SYNTHESIS OF LABELLED ORGANIC COMPOUNDS FOR SOLID STATE DIFFUSION STUDIES.

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SUMMARY

The synthesis and purification of suitable radioactive tracers for organic solid state self diffusion experiments is described. Particular attention is paid to the isotope effect which requires two tracers containing different radioactive isotopes, and with as large a mass difference as possible. The latter is accomplished by incorporating a stable isotope in one of the tracers. Active preparations of adamantane, dl-camphene, bromopentamethylethane, and hexamethylethane are reported.

Introduction

In the last decade, Sherwood (1) has established the field of diffusion in organic solids.

The commonest experimental technique is to deposit a thin layer of radioactive tracer on the surface of a pure single crystal and to analyse the rate of penetration of the tracer into the crystal for the diffusion tensor. This requires small quantities of tracer of specific activity 0.1 - 10 microcuries/milligram with mass as near as possible to that of the host species.

More detailed information about the diffusion process is available from isotope effect studies (2) in which the differential diffusion rate of two chemically identical isotopes with different molecular weights is assessed. This requires two tracers with different radioactive labels, and if the mass difference so produced is insufficient then additional substitution in one tracer by a stable isotope is essential; the object is to produce as large a mass difference as possible.

The availability of radioactive forms of carbon and hydrogen, and the stable isotope deuterium, gives organic compounds an unrivalled versatility in these respects. The possible mass difference ranges from about 14% for saturated hydrocarbons C_nH_{2n+2} to about 6-7% for such as polycyclic aromatics, approximately C_nH_n.

Sherwood and collaborators have studied diffusion in the aromatics benzene, naphthalene, anthracene, and phenanthrene; biphenyl, benzoic acid; and the plastic crystals cyclohexane, camphene, succinonitrile, and pivalic acid. Labes et al(3) have measured imidazole. In all these materials the radiotracers were obtained either commercially or by established methods(4). Chadwick(5) has synthesised radioactive forms of norbornylene, norbornane, and hexamethyldisilane for diffusion experiments.

Isotope effect experiments have been carried out on benzene(6), cyclohexane(7), and hexamethylethane (8). Napthalene has also been attempted, and synthesis of suitable tracers is proceeding for pivalic acid and adamantane(9). It is of interest to note that syntheses with deuterated compounds do not invariably proceed as for the normal compounds, as, for example in $C_6D_{11}{}^3H$ (7).

Reliable assessment of defect controlled solid state properties needs highly pure and perfect single crystals. Consequently the radiotracers must also be as pure as is reasonably possible, certainly to a degree considerably above that acceptable for, say, mechanistic studies. Classical purification methods are supplemented by techniques such as gradient sublimation, zone refining, normal freezing and crystal growth (10).

This communication reports details of the preparation, purification, and analysis of several radiotracers used in the author's research.

Experimental

a) Adamantane 1 - ^{3}H ø

Tritiated ethanol was first prepared by reacting sodium ethoxide with tritiated water (0.2 curies/ml) to obtain a higher activity than by simple equilibration. The active ethanol in ethereal solution was added portionwise to 0.64 gm sodium sand and 0.60 gm 1-Bromoadamantane in pure refluxing diethyl ether. Reduction of the halide incorporated the tritium in the adamantane 1-position. To minimise the kinetic isotope effect each portion was allowed to react completely before adding the next portion. Total time was about 36 hours.

The pale blue solution was decanted off from the excess sodium and added to 50 ml distilled water, upon which the colour vanished. Ether extraction, washing, drying, and evaporation yielded a white solid. Purification by recrystallisation from redistilled acetone and sublimation gave 0.35 gm (90%) adamantane of 99.99% purity (Vapour Phase Chromatography on Apiezon L at 180°C) and specific activity 2.87 μc/mgm. The non volatile residue could have been diadamantyl.

$$\mathrm{AdBr} + 2\mathrm{Na} \xrightarrow{\mathrm{EtO\overset{*}{H}}} \mathrm{Ad\overset{*}{H}} + \mathrm{NaBr} + \mathrm{Na\ OEt}$$

This synthesis is readily adaptable to the deuterated form, and with the availability of Adamantane 2- ^{14}C (11), the isotope effect is feasible.

ϕ Footnote

The metal - halogen exchange between 1-Bromoadamantane and n-Butyl lithium to produce adamantyl lithium, for reaction with tritiated water to give tritiated adamantane, failed to work. The 30% yield of adamantane was totally inactive, presumably having formed by reaction with the solvent ether before addition of the water. Reducing the reflux time or changing the solvent drastically cut the yield of adamantane. Another alternative reaction - reduction with lithium aluminium hydride-produced hardly any adamantane.

b) dl - Camphene - (U) ^{3}H

The racemisation of camphene under the influence of acidic catalysts(12) was adapted to a tracer synthesis. The tritium distributes throughout the camphene by exchange with and rearrangement of the carbonium ion formed by protonation at the ethylenic group. Pyruvic acid appeared likely to give the highest activity, even if not the highest purity. The purity of the crude product could almost certainly have been improved by varying the experimental conditions but this was not investigated in detail.

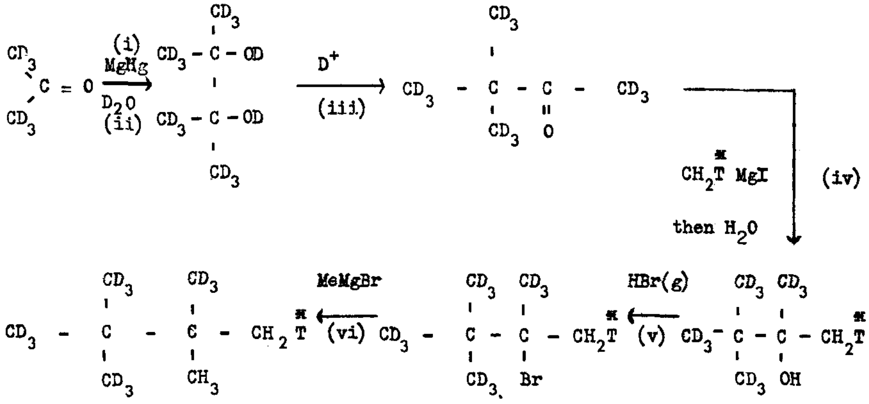
2 gms of redistilled pyruvic acid ($K_a = 3.2 \times 10^{-3}$ at 25°C) was equilibrated with about 1 ml of tritiated water (0.2 curies) and the water then distilled off under vacuum. About 2½ gm of purified DL - camphene was transferred into the active pyruvic acid and the vacuum sealed vessel held at 140- 150°C for fifteen minutes. After cooling to room temperature the pale yellow mixture was diluted with 50 ml distilled water and extracted with ether. Bicarbonate washings, drying, and removal of solvent yielded a complex mixture of terpenic compounds with camphene 60% tricyclene 17% and bornylene 7% predominant.

Fractional distillation on a micro-Vigreux column removed nearly all the lower boiling impurities. Tricyclene could not be separated except on a high efficiency spiral band column or by preparative GLC. Sublimation trhough a cold trap at 0°C, zone refining in a capillary tube using a single loop wire heater, and vapour phase crystal growth provided fairly pure camphene, 99.95% by GLC on Apiezon, apart from tricyclene which is present in all camphene syntheses. The yield of camphene was 0.5 gm, specific activity 1.74 μc/mgm.

c) Bromopentamethylethane and Hexamethylethane

Two radioactive tracers were prepared for each, one containing ^{14}C and normal hydrogen, and the other containing ^{3}H and twelve deuterium atoms. The equation for the latter is shown below

2 .



Steps (i) (ii) (iii) (Reference 13) followed established procedures to obtain pinacclone-D_{12} from acetone- D_6 via pinacol hydrate. Deuterated water and deutero-sulphuric acid were employed to avoid possible loss of D in the hydrolysis and rearrangement steps. Step (iv) (Reference 14), the Grignard synthesis of pentamethylalcohol, was chosen for incorporation of the radioactive tracer (as $CH_2\overset{*}{H}$ MgI for the deuterated precursor and as $\overset{*}{C}H_3MgI$ in the other case). Purification of the crude pinacolone by fractional distillation was essential for success; about 3 gm alcohol was obtained from 5 gm pinacolone. The alcohol was also fractionally distilled for use in step (v), and protected from moisture to avoid formation of the solid hydrate.

Step (v) - A gas saturation method was utilised to eliminate any losses of deuterium and other complications arising from the carbonium ion rearrangements noted by Roberts (14). An ethereal solution of the alcohol was saturated with hydrogen bromide from a cylinder, forming first a yellow liquid and then a white precipitate over several hours. Flushing with nitrogen, washing with carbonate, extracting and drying, and removal of solvent gave crude bromopentamethyethane, which was purified by vacuum sublimation. 3½ gm (80%) was obtained from 3 gm alcohol. The specific activity, from 25 mc of $CH_2\overset{*}{H}I$, was 1.4 μc/mgm. The tritium compound was reasonably stable, but the higher energy 14-C compound (0.1μc/mgm) underwent self-radiolysis, especially in solution, which precluded reliable diffusion measurements.

Step (vi) - This Grignard coupling, although not uncommon(15), proceeds in low yields for non-activated halides; the best yield is for the chlorides but it is still rather low for pentamethylethyl halides because of steric factors (16). It was decided to use the more conveniently handled bromide reaction with MeMgBr prepared from methyl bromide (boiling point 4°C). The Grignard solution, after filtration in an inert atmosphere, was added in threefold excess to the solution of the bromide in ether. The reaction vessel, protected by a calcium chloride drying tube was allowed to stand at room temperature for a week. This was the optimum procedure found from the trial reactions. Slow evolution of gas occurred and two liquid layers formed, the bottom one eventually yielding a white precipitate of $MgBr_2$. The layers were treated with ice cold aqueous HCl to decompose excess Grignard. 1½ gms of crude product, nearly all from the upper layer, was isolated from the ether extracts in the usual way.

Isolation, Purification, and Analysis

Analysis by vapour phase chromatography on Apiezon L at 100°C indicated 40% hexamethylethane, 30% unchanged bromide, and 30% of a saturated hydrocarbon impurity boiling around 70°C, together with a little residual ether. Isolation of the hexamethylethane proved difficult, particularly since chemical methods were unsatisfactory. A reasonably satisfactory procedure was as follows:-

(i) Sublimation under vacuum through a U-trap cooled by dry ice/acetone. The ether and hydrocarbon impurity collected as a liquid at the bottom of the trap while the HME and the bromide solidified at the top. A rapid localised heating at the bottom of the trap while still under suction removed all the impurity fraction with negligible loss of HME from the cold region.

(ii) Further sublimation, over a longer period of time, under suction through two U-traps held at $0^{\circ}C$ and $-20^{\circ}C$, with a third trap at liquid nitrogen temperatures to collect the volatile fraction. An excellent separation of the HME and the bromide resulted; the process was followed by filling the two U-traps with solid silver nitrate crystals. In the first trap at $0^{\circ}C$ the crystals turned yellow green all through, while in the second, only those at the entrance were tinged with yellow. A purity in the region of 99.5% HME was achieved, which was further enhanced by gradient sublimation and micro-zone refining. About 0.5 gms hexamethylethane - D_{12} was obtained, specific activity 2.0 μc/mgm. The C-14 synthesis yielded material of activity 0.15 μc/mgm. Both tracers were stable.

(iii) It was possible to recover about half of the unchanged bromide by resubliming the least volatile fractions through a trap at $0^{\circ}C$ till half the material had been pumped off. VPC analysis indicated nearly all the HME had been removed.

(iv) The chemical identity of the hexamethylethane tracers was shown by comparison injection on the VPC. Mass spectrometry confirmed the isotopic distribution of the deuterium tracer. The spectrum was very complex and possessed negligible parent ion peak (17). Nevertheless, the number, intensities, and distribution of the groups of fragmentation peaks indicated that the deuterium was asymmetrically distributed and in a ratio of 2:1 with normal hydrogen atoms. This is in accord with the expected structure.

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