acid, using a Potentiograph E 336 (Metrohm AG, Herisau, Switzerland) automatic titrator. The time of each sample was taken as the time the end point was reached. Generally 8–12 points were taken per run.

B. Formic Acid. In the formic acid runs, *ca.* 25 ml of formic acid was allowed to equilibrate in the constant temperature bath at 25.00 ± 0.02°. Approximately 0.4 g of ethyl trifluoromethanesulfonate was added, and after about 5 min, 2-ml aliquots were withdrawn at intervals and quenched in 8-ml portions of ice-cold propionic acid. The times were taken as the time when half the aliquot had drained into the quenching solution. The quenched propionic acid solutions were then titrated as in the acetic acid case with standard sodium acetate solution in acetic acid.

C. Ethanol. Both the 100% and the 80% ethanol solvolysis rates were determined in the same manner. About 0.4 ml of the solvent in an nmr tube was inserted in the Varian variable-temperature probe of a Varian A-60 nuclear magnetic resonance spectrometer. The desired temperature setting was made and the solvent was allowed to equilibrate. After temperature equilibration was complete, 160–300 mg of ethyl trifluoromethanesulfonate was added; the tube was shaken thoroughly and replaced in the probe. Another few minutes were allowed for reequilibration and then the methylene proton quartet of the ester was repeatedly integrated at intervals and the time of each integration was recorded. This quartet is easily identifiable since it appears at approximately 1 ppm lower field than the ethanol quartet. The true sample temperature was obtained by measuring the separation of the methanol hydroxyl and methyl peaks in a sample of methanol at the same temperature setting immediately before and after each run.

Calculation of Rate Constants. All rate constants were computed by the nonlinear least-squares method on an IBM 7090-94 computer using a modification of the LSKIN1 program of DeTar.[31]

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(31) We are indebted to Professor D. F. DeTar for a copy of his program and to H. A. Hammond for appropriate modifications.

The Mechanism of the Formation and Hydrolysis of Phenyl Ether in the Basic Hydrolysis of Chlorobenzene[1]

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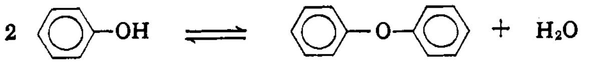
Contribution from the Benzene Research Laboratory of The Dow Chemical Company, Midland, Michigan 48640. *Received April 10, 1967*

Abstract: The mechanism of the formation and hydrolysis of diaryl ethers has been studied by carbon-14 tracer technique using phenyl ether and also by the hydrolysis of *p*-ditolyl ether. These studies have shown that phenyl ether is formed by the reaction of phenolate ion with benzyne. However, the hydrolysis of phenyl ether does not go through the benzyne intermediate. It has also been demonstrated that the loss of chloride by the chlorophenyl anion to form benzyne is a reversible reaction which can lead to carbon-14 activity distributed around the benzene ring.

The hydrolysis of chlorobenzene to phenol produces many by-products; the major one is phenyl ether, and in some instances its formation may account for 30% of the chlorobenzene.[2]

Earlier studies of the formation and hydrolysis of phenyl ether in the basic hydrolysis of chlorobenzene are summarized by Hale and Britton.[3] The mechanism was not discussed; however, the formation was depicted as a double decomposition reaction of chlorobenzene and sodium phenolate. Hale and Britton also proposed the existence of an equilibrium as shown in eq 1. This equilibrium was also proposed as occurring during the manufacture of phenol from chlorobenzene.[2]


(1)

We have found no evidence for equilibrium 1 under the conditions employed in our work. No phenol could be detected when phenyl ether was heated with excess water at 400°, and no phenyl ether was formed when phenol was heated at 400° in the presence of excess 4 *N* aqueous sodium hydroxide. Claes and Jungers have studied the kinetics of the above equilibrium in the presence of a thoria catalyst.[4]

Lüttringhaus and Sääf studied the cleavage of alkyl aryl ethers by alkalies and found the main products to be phenolates and unsaturated hydrocarbons.[5] The reaction of 2,4-dinitrophenyl phenyl ether with bases (usually weak bases such as piperidine) has been studied in detail.[6–9] However, the nitro group is involved in the mechanism of the reaction and the same mechanism would not hold for the hydrolysis of phenyl ether. The formation of phenyl ethers has been studied under conditions of the Ullman condensation,[10] but the conclusions regarding the mechanism are considered applicable only in the presence of a copper catalyst.

Lüttringhaus and Ambros proposed that benzyne was an intermediate both in the formation of phenyl ether from chlorobenzene and alkali and in the hydrolysis of phenyl ether to phenol.[11] They base their conclusions on comparison to the reaction of phenyl ether with phenylsodium in which they obtained phenol, *o*-phenylphenol, diphenylphenols, and biphenyl phenyl ethers. These are some of the same by-products that

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(1) Paper presented at the 153rd National Meeting of the American Chemical Society, Miami Beach, Fla., April 1967.

(2) H. Clough and H. Wintsch, "Manufacture of Synthetic Phenol by the Chlorination Route at I. G. Farbenindustrie," A. G. Leverkusen, PB 97853, 1947, pp 37–38.

(3) W. J. Hale and E. C. Britton, *Ind. Eng. Chem.*, **20**, 114 (1928).

(4) F. Claes and J. C. Jungers, *Bull. Soc. Chim. France*, 1042 (1962).

(5) A. Lüttringhaus and G. von Sääf, *Angew. Chem.*, **51**, 915 (1938).

(6) L. C. Raiford and J. C. Colbert, *J. Am. Chem. Soc.*, **48**, 2652 (1926).

(7) R. J. W. Le Fèvre, S. L. M. Saunders, and E. E. Turner, *J. Chem. Soc.*, 1168 (1927).

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(9) F. Pietra, *Tetrahedron Letters*, 2405 (1965).

(10) H. Weingarten, *J. Org. Chem.*, **29**, 977 (1964).

(11) A. Lüttringhaus and D. Ambros, *Ber.*, **89**, 463 (1956).

are formed during the hydrolysis of chlorobenzene. They concluded that the by-products are formed during the hydrolysis of phenyl ether, suggesting that the phenylsodium reacts with phenyl ether at room temperature by the same mechanism that sodium hydroxide reacts at 350–400°. We felt that their proposed mechanism was not generally applicable because we could find no significant amounts of phenylphenols or other by-products from the hydrolysis of pure phenyl ether.

We chose to study the mechanism of the formation and hydrolysis of phenyl ether during the hydrolysis of chlorobenzene-1-C^{14} by the carbon-14 tracer technique. Chlorobenzene-1-C^{14} was hydrolyzed at 395° for 3 min with 4 *N* aqueous sodium hydroxide. These conditions gave a 26% yield of phenyl ether and a 53% yield of phenol. First the phenol formed in the reaction was isolated and degraded to compare our conditions and results with those of Bottini and Roberts.[12] They were the first to gather conclusive evidence that the hydrolysis of chlorobenzene proceeds through the benzyne intermediate at high temperature.

The comparative results are shown in Table I. The main experimental difference in the initial hydrolysis was in the reaction temperature. Bottini and Roberts concluded that the SN2 mechanism is minimized at the higher temperatures; thus we expected and did find a decreased radioactivity in the 1 position. The observed differences in activity, however, may fall within the range of experimental variation.

Table I. Distribution of Carbon-14 Activity in Phenol Obtained from Hydrolysis of Chlorobenzene-1-C^{14}

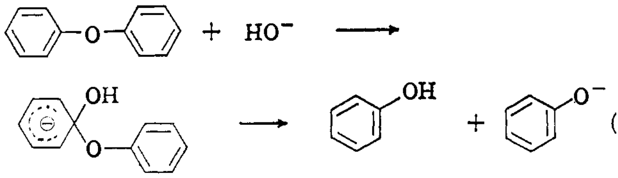
Authors	Account of initial activity, % Position in benzene ring 1	 2	 3 and 4	Reaction temp, °C
Bottini and Roberts	56.5	41.5	0.6	340
Dalman and Neumann[a]	53.5	43.0		395

[a] Based on the percentage of the cyclohexanone activity found in the $BaCO_3$ and 1,5-diaminopentane as shown in Table III.

The phenyl ether from the same reaction mixture was isolated and hydrolyzed separately to phenol under similar conditions (*i.e.*, 395–400°). This phenol was then degraded to determine the percentage of carbon-14 activity in the various positions.

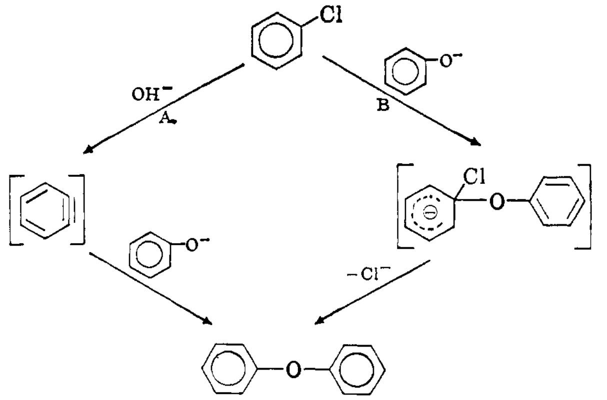
Experimentally there was found 51% of the carbon-14 activity in the 1 position, 43% in the 2 position, and 4% in the 3 and 4 positions combined. These results would best be explained by a formation of phenyl ether *via* benzyne and hydrolysis *via* an SN2 mechanism except for the relatively high activity in the 3 and 4 positions. In order to better explain these results, it was felt necessary to study the hydrolysis step separately using *p,p′*-tolyl ether. If the hydrolysis proceeded *via* a benzyne intermediate one would obtain a mixture of *m*- and *p*-cresols. The reaction was carried out and it was found that the phenolic fraction contained no *m*-cresol detectable by infrared and glpc analysis.

The results of the hydrolysis of *p,p′*-tolyl ether, together with the observation that the hydrolysis of phenyl ether produced none of the usual chlorobenzene hydrolysis by-products such as the phenylphenols, are the basis of our conclusion that the hydrolysis proceeds through a nonrearranging SN2 mechanism (eq 2). The



(2)

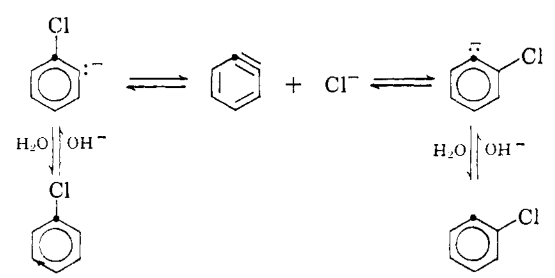
two routes considered in formation of the phenyl ether are based on a benzyne mechanism (A in eq 3) and an SN2 mechanism (B in eq 3). Both routes necessitate



a prior formation of phenol. The resulting distribution of the carbon-14 in phenyl ether prepared from chlorobenzene-1-C^{14} thus will be a function of the distribution in the phenol as well as the relative amount of rearranging or nonrearranging ether formation. The distribution of the radioactivity found agrees best with calculations based on formation of phenyl ether *via* benzyne and hydrolysis without further rearrangement.

The activity found in other than the 1 and 2 positions is attributed to the existence of a benzyne–chloride equilibrium (eq 4 and 5).[13]

(4)



(5)

To obtain support for this type of equilibrium, *o*-chlorotoluene was partially hydrolyzed with caustic under the usual conditions. The remaining chlorotoluene was isolated by fractionation and shown to contain 10% *m*-chlorotoluene by infrared spectroscopy and nmr. (See Experimental Section for details of the identification and analysis of *m*-chlorotoluene.) The dot in depicted aromatic rings indicates the position of the carbon-14 labeling. The over-all relationships are shown in eq 6.

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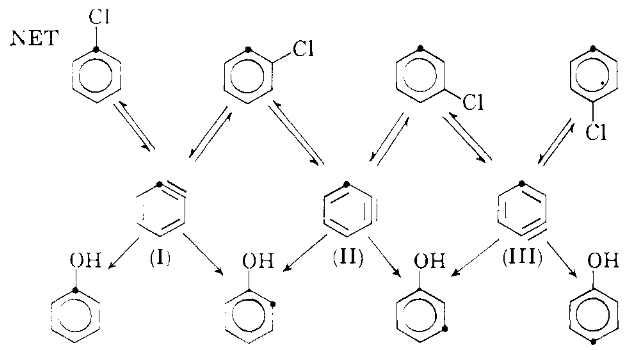
[12] A. T. Bottini and J. D. Roberts, *J. Am. Chem. Soc.*, 79, 1458 (1957).

[13] G. Wittig, *Angew. Chem. Intern. Ed. Engl.*, 4, 731 (1965).



The low radioactivity found in positions other than 1 and 2 of the phenol isolated is attributed to removal of most of the benzyne I by a rapid, irreversible phenol formation in contrast to relatively slower formations of benzynes II and III.

We have calculated the percentages of carbon-14 activity expected in the different positions of the phenol isolated from hydrolysis of the phenyl ether. In calculating, we assumed that the phenol reacting to form the phenyl ether consisted of 55% phenol-1-C^{14}, 42% phenol-2-C^{14}, and 3% combined phenol-3- and -4-C^{14}. The 55% figure is the value obtained by the present authors after normalizing to a 100% total. The remaining distribution would be obtained if 15% of the phenol were formed *via* SN2 and the remainder *via* benzyne intermediates composed of 94% isomer I and 6% isomers II and III. This benzyne isomer distribution is calculated if one assumes that the effective rearrangement of chlorobenzene-1-C^{14} to the 2-C^{14} isomer and the rearrangements of the 2-C^{14} and 3-C^{14} isomers to the 3-C^{14} and 4-C^{14} isomers, respectively, are obtained in the same 9:1 ratio as observed in the conversion of *o*- to *m*-chlorotoluene. The 94:6 ratio of benzyne I: benzyne II applied to the formation of phenol and phenyl ether from chlorobenzene-1-C^{14} would not be expected to apply to a benzyne mechanism in the hydrolysis of phenyl ether because chloride ions were not present. The relative amount of benzyne III was considered to be insignificant in these calculations and the entire 6% was attributed to isomer II for simplification. The resulting calculated values along with the experimental values are shown in Table II.

Table II. Experimental and Predicted Distribution of Carbon-14 Activity in Phenol Obtained by Sodium Hydroxide Hydrolysis of Phenyl Ether

Basis of calcn	Account of carbon-14 act., %: 1 position	2 position	3 and 4 positions
Exptl	50.7	43.5	4.1
Benzyne formation and benzyne hydrolysis	37.0	49.2	13.8
Benzyne formation and SN2 hydrolysis	51.0	46.0	3.0
SN2 formation and SN2 hydrolysis	77.5	21.0	1.5
SN2 formation and benzyne hydrolysis	60.75	35.3	3.95

The experimental values shown in Table II were obtained as follows. The starting radioactivity in the ring was taken as 0.191 μCi/mmol which is the average of the measured values for the phenol, cyclohexanone, and 6-aminohexanoic acid. The activity in the 1 position is the activity of the BaCO$_3$ (0.0968) divided by 0.191. The activity of the 1,5-diaminopentane (0.0909) divided by 0.191 gives the fraction of the original activity in the 2, 3, and 4 positions (47.6%). The radioactivity accounting of the degradation products of glutaric acid was somewhat low (79.1%) with 70.5% of the activity of the glutaric acid found in the BaCO$_3$ and 8.6% in the 1,3-diaminopropane. If we assume that the low accounting of the radioactivity is due to error in the BaCO$_3$ activity determination, the percentage of the activity found in the 3 plus 4 positions of the phenol is 4.1% (*i.e.*, 47.6 × 0.086) as shown in Table II. The activity in the two position is 43.5% by difference. Assumption of low activity accounting in the 1,3-diaminopropane would accentuate our conclusion about the scrambling of activity around the ring.

Although the value of 4.1% for the activity in the 3 and 4 positions may be in error by as much as ±20% due to the low accounting of the activity in the last degradation step, we feel that this magnitude of activity in the 3 and 4 positions is significant and qualitatively indicates that some scrambling of activity around the ring does occur.

The 4.1% value for the radioactivity in the 3 and 4 positions is several times the 0.6% found by Bottini and Roberts during the hydrolysis of chorobenzene-1-C^{14}. This difference may be due to somewhat different reaction conditions (temperature and heating–cooling times) and possible catalytic effects due to different reaction vessel materials. Bottini and Roberts also noted marked differences in product composition with seemingly minor differences in reaction procedure during their study of the hydrolysis of halotoluenes.[12]

The close agreement between calculated and observed values in Table II supports our conclusion that the phenyl ether is formed predominately through a rearranging or benzyne intermediate and hydrolyzed by a nonrearranging (SN2) route.

Experimental Section

Radiochemical Analysis. The specific radioactivity of the C^{14}-labeled derivatives was determined by counting aliquots of the samples in a Tri-Carb liquid scintillation spectrometer, Model 314-X.[14] Quench corrections and counting efficiencies were determined by the addition of an internal standard.[15] Barium carbonate samples were treated with acid in a modified Warburg flask. The evolved C^{14}O$_2$ was absorbed in an alcoholic solution of a quaternary ammonium base and counted by liquid scintillation counting techniques.[16]

Materials. Aniline-1-C^{14} hydrochloride (20 mg) with a specific activity of 3.25 mCi/mmol was purchased from New England Nuclear Corp., Boston, Mass. New England Nuclear prepared the aniline-1-C^{14} by the Schmidt reaction using benzoic-1-C^{14} acid prepared by the method of Fields, *et al.*[17a] The aniline-1-C^{14} synthesized by this method should not have any of the carbon-14 in positions other than the 1 position. The aniline-1-C^{14} hydrochloride was dissolved in 75 ml of water, and 12.96 g of unlabeled aniline hydrochloride (Matheson Coleman and Bell) was added to the solution. The resulting solution contained 0.10 mol of aniline-1-C^{14} hydrochloride with a specific activity of about 5 μCi/mmol.

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(14) Pachard Instrument Co., La Grange, Ill.

(15) J. D. Davidson and P. Feigelson, *Intern. J. Appl. Radiation Isotopes*, **2**, 1 (1957).

(16) J. M. Passmann, N. S. Radin, and J. A. D. Cooper, *Anal. Chem.*, **28**, 484 (1956).

(17) (a) M. Fields, M. A. Leaffer, S. Rothchild, and J. Rohan, *J. Am. Chem. Soc.*, **74**, 5498 (1952); (b) J. B. Conant, R. Lutz, and B. B. Corson, "Organic Syntheses" Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p 49.

Table III. Specific Radioactivities of Degradation Products

Chlorobenzene-1-C^{41}

Product	Activity[a,e]	Product	Activity[a]
Phenyl ether	0.522 ± 0.005	Phenol	*b*
↓		↓	
Phenol	0.191[d] ± 0.002	Cyclohexanone	0.2130 ± 0.002
↓		↓	
Cyclohexanone	0.185 ± 0.002	6-Aminohexanoic acid	0.2284 ± 0.002
↓		↓	
6-Aminohexanoic acid	0.198 ± 0.003	$BaCO_3$	0.1138 ± 0.001
↓		↓	
$BaCO_3$	0.0968 ± 0.004	1,5-Diaminopentane[c]	0.0916 ± 0.002
↓			
1,5-Diaminopentane[c]	0.0909 ± 0.002		
↓			
Glutaric acid	0.0210[d] ± 0.001		
↓			
$2BaCO_3$	0.0074 ± 0.0001		
↓			
1,3-Diaminopropane[c]	0.0018 ± 0.0001		

[a] Specific activity in microcuries per millimole. [b] Not determined. [c] Counted as the dibenzamide. [d] Activity after dilution with unlabeled material. [e] The ± figures indicate average deviation for three or four counts of the sample. Although the average deviation is an indication of the counting precision, a more realistic indication of over-all precision is shown by the experimental activities of phenol (0.191), cyclohexanone (0.185), and 6-aminohexanoic acid (0.198) which should all be the same.

The aniline-1-C^{14} was diazotized using the procedure described in "Organic Syntheses."[17b] The cold solution of the benzene-1-C^{14} diazonium chloride was added at a moderate rate to freshly prepared hot cuprous chloride solution. After the addition was completed the solution was stirred for an additional 0.5 hr. The contents of the flask was poured into a separatory funnel along with ether and water rinsings of the reaction flask and associated equipment. The aqueous layer was separated and washed with two 50-ml portions of ether. The original ether layer was combined with the ether extracts and washed with 50 ml of 5% aqueous sodium hydroxide and then with 50 ml of water. The ether solution was dried over calcium chloride, and the ether was removed by distillation through a 6-in. Vigreux column. The chlorobenzene-1-C^{14} was isolated by distillation through an 18-in., vacuum-jacketed Vigreux column. The yield was 7.54 g (68%) with a boiling point of 130.5–131.5°. Unlabeled chlorobenzene (10 ml) was added to the distilling pot and distilled. This operation was repeated three more times in order to recover as much of the chlorobenzene-1-C^{14} as possible. The combined distillate including the original 7.54 g was 53.49 g, boiling at 130.5–131.5°. The distilled chlorobenzene-1-C^{14} was further diluted with unlabeled chlorobenzene up to 1 mol.

Hydrolysis of Chlorobenzene-1-C^{14}. Chlorobenzene-1-C^{12} (56.12 g, 0.50 mol) and 285.3 g of 4 *M* sodium hydroxide solution were put into a 500-ml (total volume) steel pressure reactor. The reactor was rocked at 24 cycles/min and heated with an air-gas flame for 3 min at 395 ± 5°. It took about 20 min to heat the reactor from room temperature to 395°. After heating for the 3-min period at 395° the reactor was cooled with cold water spray. It took about 5 min to cool the reactor back down to room temperature. The contents of the reactor were poured out and the reactor was rinsed with two 30-ml portions of isooctane (2,2,4-trimethylpentane), two 30-ml portions of 4 *M* sodium hydroxide, and then two 30-ml portions of water. The rinsings and the original reactor contents were combined, and the mixture was extracted continuously for about 6 hr with 400 ml of isooctane. The isooctane was removed by distillation and the residue distilled through an 18-in., vacuum-jacketed Vigreux column. The fraction boiling at 122–125° (11 mm) (11.01 g; 26% yield) was collected as phenyl ether. Unlabeled phenyl ether (5 ml) was distilled through the still, and 5.12 g of distillate was collected. The two distillates were combined, and the phenyl ether-X-C^{14} had a specific activity of 0.522 μCi/mmol.

The aqueous portion from the above hydrolysis of chlorobenzene-1-C^{14} was acidified to a pH of 1 with concentrated hydrochloric acid and continuously extracted for 4 hr with 250 ml of benzene. The benzene was removed by distillation and the crude phenol-X-C^{14} was distilled through an 18-in., vacuum-jacketed Vigreux column. The fraction boiling at 72–74° (8–11 mm) was collected as phenol-X-C^{14}. The yield of phenol-X-C^{14} was 25.1 g; 53.4%.

Degradation Procedure. The phenyl ether-X-C^{14} was converted by aqueous caustic hydrolysis. To the same steel pressure reactor that was used for the hydrolysis of the chlorobenzene-1-C^{14} was added 330.2 g of 4 *M* sodium hydroxide solution and 11.80 g of phenyl ether-X-C^{14}. The reactor was heated at 400 ± 5° for 18 min. The crude phenol-X-C^{14} was isolated from the reaction mixture by the same procedure as described above. The crude phenol-X-C^{14} was distilled through an 18-in. vacuum-jacketed Vigreux column yielding 9.87 g (76%) boiling at 80–81° (15 mm). Unlabeled phenol was distilled through the system and another 5.55 g of phenol distillate was collected and mixed with the original sample. The total phenol-X-C^{14} was 15.42 g and had a specific activity of 0.191 μCi/mmol.

The procedure for the degradation of phenol-X-C^{14} was basically the same as that described by Roberts, *et al.*[18] Some modifications were made. Therefore, typical experiments in the degradation of the phenol from phenyl ether-X-C^{14} are given. The specific activities of the degradation products are shown in Table III.

Cyclohexanol-X-C^{14}. Phenol-X-C^{14} (7.05 g) was hydrogenated neat at 150° using 1.0 g of 5% palladium on carbon catalyst in a stainless steel vessel in the low-pressure, Parr shaker-type, hydrogenation apparatus. The product was removed and the vessel rinsed with methanol; the catalyst was removed by filtration, and the methanol was removed by distillation through an 18-in. Vigreux column.

Cyclohexanone-X-C^{14}. The crude cyclohexanol-X-C^{14} (9.0 g) was placed in a 500-ml, round-bottomed flask and cooled in an ice bath. A cold solution containing 14.8 g of potassium dichromate and 12.5 g of concentrated sulfuric acid in 73 ml of water was added to the cyclohexanol-X-C^{14} with rapid stirring. The reaction mixture was kept below 50° and allowed to stand for 1 hr. It was then steam distilled until 500 ml of distillate had been collected. The distillate was saturated with sodium chloride and continuously extracted with ether for 8 hr. The ether extract was dried over silica gel and the ether removed by distillation. The crude cyclohexanone-X-C^{14} was purified by distillation through an 18-in. vacuum-jacketed Vigreux column. The fraction boiling at 54–55° (25 mm) was collected (3.35 g).

6-Aminohexanoic Acid-X-C.[14] Cyclohexanone-X-C^{14} was converted to 6-aminohexanoic acid using the Schmidt reaction.[19] Concentrated hydrochloric acid (14 ml) was added to 2.42 g of cyclohexanone-X-C^{14}. Sodium azide (2.30 g) was added with stirring to the mixture as fast as the vigor of the reaction permitted. The reaction mixture was then allowed to stand overnight. It was heated on a steam bath for 2 hr and then distilled to dryness

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[18] J. D. Roberts, D. A. Semenow, H. E. Simmons, Jr., and L. A. Carlsmith, *J. Am. Chem. Soc.*, **78**, 601 (1956).

[19] P. A. S. Smith, *ibid.*, 70, 320 (1948).

in vacuo. The dry residue was extracted three times with hot ethanol. The ethanol extracts were combined, evaporated to 5–10 ml, and cooled, and then ether was added slowly to precipitate the 6-aminohexanoic acid-X-C^{14} (yield, 1.6 g).

1,5-Diaminopentane-X-C^{14}. The 6-aminohexanoic acid-X-C^{14} (1.50 g) was put into a 50-ml, three-necked reaction flask, and 4 ml of concentrated sulfuric acid was added. The flask was heated at 70–75° for 15 min at reduced pressure (20 mm) to remove the HCl. The flask was cooled to room temperature and fitted with a dropping funnel, a helium sparge tube, and gas outlet to a trapping system. The first trap utilized Dry Ice–methanol cooling to catch everything swept out of the reaction flask except the carbon dioxide from the reaction. A second container utilized liquid nitrogen cooling to trap the carbon dioxide from the reaction gases. A third trap contained saturated barium hydroxide solution which served as an inert gas-flow indicator and also prevented atmospheric carbon dioxide from getting into the system.

Helium was first passed through the entire system for 0.5 hr with no coolant in the dewar flasks of the first two traps. Fresh hydrazoic acid solution was then placed in the dropping funnel (39 ml of 0.93 *M* in chloroform prepared as previously described[20]). Helium was again passed through the system for 0.5 hr. The coolants were added to the trap dewar flasks, and the hydrazoic acid was added to the reaction mixture dropwise over a period of 45 min while a slow stream of helium was kept flowing through the system. The reaction mixture was then heated to 45° for 6 hr. The stopcocks on the trap containing the carbon dioxide from the reaction were then closed, and the trap was transferred to a carbon dioxide free drybox. The trap was removed from the liquid nitrogen dewar flask and allowed to warm; the collected carbon dioxide was allowed to flow into 100 ml of a barium hydroxide solution. The precipitated barium carbonate was collected by filtration.

A small portion of the residue from the above Schmidt reaction was used to prepare the 1,5-diaminopentane-X-C^{14}-dibenzamide by the Schotten–Baumann reaction[21] for radioassay. The melting point was 133–134° (lit.[22] 135°).

Glutaric-X-C^{14} Acid. The 1,5-diaminopentane-X-C^{14} was oxidized to glutaric-X-C^{14} acid using neutral potassium permanganate. The aqueous portion containing the 1,5-diaminopentane-X-C^{14} (18.2 mmol based on the 6-aminohexanoic acid) was neutralized to a pH of 8 with 1 *N* sodium hydroxide. The mixture was then refluxed with a solution of 16 g of potassium permanganate in 300 ml of water for 30 min. Unlabeled glutaric acid (0.80 g) was added as carrier. The manganese dioxide was removed by filtration and washed with 250 ml of hot water. The filtrate was acidified with concentrated hydrochloric acid and extracted continuously with ether for 12 hr. The ether extract was concentrated and extracted with five 10-ml portions of 20% sodium hydroxide solution. Unlabeled glutaric acid (0.40 g) was added to the combined sodium hydroxide extracts, and the mixture was acidified with concentrated hydrochloric acid and extracted with ether continuously for 12 hr. The ether was removed using a rotary evaporator and the residue recrystallized from benzene. The yield was 0.45 g of product having a melting point of 89–98°. Infrared analysis indicated it was 60–80% glutaric acid and 20–40% adipic acid. The presence of adipic acid at this point was probably due to an incomplete Schmidt reaction in the preparation of the 1,5-diaminopentane. Any unreacted 6-aminohexanoic acid should be converted to adipic acid by the potassium permanganate oxidation. The pure glutaric acid was separated from the adipic acid by chromatography as described by Marvel and Rands.[23a] After recrystallization from benzene, the yield was 0.25 g of material which had a melting point of 97–98° (lit.[23a] 97.5°).

1,3-Diaminopropane-X-C^{14}. Hydrazoic acid (6 mmol) in chloroform was added to 1.5 mmol of glutaric-X-C^{14} acid in 1.5 g of concentrated sulfuric acid in the same manner as described above for the preparation of 1,5-diaminopentane. The reaction was allowed to proceed at room temperature for 12 hr. The yield of barium carbonate was 0.20 g. The 1,3-diaminopropane isolated as the dibenzamide, after recrystallization, had a melting point of 150.0–150.5° (lit.[18] mp 150.0–150.5°).

Hydrolysis of *o*-Chlorotoluene. *o*-Chlorotoluene (63.0 g; 0.50 mol) and 280.0 g of 4.0 *N* sodium hydroxide solution were added to the same pressure reactor as was used to hydrolyze the chlorobenzene-1-C^{14}. The reaction was run at 400 ± 5° for 2.3 min. The neutral portion of the reaction mixture was isolated by extraction with isooctane. The isooctane was removed by distillation through an 18-in. Vigreux column. The unreacted chlorotoluene was isolated from the residue by fractional distillation through an 8 mm (i.d.) × 1 ft vacuum-jacketed column packed with $^1/_{16}$ in. glass helices. The fraction (3.04 g) boiling from 156 to 159° was collected. The boiling point range of the distillation fraction eliminates the possibility of interference from a low boiler such as toluene in subsequent analysis. Analysis by glpc on a $^1/_8$ in. × 10 ft, DC-410 silicone column indicated a purity of 99.6% for combined *o*- plus *m*-chlorotoluenes. Five minor components (about 0.4% of the total area) were eluted before the peak for the combined *o*- plus *m*-chlorotoluenes. Analysis by nmr (60 MHz, 20% w/v in $CDCl_3$ + 1% TMS) showed a major methyl peak at −2.34 ppm and a structured weak absorption −3.8 Hz from it. Subsequent addition of *m*-chlorotoluene caused the structured (weaker) absorption to rise and the main absorption to decrease. Essentially exact superposition of the absorption of *m*-chlorotoluene on the minor CH_3 absorption of the sample spectrum gives very good support to the identification of the smaller component as *m*-chlorotoluene. Quantitative analysis by infrared spectroscopy showed 10.0% *m*-chlorotoluene to be present in this fraction.

Infrared Analysis for *m*-Chlorotoluene in *o*-Chlorotoluene. Four known mixtures of authentic *o*- and *m*-chlorotoluenes were prepared in carbon disulfide. The out-of-plane phenyl vibrational band at 12.9 μ was used for the analysis. A plot of the absorbance at 12.9 μ *vs.* the concentration of *m*-chlorotoluene yielded a straight line. The concentration of *m*-chlorotoluene in the sample from the above experiment was determined by measuring the absorbance at 12.9 μ and reading the concentration from the calibration curve. No peaks other than those observed for *o*- and *m*-chlorotoluene were observed in the infrared spectrum of the experimental sample.

Hydrolysis of *p*-Ditolyl Ether. *p*-Ditolyl ether was hydrolyzed with aqueous sodium hydroxide in the same manner as the original hydrolysis of chlorobenzene-1-C^{14}. *p*-Ditolyl ether (13.5 g) and 330.0 g of 4.0 *N* sodium hydroxide were heated at 400 ± 5° for 41.5 min and worked up as previously described. Gas chromatographic analysis of the starting material showed 97.9% *p,p'*-ditolyl ether, 1.1% *o,p'*-ditolyl ether, and 1.0% *p*-tolyl phenyl ether.

The neutral fraction yielded 2.51 g of unreacted *p*-ditolyl ether.

The phenolic product fraction was analyzed by gas chromatography on a bentone-modified, polyester column to separate the *m*- and *p*-cresol isomers[24] and on a silicone rubber column to determine phenol. The analysis showed: 9.3 g (80% yield based on reacted *p*-ditolyl ether) of *p*-cresol and 0.55 g of phenol. No *m*-cresol could be detected by gas chromatography or infrared analysis.

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