PREPARATION OF MULTITRITIATED ARENES

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SUMMARY

The decay technique, currently applied to the study of ionic processes in gaseous and liquid systems, requires multitritiated precursors to generate labeled daughter ions. The preparation of three such precursors, namely $C_6{}^3H_xH_{6-x}$, $C_6{}^3H_xH_{5-x}CH_3$, and $C_6H_5C^3H_xH_{3-x}$ is described. The ring-labeled precursors were obtained from the cyclization of $C_2{}^3H_2$, and respectively of a $C_2{}^3H_2$/propyne mixture, carried out at 25°C over a K_2CrO_4-promoted silica-alumina catalyst. The side-chain tritiated toluene was prepared by allowing ^3H_2O and benzotrichloride to react over a Zn mirror at 200°C. Details of the procedures employed for the radiometric and the isotopic analysis of the multilabeled products are reported.

INTRODUCTION

The decay technique, which exploits the β decay of covalently bound ^3H atoms to generate organic cations, is currently applied to study the structure and the reactivity of ionic species in gaseous and condensed systems (1-4).

A demanding experimental requirement of the decay technique is the preliminary preparation of suitable multitritiated precursors, namely labeled species containing two or more ^3H atoms in the same molecule. Despite considerable difficulties, a number of such precursors has been successfully synthesized, including methane-$^3H_4$ (5-10), ethane-1,2-$^3H_2$ (11), propane-^3H_x (12), propane-1,2-$^3H_2$ (13), cyclobutane-^3H_x (14), cyclopentane-1,2-$^3H_2$ (15), benzene-$^3H_6$ (16), benzene-1,4-$^3H_2$ (17), methyl-$^3H_3$ bromide, and methyl-$^3H_3$-alcohol (18).

The present paper describes the preparation of three multitritiated arenes, $C_6{}^3H_xH_{6-x}$, $C_6{}^3H_xH_{5-x}CH_3$, and $C_6H_5C^3H_xH_{3-x}$, required as precursors for the study of aromatic cations by the decay technique. No synthetic approaches to the two multilabeled toluenes have been previously reported. While a preparation of

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multilabeled benzene has been described (16), it however was not entirely satisfactory for our studies.

EXPERIMENTAL SECTION

Preparation of ^3H_2O. The required multicurie samples of ^3H_2O were prepared according to a well-established procedure by oxidation of $^3H_2$ gas over CuO at 450 - 480°C. After a reaction period of 5 to 6 hours, the ^3H_2O formed was thoroughly outgassed and stored in pyrex tubes equipped with a break-seal tip and contained from 0.15 to 0.30 mmol ^3H_2O, corresponding to ca. 10 to 20 Ci. These samples were used in the subsequent steps described below.

The Trimerization Catalyst. The trimerization of the alkynes was promoted by a type KC Perkator D1 catalyst from Kali-Chemie, Hannover, West Germany, and consisted of 2-mm diameter silica-alumina pellets, activated with K_2CrO_4 (0.2% w/w). In order to activate the catalyst by removing traces of humidity, ca. 100 mg pellets were heated at 400°C for one hour under vacuum within a break-seal tipped pyrex vial, which was then sealed off. After the trimerization, the catalyst could be reactivated by heating for 1 h at 550 - 600° in an O_2 stream.

Preparation of $C_2{}^*H_2$ ($^*H = {}^2H, {}^3H$). Tritiated acetylene was prepared in the pyrex apparatus shown in Figure 1, following blank runs carried out with deuterated water. Vial ①, containing 0.20 to 0.30 mmol $^*H_2O$ was sealed to the side arm ② of the apparatus, that was subsequently carefully outgassed at high temperature under vacuum, then closed with stopcock ③ and transferred into a glove box flushed with dry argon.

Working within the glove box, an excess (ca. 3 mmol) of Li_2C_2 was introduced into ⑤ via ④. The apparatus was then connected via joint ④ to a vacuum line, thoroughly outgassed and sealed off at constriction ⑥.

Breaking the fragile seal with the glass hammer ⑦, allowed $^*H_2O$ to diffuse into ⑤ to react with Li_2C_2 (150°C, 30 minutes). The $C_2{}^*H_2$ formed was condensed into the cold finger ①, kept at -196°C, trapping any residual $^*H_2O$ and other condensable byproducts in ⑤, maintained at -63°C with a dry ice-chloroform slurry. The purified $C_2{}^*H_2$ was eventually condensed into ⑧, which was sealed off at constriction ⑨. The yields of $C_2{}^2H_2$ obtained in the blank runs was 80 ± 5%, and its isotopic composition, measured by mass spectrometry, was $C_2{}^2H_2 : C_2{}^2HH : C_2H_2 = 32 : 42 : 26$. In the actual preparation of $C_2{}^3H_2$, the alkyne must be prepared immediately before its trimerization to reduce its self radiolytic polymerization.

Preparation of $C_6{}^*H_6$. Vials ⑧ and ⑩, containing respectively $C_2{}^*H_2$ and the catalyst, were rapidly sealed to the side arms of the pyrex apparatus shown in Figure 2, outgassed under vacuum via joint ⑪, then sealed off at constriction ⑫. Breaking the fragile seals ⑧ and ⑩ with the glass hammer ⑬ allowed the alkyne to diffuse onto the catalyst and to react at 25°C for 30 minutes. The reaction products were then desorbed by heating the catalyst (10 minutes at 225°C) and condensed into the tube ⑭, which was sealed off at constriction ⑮.

In order to reduce the extent of its self-radiolytic decomposition, tritiated benzene was diluted with a 250-fold excess of $C_6{}^2H_6$ carrier.

Preparation of $C_6{}^*H_5CH_3$. The same procedure described in the previous section was followed, using a propyne: $C_2{}^*H_2$ = 1:10 mixture, within the apparatus shown in Figure 3, similar to the one used for the preparation of acetylene, except for the presence of the additional reservoir ⑯ containing the required amount of propyne. The crude product from the trimerization of the alkyne mixture was eventually diluted with ca. 1 ml of $C_6{}^2H_6$ carrier.

Preparation of $C_6H_5C^*H_3$. The apparatus used is shown in Figure 4, whose open side arm ⑰ was sealed to vial ⑱, containing ca. 0.15 mmol $^*H_2O$. About 20 mg of finely divided Zn were introduced into the side arm ⑲, and sealed. A fragile capillary tube, containing 9 mg of benzotrichloride, was placed in section ⑳ of the apparatus. The latter was evacuated and outgassed via joint ㉑, and sealed off at constriction ㉒. A Zn mirror was subsequently formed onto the cold walls of the apparatus by heating arm ⑲ while keeping finger ⑳ at -196°C. Breaking the fragile seal of ⑱ with the hammer ㉓ allowed $^{*}H_2O$ to diffuse onto the Zn mirror. Immediately afterwards the capillary tube in ⑳ was broken with hammer ㉓ and benzotrichloride condensed onto the Zn mirror. The whole apparatus was then heated at 200°C for 1 hour. The crude tritiated product was eventually diluted with ca. 1 ml of $C_6{}^2H_6$ carrier.

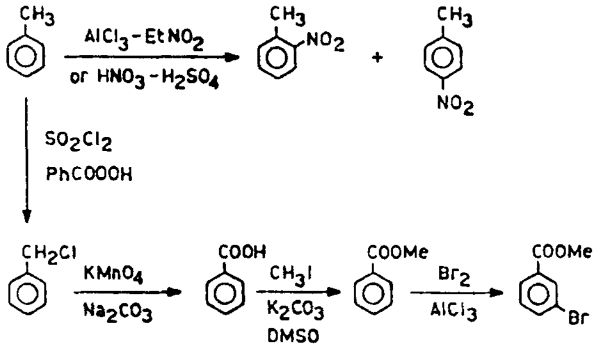
Analysis of Products. The products from the blank runs carried out with deuterated water were analyzed by glc, using a Sigma 1 instrument from Perkin-Elmer Co., equipped with a FID unit and a 6-m long, 3.1-mm i.d. glass column packed with 20% β,β'-oxydipropionitrile on 60-80 mesh Chromosorb W, operated at 50°C. The isotopic composition of the deuterated products was determined with a Model RMU 6 Hitachi-Perkin Elmer mass spectrometer.

The tritiated products were analyzed by radio glc, using a model C chromatograph from C. Erba Co., on a 2.5-m long, 4-mm i.d. stainless steel column, packed with 80-100 mesh Porapak Q, operated at 190°C. The effluents diluted with CH_4 at a 1:1 ratio, were introduced into a heated flow ionization chamber, whose current was measured with a Cary model 401 vibrating-reed electrometer.

Purification of the Crude Products. Following addition of the appropriate inactive carriers, the crude reaction products were separated and purified by preparative glc on the following columns: i- a 4-m long stainless steel column packed with SF 96 silicone oil on 60-80 mesh Chromosorb-W DMCS, operated with a linear temperature program rising at 15°C min^{-1} from 80° to 250°, and ii- a 5-m long stainless steel column, packed with 12% Apiezon L grease on 60-80 mesh Chromosorb-W DMCS, at 200°C. The purification was repeated until the specific activity of the recovered sample, measured in a Packard Tri-Carb 460 CD scintillation spectrometer, reached a constant value. The radiochemical purity of the final specimens was further checked by radio glc using the same columns.

The isotopic composition of the multilabeled benzene and toluenes after the above-described purification procedures was inferred from the overall activity of the biphenyl, or the isomeric methyl-substituted biphenyls, formed from the decay of benzene-^3H_x and toluene-^3H_x respectively after a 3-months storage period.

The distribution of the ^3H atoms within multitritiated toluenes was determined from the substitution scheme, by measuring the decrease of the molar activity in



the substituted products. The isolation and purification of the latter was obtained using the following columns: i- a 5-m long, stainless steel column, packed with 20% E 301 silicone oil: Benntone 34 1:1 mixture on Chromosorb W, 60/80 mesh, operated at 130°C for the separation of isomeric nitrotoluenes, and, ii- a 4-m long, stainless steel column packed with 20% E 301 silicone oil on Chromosorb W, 60/80 mesh, operated at 140°C for the separation of benzyl chloride, methyl benzoate and methyl meta-bromobenzoate.

RESULTS AND DISCUSSION

The preparative reactions employed, the percent composition of the labeled products formed, and the absolute yields of the products are summarized in Table 1.

Labeled Benzene. The yield of benzene-^3H_x (47%) compares well with that (ca. 30%) reported by Nefedov *et al*. (16) based on an approximate estimate. The increased yields undoubtedly arise from the much shorter reaction time that characterizes the present preparation (less than one hour overall) which substantially reduces the self irradiation of acetylene, and consequently its radiolytic polymerization.

In fact, under the conditions of ref. 16, namely 5 Ci starting activity, 9 hours required for the formation of acetylene, and 48 hours for its trimerization, a considerable fraction of the alkyne is consumed by its self-radiolytic polymerization to cuprene, as suggested by the results of a crude calculation based on the known (19,20) G ($-C_2H_2$) value of 71.9.

The same calculation leads to the rather paradoxical conclusion that much of the tritiated benzene isolated under the above experimental conditions arises from spontaneous *radiolytic* processes, rather than from the intended *catalytic* trimerization. Indeed, conversion of acetylene to benzene is known to accompany, as a secondary process with a lower yield, $G(+C_6H_6) = 5.1$, the radiation-induced polymerization of C_2H_2 to cuprene.

The isotopic composition of deuterated benzene, $C_6{}^2H_xH_{6-x}$, from the blank runs, as determined by mass spectrometry, was found to correspond quite closely to that calculated, assuming the absence of isotope effects, from the known isotopic composition of the starting deuterated acetylene.

Use of multitritiated benzene, $C_6{}^3H_xH_{6-x}$, as a precursor in the decay experiments, does not require a detailed knowledge of its isotopic composition, provided that $x \geqslant 2$.

In order to verify whether this condition was satisfied, a decay experiment was undertaken in which a very dilute solution of $C_6{}^3H_xH_{6-x}$ in $C_6{}^2H_6$ (1.0 mCi, 0.30 mCi mmol^{-1}) was allowed to stand in the dark at room temperature for 3 months. The activity of biphenyl from the decay promoted reaction sequence

$$C_6H_5{}^3H \xrightarrow[\text{decay}]{\beta} C_6{}^*H_5{}^+ \xrightarrow{+C_6{}^2H_6} C_6{}^2H_6\text{-}C_6{}^*H_5{}^+ \xrightarrow{+B,\ -B^2H^+} C_6{}^*H_5\text{-}C_6{}^2H_5 \quad (1)$$

corresponded very closely (12.3 ± 0.3 μCi versus 11.7 ± 0.3 μCi) to the value calculated assuming that the starting $C_6{}^3H_xH_{6-x}$ sample contained no monotritiated benzene.

Tritiated Toluenes. The general value of the synthetic approach based on the cyclization of alkynes is demonstrated by the preparation of ring-tritiated toluene. It was found that cyclization of a C_2H_2/propyne mixture containing less than 10 mol % C_3H_4 over the trimerization catalyst gave both benzene and toluene (Table 1). Higher concentrations of propyne are undesirable, in that increasing amounts of xylenes are formed. Mass spectrometric analysis of the isotopic composition of the $C_6{}^2H_xH_{5-x}CH_3$ samples from the blank runs revealed that x values peaked around 3, while an appreciable (ca. 10%) fraction of toluene contained more than the four ^3H atoms allowed by the stoichiometry of the cyclization.

$$2\ C_2{}^2H_2 + C_3H_4 \longrightarrow C_7{}^2H_4H_4 \qquad (2)$$

This finding points to the occurrence of isotopic exchange processes over the catalyst, which in turn could lead to isotopic mixing within the molecule of labeled toluene. In order to verify this possibility, the distribution of ^3H within multilabeled toluene was determined by a degradation procedure. The results, compared to the distribution expected in the absence of ^3H reshuffling, i.e. methyl group = 0% (0%), ortho positions = 31% (25%), meta positions = 53% (50%), para position = 16% (25%) show that isotopic scrambling does indeed occur, if to a rather limited extent. The methyl group is not affected at all, whereas most of the ^3H loss involve apparently the para position.

In principle, the preparation of the side-chain multilabeled toluene could be carried out using reaction (2).

However, considerable difficulties are encountered in the preliminary preparation of the required methyl-^3H-propyne. Consequently, the side-chain multitritiated toluene was prepared according to a different procedure, based on the dehalogenation of benzotrichloride with tritiated water. This represents an adaptation of the method described by Leblank, Morse and Leitch (21) for the preparation of deuterated alkanes. The zinc dust originally employed by these authors is not suitable in the preparation of ^3H-labeled toluene on a micro scale. The relatively high content of H_2O, light hydrogen etc. causes a dilution of the ^3H, and the formation of partially tritiated species. However, such a drawback is substantially reduced if Zn is evaporated under vacuum on the clean walls of a pyrex reaction tube to produce a mirror, a procedure that eliminates most of the unwanted hydrogenated impurities.

It was found that reaction of ^2H_2O with benzotrichloride over a clean Zn mirror gives methyl-deuterated toluene, together with deuterated benzene. The mass spectrometric analysis of the product showed that an appreciable fraction (17.5%) of the toluene molecules contains <u>more</u> than the 3 ^2H atoms allowed by the stoichiometry of the dehalogenation process

$$C_6H_5CCl_3 + 3\ ^2H_2O + 3\ Zn \longrightarrow C_6H_5C^2H_3 + 3\ ^2HCl + 3\ ZnO \qquad (3)$$

This must be traced to the occurrence of isotopic exchange processes and shows that the ring positions must contain some deuterium. In fact, degradation of the purified toluene-^3H from reaction (3) gave the following distribution of the ^3H activity:α positions = 83%, <u>ortho</u> positions = 0%, <u>meta</u> positions = 4%, <u>para</u> position = 13%.

Since the planned application of the product as a precursor in decay experiments required that no activity was contained within the ring, the multitritiated toluene, following the purification procedure, was allowed to repeatedly exchange at room temperature with a large excess of 7 M perchloric acid. The acid-catalyzed isotope exchange effectively removed any tritium from the ring positions, without affecting at all the ^3H content of the methyl group.

Following the above procedure, ca. 92 mCi of $C_6H_5C^3H_xH_{3-x}$ were obtained from 115 mCi of the purified tritiated toluene sample.

As for $C_6{}^3H_xH_{6-x}$, decay experiments of individual samples of tritiated toluenes (1.0 mCi, 0.30 mCi mmol^{-1}) in $C_6{}^2H_6$ (3 months) lead to formation of the corresponding isomeric biphenyls and diphenyl methane, respectively, at activities demonstrating that most of the toluene precursor molecules (> 80%) contain more than two tritium atoms.

A final consideration concerns the absolute yields of multitritiated products which appear, in general, lower than those from deuterated reagents measured in the blank runs. The discrepancy can be traced either to an incomplete conversion of $^3H_2$ to ^3H_2O, or to a partial self-radiolytic decomposition of the latter back to $^3H_2$, which would cause the tritiated acetylene to contain less ^3H activity than calculated.

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