THE SYNTHESIS OF 2-CHLOROBIPHENYL-1',2',3',4',5',6'-$^{14}C_6$*, [1]

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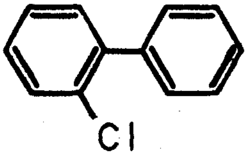
SUMMARY

Modification of the traditional Gomberg reaction conditions provides a simple, economical route to 2-chlorobiphenyl-1',2',3',4',5',6'-$^{14}C_6$ (I). The reaction of benzene-U-$^{14}C_6$ with an excess of the diazonium salt from 2-chloroaniline produces ^{14}C-labelled I in 10% radiochemical yield. This method should be applicable to the preparation of any chlorinated biphenyl having one unsubstituted ring.

In recent years the scientific community has come to a general understanding of the adverse effects of the polychlorinated biphenyls (PCBs) in the environment[2]. However, our knowledge of structure-activity relationships in the toxicity and environmental persistence of these compounds is limited, in part, by the general unavailability of pure radio-labelled chlorobiphenyls[3]. We report here the preparation of 2-chlorobiphenyl-1',2',3',4',5',6'-$^{14}C_6$ (I) by a route which should be applicable to the synthesis of any chlorinated biphenyl having one unsubstituted ring.



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In an attempt to minimize both the complexity of the reaction mixture and expense we chose to approach this problem by reacting the diazonium salt of an unlabelled chlorinated aniline with commercially available benzene-$^{14}C_6$[4]. This route minimizes the expense of the preparation by utilizing inexpensive ^{14}C-labelled benzene but requires modification of the normal Gomberg conditions in that the benzene cannot be used in excess if one is to avoid undue dilution of label in the product.

The modifications required for the preparation of I from benzene and excess diazonium salt of 2-chloroaniline were developed using unlabelled benzene on a 100 mg scale. The optimum conditions for this reaction are very similar to those described in the literature for the preparation of I by the normal Gomberg route[5]. However, one must shorten the reaction time to prevent the accumulation of terphenyls and must quench the excess diazonium salt with cuprous cyanide. Under these conditions one obtains an easily separable mixture consisting primarily of 2-chlorobenzonitrile, 2-chlorobiphenyl, and 2,2'-dichlorobiphenyl.

Using this procedure, the synthesis of ^{14}C-labelled I is straightforward. Diluted benzene-U-$^{14}C_6$ is vacuum-transferred to a reaction vessel and coupled with excess diazonium salt from unlabelled 2-chloroaniline. Following quenching and chromatographic purification one obtains a ten percent radiochemical yield[6] of I having a specific activity of 300 µCi/mmol.

This method should be a versatile one for the preparation of radiolabelled chlorinated biphenyls in that one can vary the substitution pattern in one of the rings merely by choice of substitution pattern in the aniline. This choice fixes the position of substituents in the product and assures the production of only one labelled chlorobiphenyl. When required one can also increase the specific activity of the product by decreasing the amount of carrier benzene.

Experimental

Carrier benzene (70µl, 0.79 mmol) was vacuum-transferred to a three-neck flask chilled in liquid nitrogen and fitted with a Dewar condenser containing liquid nitrogen. Following subsequent vacuum-transfer of benzene-U-$^{14}C_6$ (100µCi, 53 mCi/mmol, ICN) the apparatus was allowed to warm until the benzene (calculated specific activity = 130µCi/mmol) began to melt. A chilled, filtered solution of the diazonium salt prepared by the reaction (0°C) between 2-chloroaniline (1.2 g, 9.4 mmol) in 4.6 ml of 6.4 N HCl and sodium nitrite (0.75 g, 10.9 mmol) dissolved in 1.8 ml water was added. A solution of sodium acetate trihydrate (3.5 g, 5.5 mmol) in 7 ml of water was added dropwise to the stirred mixture at 0°C. After stirring for 3 hours at 0°C and 20 hours at 25°C, the reaction mixture was cooled to 0°C and neutralized (pH 7) with saturated Na_2CO_3 Solution. A chilled CuCN solution (freshly prepared from 1.23 g CuCl and 1.62 g NaCN in 7.5 ml water) was added with vigorous stirring. This mixture was stirred at 25° for 3 hours, warmed to 50° and allowed to cool to 25°. Following workup (hexane/water), the hexane solution was dried (Na_2SO_4), filtered, and concentrated on a rotary evaporator to afford 48 mg of semi-crystalline material.

Pure ^{14}C-2-chlorobiphenyl was isolated by preparative tlc (Brinkman Silica Gel PF-254, benzene eluent) followed by preparative glpc (2% OV-1 on Chromsorb W, 2m x 1/4", 127°C). This procedure yielded 2-chlorobiphenyl-1',2',3',4',5',6'-$^{14}C_6$ (12µCi) with a specific activity of 300µCi/mmol[7],[8]. Autoradiography (Brinkman Silica Gel 60 F-254 Precoated Plate, benzene eluent) demonstrated the radiochemical purity of the product.

References

1] Financial support from IDOE (Grant IDP 75-03677) and the National Institutes of Health (Biomed Support Grant) is gratefully acknowledged.

2] For a comprehensive review see:
Hammond, P. B., Nisbet, I.C.T. Sarofim, A.F., Drury, W.H., Nelson, N., Rall, D.P., *Environ. Res.,* 5 (3), 249 (1972).

3] a) For a compilation of radiolabelled chlorinated biphenyls prepared before 1974 see: Hutzinger, O., Safe, S., Zitko, V., *The Chemistry of PCB's,* CRC Press, Cleveland, 1974. b) Melvas, B., *J. Labelled Compounds,* 10, 324 (1974); c) Hoizumi, K. and Moriya, T., *ibid.,* 10, 499 (1974). d) Sundstrom, G., *Bull. Environ. Contam. Toxicol.,* 11, 39 (1974).

4] A ^{14}C-labelled 2-chlorobiphenyl has been obtained in the course of mechanistic studies of the decomposition of ^{14}C-N-nitrosoacetanilide in chloro-

benzene. However this is not a practical route to labelled material since ^{14}C-aniline is relatively expensive and the reaction produces a mixture of all three monochlorobiphenyls. Migita, T., *Yuki Gosei Kagaku Kyokai Shi.*, 19, 480 (1961); *Chem. Abstr.*, 56, 10008 (1962).

5] Elks, J., Haworth, J.W., and Hey, D.H., *J. Chem. Soc.*, 1284 (1940).

6] Little of the remaining 90 percent of the original radioactivity is extractable either by benzene or hexane. Some may be lost by vaporization of benzene before it has reacted but most is probably incorporated into the residual tars inevitably produced in these free-radical reactions.

7] The amount of 2-chlorobiphenyl present in this sample was determined by ultra-violet spectroscopy (246 nm absorption in hexane) and by analytical glpc (5% SE-30 on Chromosorb W, 2m x 1/8", 120°C).

8] We feel that the discrepency in specific activities of I and starting benzene are due to loss of unlabeled benzene in the vacuum-transfer step before the labelled benzene is added. Our procedure is to vacuum-transfer the unlabelled benzene, break the vacuum, open the system, attach the vial of labelled benzene, and transfer it. Our experience has been that even at low temperatures a substantial portion of a small amount of a volatile substance is lost when it is open to the atmosphere.