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CAPILLARY COLUMN GAS CHROMATOGRAPHIC METHOD FOR THE STUDY OF DYNAMIC INTRAMOLECULAR INTERCONVERSION BEHAVIOUR

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SUMMARY

Reversible reactions which proceed unimolecularly and are mediated by temperature may be suited to gas chromatographic (GC) study. This paper describes the study of a series of intramolecular sterically-hindered isomerisations of some novel aromatics in which the isomers possess different capacity factors on the column, and where by appropriate selection of operating temperature and gas flow-rate, the extent of interconversion can be altered. Restricted rotation about the C=N bond in oximes can also be readily observed and quantified as it occurs on the GC column, leading to derivation of rate and activation parameters (for forward and reverse processes). Capillary columns enhance the resolution of isomers and interpretation of data. Some equations are presented to describe the on-column phenomenon in a simplified way. The route to activation parameters afforded by GC, especially at high temperatures, is a possible adjunct to the use of variable-temperature NMR studies. Activation energies in the order of 100–140 kJ mol^{-1} were obtained for the sterically-hindered aromatics, and the oximes gave energies of about 70 kJ mol^{-1} by the GC method, but coalescence of NMR signals was not observed even up to 150°C.

INTRODUCTION

The variable-temperature nuclear magnetic resonance (VTNMR) method is well established as a means of estimating the free energy of the transition state (ΔG^*) for conformational interconversion using the coalescence temperature (T_c) and the frequency difference ($\partial\nu$) of the particular resonances of the two conformers whose coalescence is to be monitored. Studies have shown that chromatographic techniques may be applied to study various processes, such as decomposition reactions[1,2] and interconversions of molecules[3]. Evidence for dynamic behaviour in thin-layer

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chromatography was presented as early as 1960[4], however it was some time before column chromatographic methods were employed in this respect.

In a series of papers dealing with kinetic studies of fast equilibrium using high-performance liquid chromatography (HPLC), Moriyasu and co-workers investigated a number of isomer interconversions including acetanilides[5,6], rotamers of palladium dialkyldithiocarbamates[7], sugar anomers[8], and the classical keto–enol tautomerism phenomenon[9,10]. In some of these reports, VTNMR data are compared with those obtained using the dynamic HPLC method. The temperature regime of HPLC is encompassed within that of VTNMR, and so application of HPLC to fluxional processes will be, to a large extent, also possible by VTNMR. Melander *et al.*[11] have reported the *cis–trans* isomerisation of proline-containing dipeptides during chromatography, illustrating the effect of flow-rate, temperature and pH upon the elution profile.

The observation of peak broadening and multiple peaks in HPLC and electrophoresis of proteins has been attributed to conformational equilibria and interconversion between native and unfolded or denatured forms of the protein[12] where the separation takes place on a similar time scale to that of the equilibration phenomenon. No thermodynamic parameters have been reported for the HPLC data however, although the NMR studies of proteins, with particular reference to conformational behaviour, have received attention[13].

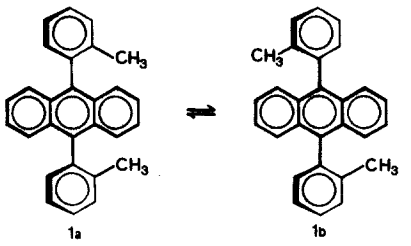
Temperature limits for VTNMR (*ca.* 150–180°C) impose restriction on the range of barrier energies which may be conveniently studied. In order to obtain information on sterically hindered molecular motions with energy barriers which require higher temperatures, complementary methods must be found such as time dependent techniques involving an iterative routine of heating followed by measurement of a physical property which differentiates the isomers. This was found to be necessary in a study of barriers to enantiomerisation in helical phenanthrenes[14]. For high rotational barriers the use of gas chromatography (GC) may provide a means whereby dynamic interconversion can be followed, as we have recently reported for 9,10-bis(2,3-dimethylphenyl)phenanthrene[15]. We have also recently investigated two examples of fluxional processes involving lability of coordination to chromium, one in *cis–trans* isomerization of a tris-chelate and another in structural isomerisation accompanying a shift in complexation of $Cr(CO)_3$ from one ring to another is substituted naphthalene[16]. On-column inversion of labile enantiomeric nitrogen invertomers has been followed by complexation GC[17].

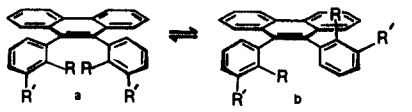
In this paper we wish to highlight further applications of GC to conformational analysis which are out of the scope of VTNMR, and to propose the potential use of the technique as an adjunct to dynamic NMR to obtain activation parameters.

EXPERIMENTAL

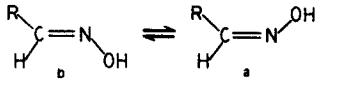
Reagents

9,10-Bis(2-methylphenyl)anthracene (1a, 1b) was synthesised following the procedure of Grein *et al.*[18]. Instead of using the aryl lithium reagent, the corresponding Grignard reagent was used. 9,10-Bis(2,3-dimethylphenyl)phenanthrene (2a, 2b) and 9,10-bis(3-chloro-2-methylphenyl)phenanthrene (4a, 4b) were synthesised as recently has been reported by one of us[19]. 9,10-Bis(2-methylphenyl)phenanthrene





2a, 2b; R=R'=CH_3
3a, 3b; R=CH_3, R'=H
4a, 4b; R=CH_3, R'=Cl
5a, 5b; R=H, R'=CH_3



6a, 6b; R = $-CH_3$
7a, 7b; R = $-CH(CH_3)_2$
8a, 8b; R = $-CH_2CH_2CH_3$

(3a, 3b) and 9,10-bis(3-methylphenyl)phenanthrene (5a, 5b) were synthesised as reported in a recent paper[20]. Acetaldoxime (6a, 6b) was purchased from Tokyo Kasei and used as received. The *anti*:*syn* isomer ratio was *ca.* 55:45. Isobutanaldoxime (7a, 7b) and butanaldoxime (8a, 8b) were prepared based upon standard procedures[21] by adding sodium hydroxide followed by hydroxylamine hydrochloride to the appropriate aldehyde. Carbon dioxide was passed through the mixture until a surface emulsion formed. The solution was extracted with diethyl ether, the diethyl ether was dried and the excess solvent removed. The oxime was then distilled over and collected under reduced pressure. *Anti*:*syn* ratios were approximately: 7a:7b, 80:20 and 8a:8b, 60:40.

Capillary GC was performed on a Hewlett-Packard Model 5790A GC using nitrogen or hydrogen carrier gas, flame ionisation detection and split injection with a Hewlett-Packard Model 3390A computing integrator. Capillary columns used in this work were a Chrompack free fatty acid phase (FFAP)-coated fused-silica capillary (6 m × 0.23 mm I.D.) for the oxime samples, and a Scientific Glass Engineering dimethylsiloxane-coated fused-silica capillary column (25 m × 0.023 mm I.D.) for the anthracene and phenanthrene compounds. Internal standards were benzaldehyde or amylalcohol for the oximes and *n*-octacosane for the aromatics.

GC protocol

The requisite data were obtained according to the procedure outlined briefly elsewhere[15]. The method involves estimation of the extent of "reaction" or "interconversion" that each of the isomers undergoes for each of a number of carrier gas flow-rates and column temperatures. The data are then analysed using an Arrhenius type procedure in order to obtain activation parameters, which entailed calculation of the rates of conversion, k, of the isomer at a number of different temperatures, T, followed by plotting $\ln k$ against $1/T$ which produces a line whose slope is equated to $-E_a/R$, where E_a is the activation energy and R is the universal gas constant.

To quantify the interconversion involves monitoring the disappearance of the

peak corresponding to the unconverted isomer and normalising this against an inert internal standard. This is done at each carrier gas flow setting as the flow-rate of carrier gas is altered which has the effect of changing the residence time of the compound on the column; as the time increases the extent of "reaction" that takes place will likewise increase. The most important determination is that of the amount of isomer that has not undergone isomerisation during passage along the column. Looking forward to Fig. 2 we can discern the three regions corresponding to elution of the two isomers; the peak for unconverted compound 6a, the peak for unconverted compound 6b, and the broad intra-peak zone which arises from isomers 6a and 6b which have undergone isomerisation. Since there will necessarily be some overlap of the regions for unconverted and converted peaks, baseline correction must be taken into account[22]. Manual area calculation with baseline correction for product/reactant overlap poses some problems with narrow capillary GC peaks, although using fast chart speeds overcomes some of the errors involved. For greater accuracy, computerised data acquisition and handling would be preferred. Component separation commences immediately upon conversion of reactant into product.

For the process A → B, if an isomerisation event occurs at time t, the product B molecules will commence to be chromatographically resolved from A according to their relative capacity ratios, k' (A) and k' (B). Clearly those product B molecules will elute with a retention time neither the same as unconverted A molecules [for which $t_R(A) = t_M k'(A)$, where t_M is the column dead time] nor the same as any molecules of B originally injected and passing through the column unchanged [for which $t_R(B) = t_M k'(B)$]. Rather, the molecules of B formed from A at time t, hereinafter denoted B′, will have retention times of

$$t_R(B') = t + [t_R(A) - t]\,[t_R(B)/t_R(A)] \tag{1}$$

This equation can be rationalised thus: after time t, the compound B′ travels under the capacity ratio conditions of B. The compounds A and B have a relative retention time ratio of $t_R(B)/t_R(A)$, so the additional retention time of B′ after time t when the isomerisation occurs will be the differences in the retention time of A and t, multiplied by the relative retention time ratio of B and A.

Similarly for the process B→ A,

$$t_R(A') = t + [t_R(B) - t]\,[t_R(A)/t_R(B)] \tag{2}$$

Since all values of t are possible from 0 to $t_R(A)$ (for A → B), product B′ molecules will potentially have values of $t_R(B')$ from $t_R(A)$ to $t_R(B)$, with the distribution of B′ molecules related to the relative rate of conversion A → B. This will of course be superimposed on the A′ distribution.

For eqn. 1, if $t = 0$, *i.e.* the interconversion event occurs at the time of injection, then

$$t_R(B') = 0 + t_R(A)\; t_R(B)/t_R(A) = t_R(B)$$

and B′ will elute with the same retention as original molecules of B injected.

Similarly

$$\text{if } t = t_R(A), \text{ then } t_R(B') = t_R(A)$$
$$\text{if } t = t_R(A)/2, \text{ then } t_R(B') = [t_R(A) + t_R(B)]/2 \quad (3)$$

with B′ eluting midway between A and B.

Likewise for eqn. 2,

$$\text{if } t = 0,\ t_R(A') = t_R(A)$$
$$\text{if } t = t_R(B),\ t_R(A') = t_R(B)$$
$$\text{if } t = t_R(B)/2,\ t_R(A') = [t_R(B) + t_R(A)]/2 \quad (4)$$

The similarity of results in eqns. 3 and 4 can be readily appreciated.

The efficacy of resolution is reflected in the equation

$$R_S = (\sqrt{N}/4)\,[(\alpha - 1)/\alpha]$$

thus either high-resolution columns (high N values) and/or increased phase selectivity (higher α values) is required. Both of these advantages were exploited by Bürkle *et al.*[17] in his invertomer work. In our experience, not only do capillary columns provide the necessary resolution for the appropriate choice of liquid phase, they also exhibit the interconversion phenomenon most nicely, and this enhances the accuracy of the analysis of the resulting chromatogram and would aid computer fitting of data to a model describing the process.

The rate processes pertaining to intramolecular interconversion and chromatographic resolution in this work, with a simple two-component system, are presented in Fig. 1. Reversible conversion occurs both in the gas and liquid phases according to the rate constants governing each phase. For simplification of our approach, the rates in both phases are considered to be equivalent and only a function of temperature. For thermally labile rotamers with reasonably non-polar phases and a transition state not affected by stabilization through interactions with polar solvents, this assumption seems reasonable. We believe that on the liquid-phase coated silica columns any potential surface catalytic effects play a negligible role in the interconversion process we are investigating.

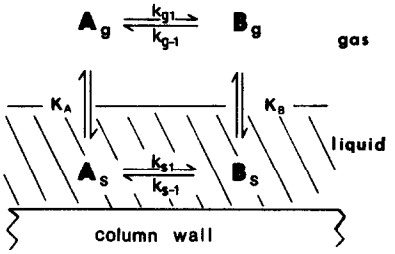


Fig. 1. Partitioning and interconversion process for the reaction A ⇌ B within the gas–liquid chromatography column. k = rate constants for interconversion; K = partition coefficient for the compounds subscript g and s refer to gas phase and stationary phase species and rates respectively.

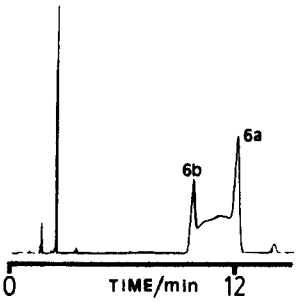


Fig. 2. Chromatogram of *anti* (6b) and *syn* (6a) acetaldoxime on a free fatty acid phase-coated capillary column at 50°C. The early-eluting peak(s) in this and other chromatograms is due to the solvent.

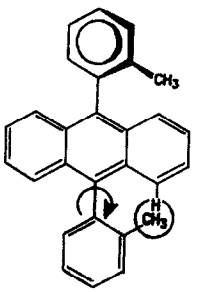
Fig. 2 exhibits a classic dynamic GC trace, in this case for acetaldoxime. The terminal peaks are sharp and well resolved from each other. The inter-peak zone illustrates the baseline shift which corresponds to the interconversion between isomers. In comparison to the packed column work of Langer *et al.*[23], the advantages accruing from capillary column methodology can be appreciated.

RESULTS AND DISCUSSION

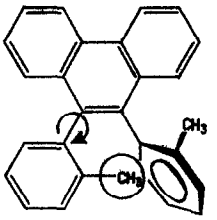
Phenanthrene/anthracene compounds 1–5

We have previously reported a study on one member of this group of compounds[15], 2a, 2b. We were interested in the sterically hindered rotation about the C–C single bond for the 2-methyl substituted aromatics, where steric interaction between the methyl group and the planar fused aromatic parent ring results in a barrier to the free rotation. During rotation, the benzene substituent will be coplanar with the aromatic parent. For 1a, 1b, the substituent methyl group will interact with the C-1 proton of the parent ring (Scheme 1). This same scheme may be invoked for one possible intermediate for substituent rotation in (2–4)a, (2–4)b. The other main interaction possible for steric hindrance in this series of compounds is represented in Scheme 2, where the *o*-methyl group approaches the neighbouring aryl ring substituent. We discount any interaction between *ortho* protons on the phenyl substituent and the C-1 proton, analogous to that represented in Scheme 1, since compounds 5a, 5b have considerably lower barrier to interconversion (see later).

The preparative procedures produce isomers a and b in different proportions,



SCHEME 1



SCHEME 2

according to the conditions employed. However for the anthracene 1a and 1b, both isomers are of essentially equal abundance and they apparently interconvert with almost equal facility as evidenced in the GC study (Fig. 3). The overall GC distribution maintains good symmetry as isomerization progresses. The *trans*, or *anti*, isomer is presumed to elute as the later GC peak in accordance with usually observed relative GC retentions for positional isomers of such compounds as alkylbenzenes, where *trans* isomers elute after those in which the substituents are not trans. The free energy difference between the ground states of the anthracene isomers is small, as is shown by their approximately equal abundance at equilibrium. Thus in order to carry out a conventional time-dependent study of isomerization it would be necessary to separate the isomers. However, for the GC reactor study prior separation is not required since isomer separation is inherent in the column-based method.

For the phenanthrene compounds 2–4, one isomer is usually produced in far greater proportion. For 2a, 2b the minor isomer abundance was about half that of the major isomer[15]. In 3a, 3b, the major isomer was considerably more abundant (Fig. 4), with the minor one about 5%. Thus there is considerable preference energetically for one isomer. In this series of compounds, the two phenyl substituents at the 9,10 positions on the phenanthrene will be expected to experience interaction through the delocalized electron density and some ring tilting may result, thereby leading to the

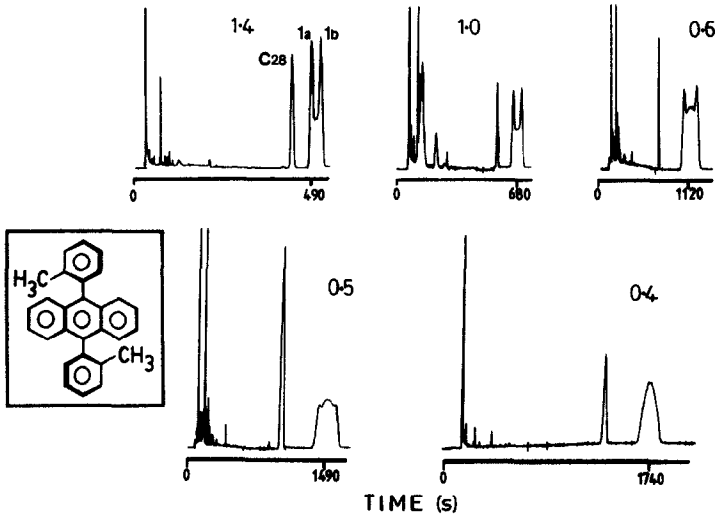


Fig. 3. GC study of interconversion of anthracene isomers 1a and 1b at 240°C and using different hydrogen carrier gas flow-rates. The flow-rates are set by the capillary pressure, given in dyne · cm^{-2} × 10^{-6} indicated on each individual chromatogram. 1a is believed to elute first. C28 = internal standard; *n*-octacosane.

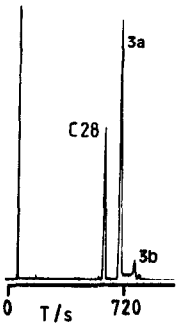


Fig. 4. Gas chromatogram of 3a and 3b at 240°C. The later eluting lesser abundant conformer, 3b, is about 5% abundance. Some evidence of a plateau and hence interconversion between 3a and 3b can be discerned. C28 designated as in Fig. 3.

observed preference for one isomer. The early eluting isomer is in most cases also the one of greater abundance, and by similar reasoning to the above, we might conclude this to be the *cis* isomer. In those instances where the second isomer was of very low abundance, no estimation of its barrier to interconversion could be made.

Fig. 5 shows a series of chromatograms for 3a, 3b at different temperatures from 280 to 320°C. At the lower temperatures, the shoulder extending to longer time is typical behaviour observed for the interconversion process where the later isomer has essentially completely undergone an isomerization event into the earlier eluting isomer. No unconverted later-isomer peak can be identified. At 300°C the first isomer can no longer be seen as a separate peak and the recorded profile becomes broad and squat with slightly distorted downslope. At 320°C the peak has sharpened and becomes more symmetric. We interpret this to be indicative of rapid interconversion between the two isomers.

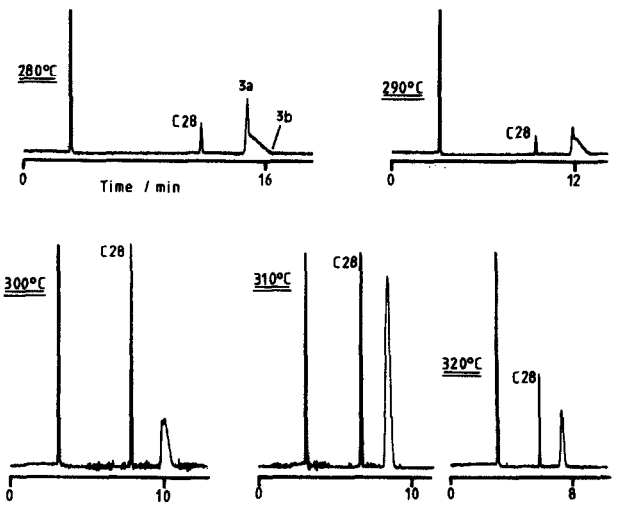


Fig. 5. Chromatograms illustrating progression in dynamic interchange between 3a and 3b with increasing column temperature. C28 designated as in Fig. 3.

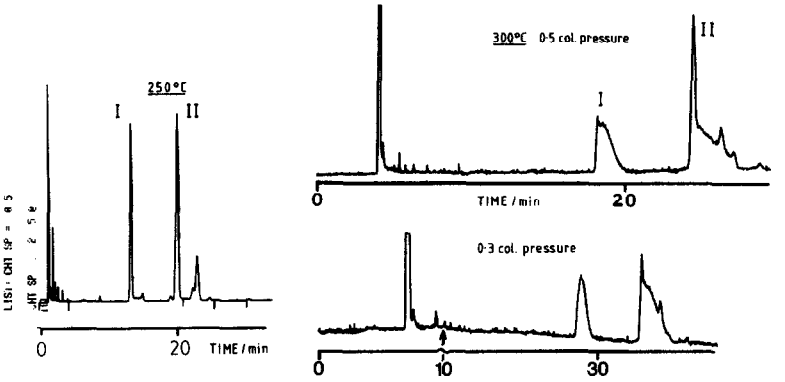


Fig. 6. Chromatograms of 4. At 250°C two groups of peaks are seen, I and II, each with one large (earlier) and one small (later) peak. At 300°C and 0.5 dyne · cm^{-2} × 10^{-6} pressure, I almost fully isomerises but II has appreciable unconverted isomer still present. Peak II corresponds to 4, whereas peak I appears to be a mono-chloro analogue of 4.

Compounds 4a, 4b behaved much like their analogues 2a, 2b reported earlier[15]. Chromatograms are given in Fig. 6. The minor isomer occurs in much less abundance, however the chromatogram illustrates two groups of peaks, labelled I and II. Peaks II correspond to 4a and 4b and from GC–mass spectrometry peaks at I contain only one chlorine. Whilst the chromatogram suggests I undergoes isomerisation more readily than II, the occurrence of I in the sample has not yet been explained. The analogue without a methyl group in the *ortho* position of the phenyl substituents, 5a, 5b, were then prepared for comparison purposes. Even though VTNMR studies[20] indicated both isomers to be present, no resolution of two peaks could be achieved on the GC even at temperatures as low as 200°C (the lowest temperature at which it could be chromatographed). We believe this to be indicative of rapid interchange such that only the averaged retention is seen. The alternative possibility, that the two isomers are not resolved, is rejected since if the conformers were stereochemically rigid at the temperatures used isomer separation would be expected on the basis of the ready

TABLE I

CALCULATED BARRIERS TO INTERCONVERSION USING THE GC METHOD

Compound	E_a *(kJ* mol^{-1}*)**
1	123, 104
2	145, 115
3	132, NA**
4	***
5	85§
6	52, 48
7	64, 69
8	70, 66

* The first entry is for the major isomer of the compound.
** The minor isomer is in too small abundance to allow for reliable measurement of the energy.
*** The values for this compound were not estimated.
§ This value was obtained by VTNMR (refer to text) and so it is ΔG^*.

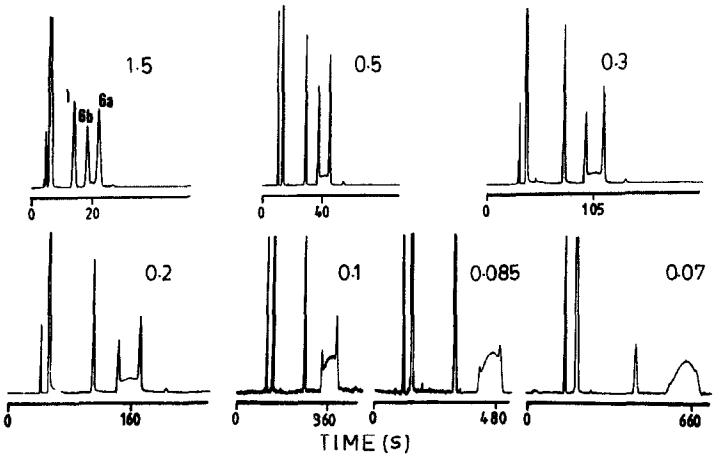


Fig. 7. Chromatograms of oximes 6a and 6b at 65°C for varying carrier flow-rates. I = internal standard = benzaldehyde.

resolution of the isomers of the other compounds of this series. Clearly, the steric interactions illustrated in Schemes 1 and 2 cannot play a role in this molecule.

Calculations of some example energy barriers give the results in Table I. VTNMR has not been successful in estimating ΔG^* for the compounds (1–4)a, (1–4)b. With high energy barriers in excess of 100 kJ mol^{-1}, no coalescence phenomena of ^1H NMR signals could be seen up to 150°C. However for 5a, 5b, T_c = 98°C with ΔG_c^* = 85 kJ mol^{-1} (ref. 20). This supports the conclusion above that rapid isomerisation precludes the resolution of the isomers of 5.

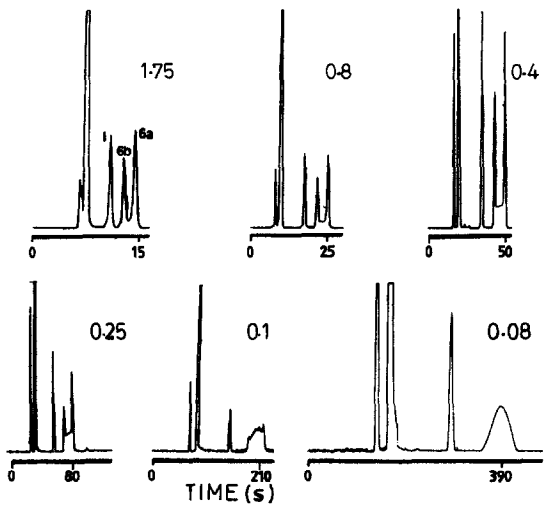


Fig. 8. Same compounds as Fig. 7 but at 80°C. Note that after 390 s a smooth-peaked distribution is obtained, whereas at 65°C the distribution still shows traces of unconverted starting isomer even after 660 s.

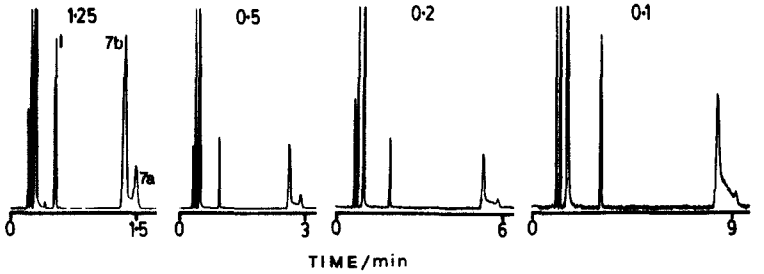


Fig. 9. Chromatograms of 7a and 7b at 70°C. I = benzaldehyde.

Oxime compounds 6–8

The example of Langer *et al.*[24] of on-column interconversion of acetaldoxime, widely quoted in treatments on physicochemical GC work, was reinvestigated in this study in order to attempt to evaluate the GC data for activation energy (not done in the earlier work) and at the same time to try to correlate the GC study with a VTNMR study on the same molecular system. Oximes 6–8 were chromatographed over the temperature regimes of 50, 65 and 80°C, 70, 85 and 100°C and 75, 90 and 105°C, respectively. The higher temperatures for 7 and 8 reflect their slightly longer retention and lower volatility compared with 6. If rates of interconversion are similar at these different temperatures, then we might conclude that 7 and 8 would have higher activation energies by virtue of the higher temperatures. The data do appear to support this. However even with E_a in the region of 50–70 kJ mol^{-1}, VTNMR did not exhibit coalescence up to 150°C for any of the compounds.

Representative GC traces are illustrated in Figs. 7–10. The chromatographic data are reproduced reasonably fully in order to faithfully represent and illustrate how the process of interconversion proceeds at different temperatures, and under varying conditions of carrier flow-rates. In some cases coalescence of peaks is included, with a resultant smooth and broad peak observed. The different forward and reverse activation energies (Table I) indicate the different ground state energies of the two isomers.

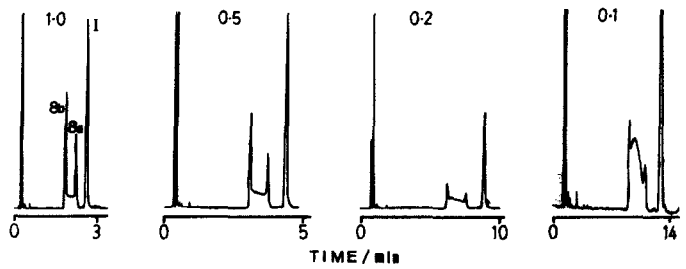


Fig. 10. Chromatograms of 8a and 8b at 75°C. I = amylalcohol.

CONCLUSION

The primary limitation on GC, and indeed HPLC also, for dynamic chromatographic study is the need for chromatographically distinguishable antipodes or isomers in the exchange process. Whilst "symmetrical" compounds such as dimethylformamide or N,N-dimethylcarbamates[25] are eminently suited to dynamic NMR, they would not be suited to dynamic chromatography. Dynamic chromatography can be applied to some systems with high activation barriers, it can be used in situations where the isomers are not of similar abundance, and does not require prior separation of equilibrium mixtures (which is necessary for time-dependent studies such as continuous heating/analysis methods). It is applicable to the resolution and interconversion of thermally labile optical isomers on optically active columns —an application not suited to solution NMR work. Having received attention only relatively recently, and with the limited range of applications studied to date, it is to be expected that an increasing number of molecular motions will be subjected to chromatographic scrutiny in the future.

Whether any special information is derivable from the conditions of coalescence of chromatographic peaks, much as is employed to derive ΔG^* from T_c in VTNMR, will await further detailed analysis of the theory of the dynamic chromatography method and interpretation of the data.

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