might be difficulties, however, in getting sufficient material for product-ratio analysis from flash-photolysis experiments. Case 5 would apply, for example, to mixtures of conformers produced in an electronically excited state, and an interesting such example has recently been described[14] in the literature.

Case 3 covers our own approaches using photogenerated electrophiles described below, and probably also previous work[4] where conformationally mobile bases were mixed in the liquid phase with strong acids (minimum mixing time for two liquids $\sim 10^{-3}$ sec.). Indeed, case 3 is likely to correspond to the commonest applications of the method of fast reactions in conformational analysis.

In cases 1, 3 and 4 the equilibrium conformer ratio $K = N_1/N_2$ will be maintained throughout the reaction, Eq (1), and as appropriate Eq (3) or its equivalent will apply, and the conclusions drawn above are unaffected by competitive chemical reactions of the mixture of conformers.* These statements need not be true, however, for cases 2 and 5; the conclusions for case 5 could also be upset by competitive photophysical processes.

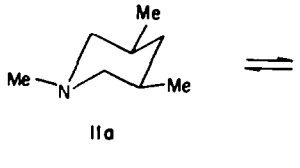
It is extremely interesting that *equality* of rate-constants rather than their *magnitude* is the important criterion here, despite the designation of the general method: speed is merely a (hopeful) prescription for equality. Very high rate constants need not imply equal rate constants, but in the limit of course all reactions are collision—or in solution diffusion-controlled. Since lack of kinetic discrimination by the reagent between conformers rather than high speed *per se* is the fundamental requirement if the experimental conditions of case 3 apply, one may check the suitability of a particular reagent as a conformational probe by doing competitive experiments with mixtures of models between which an unsuitable probe is likely to discriminate more than it will between the conformers. Examples of this approach are given in our own work on photogenerated carbenes and nitrenes described below. Alternatively, one should check if the rate constants *are* at the diffusion-controlled limit, for example by using laser flash-spectroscopy.

"Cross-products", or direct formation from one conformer of the product stereochemically corresponding to the other (dotted arrows in Scheme 1) is a possibility, as we have pointed out,[10] for the intermolecular case 1 but this would not affect the kinetic analysis[10]. Cross-products might also arise in case 3, but a similar result for case 2 seems energetically very improbable on a classical picture. However, for any of the cases the conformer-inversion barrier might also be *tunnelled* by a proton used as a probe say for the conformational equilibria of tertiary bases $3 \rightleftharpoons 4$, and this would lead to cross-products in a different manner which might upset the application of the fast chemical reaction method. Fortunately it is easy to check experimentally for such tunnelling by the parallel use of a deuteron acid; tunnelling by a deutron is very unlikely and by any other reagent virtually impossible.

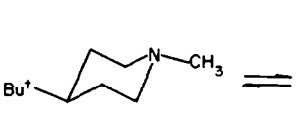
Previous work on conformational analysis of N-alkyl orientations in N-alkylpiperidines. Conflicting results have been obtained by application of a variety of physical methods; for example, in recent work the equator-

*Competitive intermolecular reactions at or near the diffusion-controlled limit would cause a departure from the conditions stated above for the intermolecular cases, and could indeed prevent observation of the reactions of interest.

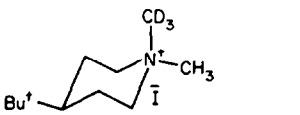
ial: axial ratio for N-methyl is given as 3:1 for 1-methyl-4-phenylpiperidine in benzene or cyclohexane from dipole-moment measurements,[15] and as 16:1 for N-methylpiperidine in carbon tetrachloride from infra-red spectroscopic work.[16] By rapid apparently irreversible protonation of the base **11** with excess of trifluoroacetic acid, and by taking the conformer and product ratios as equal, a ratio of $\geqslant$ 16:1 for [**11a**]:[**11b**] was deduced.[4b] These values for one N-alkyl group seem to differ far more than variation in solvent, ring-substituent, or other conditions would warrant.



11a **11b**



12a **12b**

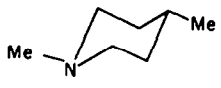


13 **14**

We find[17] that the archtypical 1-methylpiperidine, namely the 4-t-butyl derivative **12**, gives products **13**, **14** in ratio 4:1 on quaternisation with trideuteriomethyl iodide in acetonitrile at room temperature. If the conformers **12a**, **12b** were in the low ratio 3:1 given above (the solvent change is thought[12] to be unimportant), then, from equation 3, k_{ax}: k_{eq} = 1·33:1. Such results (*cf* also Ref 11) seem unusual rather than impossible: the idea of "preferred approach from the less hindered side" is of course inapplicable[18] for such conformationally flexible systems. There does, however, seem to be a need for caution regarding the acceptance of N-methyl conformer ratios of less than ~4:1 in 1-methyl-4-substituted piperidines, although the theoretical expectation[19] that this ratio is likely to be substantially lower than the analogous ratio for methylcyclohexanes ([**1**] : [**2**] ≈ 18:1 for R = Me) seems well founded.

We also have studied[13] product-ratios obtained from protonation of N-alkylpiperidines with excess of trifluoroacetic acid, but we were reluctant to calculate base-conformer ratios from our results because of the possibility of part equilibration of the proton salts *during* the mixing. There have been apparently conflicting experimental observations on this point in the subsequent literature.[3,4b] Apart from this potential serious difficulty, proton (or perhaps better, as stated above, deuteron) acids should make excellent conformational probes for the base-conformer equilibria according to the requirements of case 3 discussed above: proton transfers from strong acid to amines will probably be at the diffusion controlled rate limit.

In our own work we could not determine the appropriate product ratios by NMR spectroscopy when either 4-t-butyl- or 4-phenyl-1-methylpiperidine was rapidly acidified with excess of trifluoroacetic acid, because of overlapping signals. However, when the 1,4-dimethyl base was likewise acidified the ratio of diastereoisomeric proton salts was observed to be 6·5:1. *If* it is assumed that control of protonation was strictly kinetic and the reaction was non-discriminatory, then ([**15**] + [**17**])/([**16**] + [**18**]) = 6·5. An extrapolation from the known[20] equilibrium constant for methylcyclohxane conformers gives [**15**]/[**18**] = [**16**]/[**17**] ≈ 18, and hence it may be calculated that [**15**]/[**16**] = [**18**]/[**17**] ≈ 10, which would accordingly be the value for the N-methyl equatorial: N-methyl axial conformational equilibrium constant in this system. However, we feel that more work on the protonations is necessary to exclude rigidly the possibility of part-equilibration of products, and a major attraction for ourselves in seeking to develop alternative very reactive electrophiles as conformational probes for N-alkylpiperidine systems is that other potentially useful electrophiles react with the bases irreversibly under the conditions employed, leaving one free to concentrate on the (quite stringent!) kinetic requirements.



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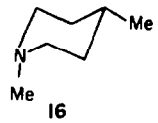

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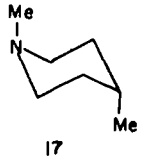

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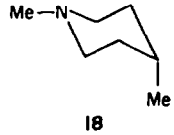

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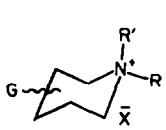

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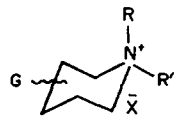

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Variations in transition-state structure in reactions of N-*alkylpiperidines.* Several authors have discussed[11,21] the variation in product ratios **19**:**20** from the quaternisations of piperidines **3** ⇌ **4** with different reagents R′X (or with the same reagent in different solvents) in terms of variable partial N....R′ bond lengths during the reactions. The argument, based on the "Hammond postulate",[22] has been that in faster quaternisations the partial N...R′ bond lengths are longer (more "reactant-like") than in slower quaternisations, and hence the product ratios **19** : **20** from the faster reactions should lie nearer to the conformer ratios [3] : [4]. The underlying intention was not to determine the actual conformer ratios, but rather to help elucidate the configurations of the diastereoisomeric products, and thus the preferred direction of quaternisation. However, since these approaches are seen to be crudely related to the fast chemical-reaction method of conformational analysis, and since in the design of conformational probes we also have had to take into consideration the question of partial bond lengths to nitrogen in the relevant transition states, we give a brief analysis of the general topic at this point.

From the outset[10,23] we have been critical of the attempts to elucidate product configurations along the lines indicated above, partly because of the expected relatively small differences in rate constants for the particular reactions under comparison, and partly because of the inadequate theoretical basis (the Hammond postulate) employed in the analysis. Experimental variations in reactants $R^1R^2R^3N + R^4X$ included changes in steric hindrance to electrophilic attack in the base, changes in the leaving group X, typically halide or aryl sulphonate, and changes in R^4, for example, introduction of electron-attracting or donating groups in the *p*-position when R^4 was benzyl. An analysis of this reaction system by Thorton's method,[24] which leads to anticipated effects of various perturbations on the partial bond lengths, is given in Table 2; perturbations which are the opposite (poorer nucleophile, etc.) of those listed lead to the opposite predictions for changes in bond lengths. It is not possible to discuss the background of this theory in the space abailable here, but we may say that it is far superior to the Hammond postulate approach in that changes in transition-state position on a reaction (hyper) surface *other* than just those along the reaction coordinate are considered; only the latter are of course covered in Hammond's treatment.

It is seen that variation in the nucleophile leads to *no* clear prediction of the direction of the accompanying change in the partial nitrogen to electrophile bond in the transition state for the displacement process. A better leaving group is formally predicted to give a longer such bond, but the observed effect of this on product selectivity may easily be offset by variation in solvation around the different developing leaving groups, and the influence this may have on axial *vs* equatorial quaternisation preferences. Such considerations may explain the somewhat remarkable results we observed[25] when some N-alkylpiperidines were quaternised with both trialkyloxonium salts and alkyl iodides (Table 3). Contrary to the then standard predictions, the faster oxonium-salt alkylations gave less product derived by axial quaternisation than did the alkyl iodide reactions; and one could hardly argue, for example, from the ethylation results with 1-methyl-4-phenylpiperidine that the N-methyl equatorial: N-methyl axial conformer ratio in the base is nearer to 1:1 than 1·6:1. The ratios quoted in Table 3 indicate that the faster alkylating agents are *more* subject to steric compressional effects (more selective) than are the slower. Such results, presumably consequent on variable steric hindrance to leaving group solvation, are likely to be rather

Table 2. Effects of perturbations on partial bond lengths in transition-states for bimolecular displacements $R^1R^2R^3N \overset{\frown}{R^4} \overset{\frown}{X}$: zero-order Thornton analysis

Perturbation	Effect of Perturbation			
	Via "parallel" vibrational mode (reaction-coordinate)		*Via* "perpendicular" vibrational mode (symmetrical stretch)	
	$N...R^4$ bond	$R^4...X$ bond	$N...R^4$ bond	$R^4...X$ bond
Better nucleophile	longer	shorter	shorter	shorter
Better leaving group	longer	shorter	longer	longer
Electron donating group introduced into R^4; e.g., p-OCH_3 in benzyl group	little change	little change	longer	longer

Table 3. Ratios of axial to equatorial quaternisation for ethylations (in dichloroethane; room temperature) and methylations (in nitromethane; room temperature)

Base system	>NMe + $Et_3\dot{O}\ BF_4^-$	>NMe + EtI	>NEt + $Me_3\dot{O}\ BF_4^-$	>NEt + MeI
1-Alkyl*trans*-decahydroquinoline	0·50:1	0·70:1	3·5:1	6·0:1
1-Alkyl-2-methyl-piperidine	0·65:1	0·75:1	2·2:1	3·2:1
1-Alkyl-4-phenyl-piperidine	1·00:1	1·60:1	3·2:1	3·3:1

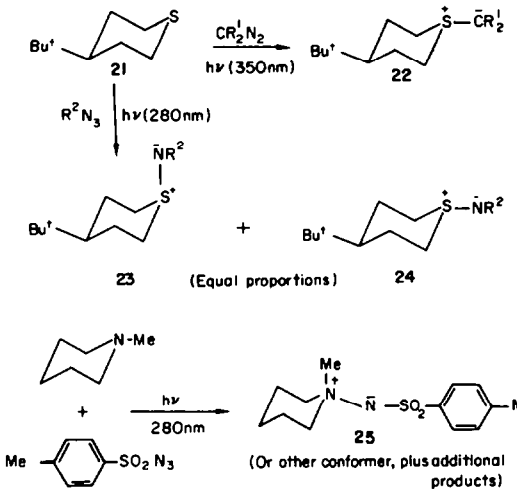
specific for particular types of substrate base, and we find[17] that trimethyloxonium fluoroborate and also methyl fluorosulphate are usually but not invariably *less* selective than methyl iodide in competitive reactions with mixed aliphatic/alicyclic tertiary amines. In the competition experiments none of these methylating agents exhibits anything like the required zero discrimination of an ideal conformational probe as discussed in earlier sections: evidently very much faster reagents still are needed.

Generally, the approaches outlined in this section have been unsuccessful, as we predicted might unfortunately be the case. The smoothest experimental correlations observed[11] have related to the effects of variable *p*-substituents in benzyl halides or sulphonates on the quaternisation product ratios. For any particular tertiary piperidine and leaving group, the differential solvent effect noted above and any other associated differential effects are eliminated, and the observed ratio of axial to equatorial quaternisation product does indeed increase in the reactivity order $p\text{-}NO_2 < p\text{-}H < p\text{-}OCH_3$, as predicted; *cf* the opposite type of result for the more reactive reagents in Table 3. It was accordingly concluded[11] for the benzylations that "here the Hammond postulate is valid". As is clear from Table 2, this statement is almost exactly the opposite of the truth, since the perturbations associated with the variable *p*-substituents affect primarily the "perpendicular" vibrational modes in the transition state: variable rate constants in this particular reaction system are *not* predicted to correspond to more or less reactant–or product—like character. Rather an electron-attracting *p*-substituent shortens, and an electron-donating *p*-substituent lengthens, *both* reacting bonds in the transition state.

Carbonium ions, carbenes, and nitrenes as potential conformational probes for N-alkylpiperidines. These reagents may be added to the bases to give quaternary salts, ylides, or ylide-like products (aminimides), and the reactions would be expected to be very fast indeed. In Thornton's analysis for such formal 2-body interactions (compare the formal 3-body displacement reactions discussed above) there is only one vibrational mode, *viz*, that ("parallel") along the reaction coordinate. In this case, therefore, both Thornton's analysis and application of the Hammond postulate give the same prediction, that the partial nitrogen to electrophile bond in the transition states for the very fast associative reactions should be quite long. This is one important feature favouring lack of steric discrimination, but clearly absence of bulky groups around the reaction centre in the electrophile would also be highly desirable, as would indeed be a minimum of substituent groups whether large or small. Hence the utility order of the active species for the intended purpose is predicted to be $R_3\dot{C} < R_2C < RN$ when all substituents are equivalent.

To avoid the difficulty of competitive bimolecular displacements in thermal reactions we attempted[26] to add N-alkylpiperidines to the 3,5-dimethoxybenzyl carbonium ion (or its near-equivalent) photochemically generated[27] from 3,5-dimethoxybenzyl acetate. Sterically, this seemed as suitable a carbonium ion as one could choose for use as a conformational probe for the system under study. However, we found[28] that benzyl quaternary salts themselves suffered photolysis to a mixture of products derived *via* ionic and radical intermediates under the conditions required for their preparation from the acetate. At the same time it became clear[29] that the photochemically generated benzyl carbonium ion was discriminatory in its attack on mixtures of simple aliphatic alcohols, so that such an active species would in any case be unsuitable for our purpose.

Our initial investigation[5] of the selectivities of electrophilic additions of carbenes CR_2^1 (R^1 = $-COCH_3$, $-COOCH_3$, or $-COOC_2H_5$) and nitrenes NR^2 (R^2 = $-COOC_2H_5$ or $p\text{-}CH_3C_6H_4SO_2-$) has been based on the use of aliphatic and cyclic sulphides as nucleophilic substrates since competitive reactions such as bond-insertions are easier to avoid with sulphides than with amines. The active species were made *in situ* by photolysis of diazo compounds or azides. Additions to 4-t-



SCHEME 2

butylthiacyclohexane (**21**, Scheme 2) were highly selective for all the carbenes, only one ylide (**22**) being obtained in each case, formulated as the product of equatorial addition. On the other hand, both nitrenes were quite unselective, the diastereoisomeric iminosulphuranes (**23**, **24**) being formed in each case in ratio 1·0:1. Product ratios correspond strictly to kinetic control: no thermal or photochemical equilibration takes place under the reaction conditions. A similar differentiation between these carbenes and nitrenes was evident in their reactions with mixtures of dimethyl and diisopropyl sulphides. The rate-constant ratio for competitive additions was 5·3:1 for $C(COOCH_3)_2$, but 1·0:1 for both nitrenes. It is of interest that the quite selective carbene $C(COOC_2H_5)_2$ reacts so rapidly with dimethyl sulphide that we could not observe transients in a flash-photolysis apparatus with a time-resolution of ~ 1 microsecond. These results dramatically illustrate the care needed in attempts to correlate speed and selectivity in chemical reactions.

The lack of selectivity of both nitrenes in these electrophilic additions is noteworthy, in particular the absence of in-cage discrimination in addition to the cyclic sulphide (**21**). The potential utility of the nitrenes as conformational probes is evident, and work is in progress on the addition of *p*-$CH_3C_6H_4SO_2N$ (in the first instance) to N-alkylpiperidines. We have already found[26] suitable conditions for addition of the photogenerated nitrene to the parent N-methylpiperidine, and have isolated and characterised the derived aminimide (**25**).

REFERENCES

[1] *cf* E. L. Eliel, N. L. Allinger, S. J. Angyal and G. A. Morrison, *Conformational Analysis* Interscience, New York (1965)

[2] *inter alia* H. Kwart and T. Takeshita, *J. Am. Chem. Soc.* **86**, 1161 (1964); J. L. Mateos, C. Perez and H. Kwart, *Chem. Comm.* 125 (1967)

[3] *cf* M. J. T. Robinson, *Pure and Applied Chemistry* **25**, 635 (1971)

[4] [a]H. Booth, *Chem. Comm.* 802 (1968); [b]H. Booth and J. H. Little, *J. Chem. Soc. Perkin II* 1846 (1972)

[5] D. C. Appleton, D. C. Bull, J. McKenna, J. M. McKenna and R. A. Walley, *Chem. Comm.* 140 (1974)

[6] *cf* E. L. Eliel, *Pure and Applied Chemistry, Special Supplement VII* 219 (1971)

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

[8] B. G. Hutley, J. McKenna and J. M. McKenna, unpublished work

[9] J. -L. Imbach, A. R. Katritzky and R. A. Kolinski, *J. Chem. Soc.* (B) 556 (1966)

[10] J. McKenna, *Top. Stereochem.* **5**, 275 (1970)

[11] Richard A. Y. Jones, A. R. Katritzky and P. G. Mente, *J. Chem. Soc.* (B), 1210 (1970)

[12] R. P. Duke, Richard A. Y. Jones and A. R. Katritzky, *J. Chem. Soc. Perkin II* 1553 (1973)

[13] J. McKenna and J. M. McKenna, *J. Chem. Soc.* (B), 644 (1969)

[14] R. D. Lewis and R. W. Johnson, *J. Am. Chem. Soc.* **94**, 8914 (1972)

[15] Richard A. Y. Jones, A. R. Katritzky, A. C. Richards and R. J. Wyatt, *J. Chem. Soc.* (B), 122 (1970); I. D. Blackburne, R. P. Duke, Richard A. Y. Jones, A. R. Katritzky and K. A. F. Record, *J. Chem. Soc. Perkin II* 332 (1973)

[16] M. Tsuda and Y. Kawazoe, *Chem. Pharm. Bull. Japan* **16**, 702 (1968)

[17] J. S. Bartlett, J. McKenna, and J. M. McKenna, unpublished work

[18] *cf* J. McKenna, *Royal Institute of Chemistry Lecture Series* 49 (1966)

[19] R. J. Bishop, D. Dineen, Richard A. Y. Jones, A. R. Katritzky, L. E. Sutton and R. J. Wyatt, *J. Chem. Soc.* (B), 493 (1967)

[20] *cf* Ref 1, p. 44

[21] A. T. Bottini and M. K. O'Rell, *Tetrahedron Letters* 423 (1967); A. T. Bottini, B. F. Dowden and R. L. Van Etten, *J. Am. Chem. Soc.* **87**, 3250 (1965); H. O. House, B. A. Tefertiller, and C. G. Pitt, *J. Org. Chem.* **31**, 1073 (1966)

[22] G. S. Hammond, *J. Am. Chem. Soc.* **77**, 334 (1955)

[23] D. R. Brown, R. Lygo, J. McKenna, J. M. McKenna, and B. G. Hutley, *J. Chem. Soc.* (B), 1184 (1967)

[24] E. R. Thornton, *J. Am. Chem. Soc.* **89**, 2915 (1967); *cf* C. G. Swain and E. R. Thornton, *Ibid.* **84**, 817, (1962); T. M. Bare, N. D. Hershey, H. O. House and C. G. Swain, *J. Org. Chem.* **37**, 997 (1972); J. C. Harris and J. L. Kurz, *J. Am. Chem. Soc.* **92**, 349 (1970)

[25] D. R. Brown, J. McKenna and J. M. McKenna, *Chem. Comm.* 186 (1969); J. McKenna and J. M. McKenna, unpublished work

[26] D. C. Appleton, PhD. Thesis, University of Sheffield (1973)

[27] H. E. Zimmerman and V. R. Sandel, *J. Am. Chem. Soc.* **85**, 915 (1963)

[28] D. C. Appleton, D. C. Bull, R. S. Givens, V. Lillis, J. McKenna, J. M. McKenna and R. A. Walley, Chem. Comm. (1974); *cf* ref. 29 unpublished work

[29] M. A. Ratcliff, Jr. and J. K. Kochi, *J. Org. Chem.* **36**, 3112 (1971)