

mL of hexamethylphosphoramide was vigorously stirred under nitrogen while being heated at 110 °C for 7 h. After being cooled to room temperature, the reaction mixture was poured into 150 mL of water and extracted with ether (2 × 250 mL). The combined extracts were washed with an equal volume of water and dried. The residue left upon evaporation of the ether was passed through a column of basic alumina (3 cm × 3 cm, elution with 125 mL of 9:1 hexane-ether). Concentration of the eluate afforded a colorless oil that solidified with external dry ice cooling, leaving 457 mg of a crystalline mass. Several recrystallizations of a small sample of the above from methanol furnished the diene in pure form: mp 74 °C; IR (CDCl₃) ν_{max} 3020, 2960, 1600, 1490, 1440, 1070, 1030, 900 cm⁻¹; 200 MHz ¹H NMR (CDCl₃) δ 7.13-6.95 (m, 10 H), 6.56-6.47 (m, 2 H), 6.02-5.96 (m, 2 H), 3.45 (s, 2 H), 3.39-3.36 (m, 2 H); ¹³C NMR (CDCl₃) 142.4, 137.6, 127.8, 126.8, 125.4, 124.5, 44.0, 39.8 ppm; mass spectrum, calcd *m/e* 258.1408, obsd 258.1402; UV (isooctane) 268 nm (ϵ 550), 273 (950), 286 (1300), 295 (960). This material yellowed rapidly when in solution and exposed to light. It was therefore expedient to purify samples immediately before use.

Method B. A solution containing allylic alcohol **22a** (240 mg, 0.86 mmol) in 1.5 mL of hexamethylphosphoramide was stirred at 60 °C under nitrogen while methyltriphenoxyphosphonium iodide (780 mg, 1.73 mmol) was added in one portion. After 2 h at 60 °C, the resultant solution was heated for an additional 5 h at 105 °C. The contents were cooled to room temperature, poured into 15 mL of 2.7 M aqueous potassium hydroxide solution, and extracted with 1:1 pentane-ether (2 × 250 mL). The total organic layer was washed once with brine (100 mL), dried, and evaporated. The remaining oil was chromatographed on neutral alumina (thick-layer plate, double elution with hexane). This served to separate most of the yellow chromophoric material and afforded a broad band which amounted to 136 mg and whose composition was indicated by analytical TLC to consist mostly of the desired diene and a slower moving component (presumed to be **22b**). This material was dissolved in 2 mL of tetrahydrofuran, an excess of 1,8-diazabicyclo[5.4.0]undec-7-ene was added, and the solution was magnetically stirred at room temperature under nitrogen. After 36 h, the lower *R_f* spot had disappeared. Silica gel chromatography of the residue (thick-layer plate, elution with hexane) afforded 20 mg (9%) of **10** as a colorless oil. This material crystallized after standing overnight at 0 °C and was identical with those samples of **10** prepared above. For allylic iodide **22b**: ¹H NMR (CDCl₃) δ 7.33-6.76 (br m, 10 H), 6.26-5.33 (series of m, 3 H), 3.46-3.13 (m, 2 H), 3.13-2.83 (m, 2 H), 2.70-2.40 (m, 2 H).

Photolysis of 10: *all-trans*-1,8-Diphenyl-1,3,5,7-octa-tetraene (**24**). Into a quartz NMR tube was placed **10** (46 mg) as a solution in 0.5 mL of glyme-*d*₁₀. Irradiation for 10 min in a Rayonet chamber equipped with a bank of ten 254-nm bulbs

left a yellow solution whose NMR spectrum already showed a scattering of the phenyl signals. Additional irradiation occasioned the deposition of bright yellow platelets. After a total of 150 min, the irradiation was halted. More precipitation was prompted by cooling the tube at 0 °C for several minutes. The crystals so obtained amounted to 18.6 mg: mp 221-229 °C (lit.^{39,40} mp 232 °C); ¹H NMR (CDCl₃) multiplets at δ 7.39-7.26 and 6.64-6.42 with a ratio of 10:8, respectively; mass spectrum, calcd *m/e* 258.1408, obsd 258.1415. The decanted portion of the reaction mixture was chromatographed on silica gel to afford 6 mg of unreacted diene and a complex mixture of other yellow materials.

Crystal Data, Data Collection, Structural Solution, and Refinement. The crystals of **10** were orthorhombic, space group *Pcab*, with *a* = 10.489 (4), *b* = 10.677 (3), and *c* = 26.524 (7) Å and with *d*_{calcd} = 1.155 g cm⁻³ for *Z* = 8 (C₂₀H₁₈, *M_r* = 258.36). The intensity data were measured on a Hilger-Watts diffractometer (Ni-filtered Cu K α radiation, θ - 2θ scans, pulse-height discrimination). The size of the crystal used for data collection was approximately 0.20 × 0.5 × 0.6 mm. A total of 2004 independent reflections were measured for $\theta < 57^\circ$, of which 1597 were considered to be observed [*I* > 2.5 σ (*I*)]. The structure was solved by a multiple-solution procedure⁴⁹ and was refined by full-matrix least-squares methods. Three reflections which were strongly affected by extinction were excluded from the final refinement and difference map. In the final refinement, anisotropic thermal parameters were used for the nonhydrogen atoms, and isotropic temperature factors were used for the hydrogen atoms. The hydrogen atoms were included in the structure factor calculations, but their parameters were not refined. The final discrepancy indices are *R* = 0.040 and *R_w* = 0.046 for the remaining 1594 observed reflections. The final difference map has no peaks greater than ± 0.1 eÅ⁻³.

Acknowledgment. This work was supported by the National Science Foundation and the National Institutes of Health (Grants AI-11490 and CA-12115).

Registry No. **10**, 83681-47-4; **12**, 528-38-1; **12** dichloride, 20324-70-3; **13**, 83729-96-8; **14**, 83681-42-9; **15** (isomer 1), 83681-41-8; **15** (isomer 2), 83709-52-8; **16**, 83692-50-6; **17**, 83681-43-0; **18**, 83681-45-2; **19**, 83681-46-3; **20** (isomer 1), 83729-99-1; **20** (isomer 2), 83681-44-1; **21**, 83681-49-6; **22a**, 83681-50-9; **22b**, 83681-51-0; **23**, 83681-48-5; **24**, 22828-29-1.

Supplementary Material Available: Final atomic (Table IV) and anisotropic thermal parameters (Table V) for **10** (2 pages). Ordering information is given on any current masthead page.

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Formation of Nonaromatic Products in the Chlorination of Simple Substituted Aromatic Ethers

William David Watson

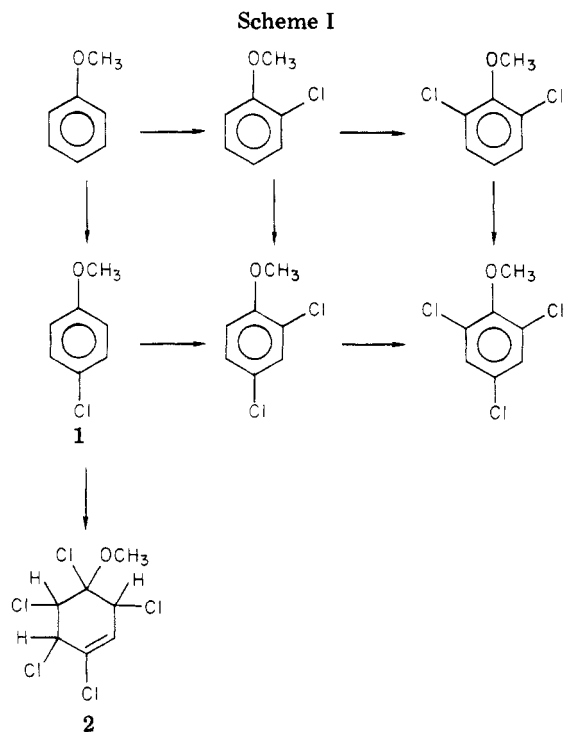
Organic Chemicals Research, The Dow Chemical Company, Midland, Michigan 48640

Received July 26, 1982

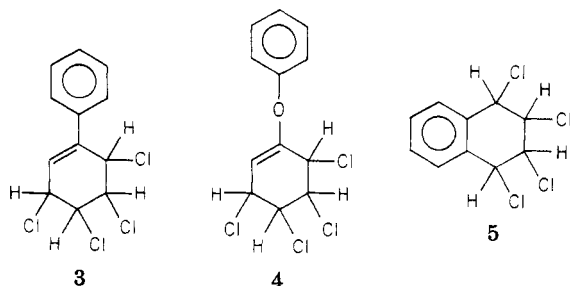
The neat chlorination of 4-chloroanisole produces 1,3,4,5,6-pentachloro-4-methoxycyclohexene in 35% yield. Mono- and dichlorinated anisoles and a variety of simple substituted anisoles were chlorinated to determine the generality of nonaromatic product formation. 3,4-Dichloroanisole, 4-fluoroanisole, 4-bromoanisole, 4-methylanisole, and 4-chlorophenetole form similar products based on their spectral properties. These products are proposed to form by a *cis*-1,2 chlorine addition followed by a rapid *cis*-1,4 chlorine addition. On the basis of the NMR data, a predominate configuration is proposed.

Previously we reported that during the neat chlorination of anisole there is, in addition to the expected aromatic products, a nonaromatic product, 1,3,4,5,6-pentachloro-4-

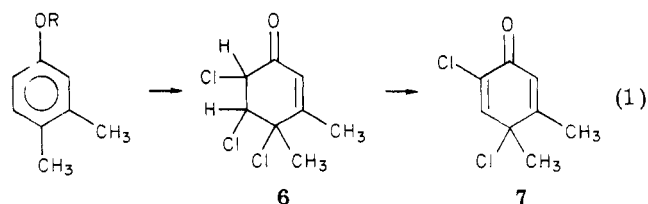
methoxycyclohexene, **2**, which forms in 28% yield (Scheme I). The formation of **2** was determined to originate not from anisole but from 4-chloroanisole, **1**, in 35% yield.¹



As more reactions are reinvestigated that were once thought to be exclusively electrophilic aromatic substitutions, the phenomena of formation of nonaromatic products is becoming an increasingly exciting field of study. This is especially true for halogenations of aromatic compounds. In fact, a recent review has been written on the above subject.² For example, 1-phenyl-3,4,5,6-tetrachlorocyclohexene, **3**, is formed when biphenyl is chlorinated in acetic acid.³ We have recently reported a similar product, phenyl 3,4,5,6-tetrachloro-1-cyclohexen-1-yl ether, **4**, when diphenyl ether is chlorinated neat.⁴ Naphthalene also forms naphthalene tetrachlorides⁵ (**5**).



Another example cited in this review is the chlorination (eq 1) in acetic acid of 3,4-dimethylanisole (or phenol or phenyl acetate) to produce, in addition to the chlorinated aromatic products, the cyclohexenone **6** and the cyclohexadienone **7**.^{6,8} The formation of **6** has recently been proposed to proceed via initial ipso attack⁷ at the 4-position.⁸



Ipsso attack in aromatic nitrations leading to both unusual aromatic and nonaromatic products has also been the subject of a recent review.⁹

Despite the fact that there is an increasing number of papers dealing with these nonaromatic products from aromatic chlorinations, the studies have been limited to biphenyl, naphthalenes, and 2,6- and 3,4-dialkylphenolic derivatives. In addition, the systems studied have been complicated by the use of acetic acid as the solvent, since various solvent-reagent interactions are possible.

Many papers have been written on the chlorination of anisole. However, most are concerned with kinetic measurements,¹⁰⁻¹⁴ various chlorinating agents,¹⁵⁻²⁹ specific solvent systems,³⁰⁻³³ or other parameters.³⁴⁻³⁹ There is, in fact, only one report describing the neat chlorine chlorination of anisole.⁴⁰ In that work, the conversions were kept low to obtain accurate *para/ortho* ratios.

A similar situation exists for the simple substituted anisoles. Few reports are available that describe detailed

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Table I. Results of the Neat Chlorination of Simple Substituted Aromatic Ethers

reactant	GC anal., wt % ^a									
	unreacted	2Cl	3Cl	4Cl	5Cl	6Cl	higher chlorinated	para/ortho	nonaromatic product, ^b %	
anisole	22.5	15.4	ND	61.1			1.0	3.96	tr	
2-chloroanisole	14.8		ND	78.8	ND	4.3	2.2	18.4	ND	
3-chloroanisole	9.0	3.5		64.5	ND	18.4	4.5	2.94	ND	
4-chloroanisole	0.0	52.3	ND				47.7		35 (2)	
2,3-dichloroanisole	12.1			80.8	ND	6.9	ND	11.7	ND	
2,4-dichloroanisole ^c	42.3		ND		ND	33.8	23.9		ND	
2,5-dichloroanisole	26.8		ND	68.8		1.0	3.4	69.0	ND	
2,6-dichloroanisole ^d	100		ND	ND	ND		ND		ND	
3,4-dichloroanisole	5.5	13.5			ND	48.9	32.1	3.61	26 (8)	
3,5-dichloroanisole	13.2	24.5		61.0			1.3	2.45	ND	
4-fluoroanisole	1.3	75.7	ND				23.0		20 (9)	
4-bromoanisole	0.0	ca 100	ND						34 (10)	
4-iodoanisole ^e	3.7	76.8	ND				19.5		ND	
4-methylanisole	0.0	40.7	ND				59.4		23 (11)	
4-chlorophenol	6.5	93.5	ND				ND		ND	
4-chlorophenetole	2.6	56.9	ND				40.5		34 (12)	
bis(4-chlorophenyl) ether ^f	100	ND	ND				ND		ND	

^a ND means not detected. Lower limit of detection ca. 0.5%. ^b Nonaromatic product percentage determined by NMR by integration of the relative areas of the methoxy protons. Lower limit of detection ca. 2% (tr = trace). ^c 2,4-Dichloroanisole chlorinated very slowly. The above results were obtained after 4.5 days, and there was no indication of the formation of nonaromatic product. ^d After 24 h there was no reaction. ^e The chlorination of 4-iodoanisole gave in addition to the expected products ca. 15% mono-, di-, and trichloroanisoles. ^f After 2 h there was no reaction. After 6 h at 60–100 °C only 1.6% conversion was observed.

product analysis for monochloroanisoles, dichloroanisoles, or other simple monosubstituted anisoles.^{12,41–47} No reports exist on neat chlorinations except our previous communication.¹ Because this void exists in the area of neat chlorinations of simple substituted anisoles, it was decided to investigate these reactions to determine product distributions and the generality of nonaromatic product formation.

Results

The neat chlorinations were done by bubbling gaseous chlorine into the aromatic ether at 30 ± 5 °C. Approximately 1 equiv of chlorine was added over 2–4 h. Samples were analyzed at regular intervals by both GC and NMR.

For example, the chlorination of 4-chloroanisole produces 35% of 1,3,4,5,6-pentachloro-4-methoxycyclohexene, **2**, based on the integration of the methoxy protons in the NMR.¹ The methoxy protons are a good NMR probe since the nonaromatic protons of **2** are shifted upfield relative to the methoxy protons attached to the aromatic nucleus.

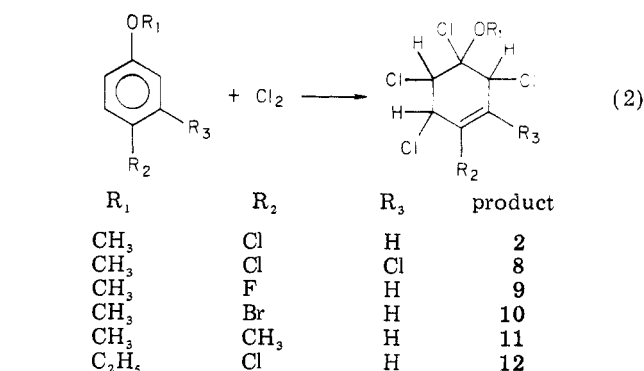
The GC of the reaction mixture is complicated because **2** thermally decomposes to produce a variety of products.

2 was isolated by removing most of the chloroanisoles by distillation at temperatures of less than 125 °C at low pressure and passing the residue through a column of deactivated alumina containing 5–8% water. Crude **2**, mp 64.5–67.0 °C, was recrystallized from hexane, producing a white crystalline product, mp 75.5–76.0 °C. A similar procedure was used to isolate the nonaromatic products discussed later.

2 has previously been identified on the basis of its spectral properties including NMR, IR, and mass spectra, and elemental analysis, in addition to ebullioscopic measurements that show it to be monomeric. Table I summarizes the product distribution obtained from the chlorination of the simple substituted aromatic ethers studied in this work.

The reactants can be classified into three groups: (1) those that form nonaromatic products; (2) those that form only aromatic products; (3) those that essentially do not react. 4-Chloroanisole, 3,4-dichloroanisole, 4-fluoroanisole, 4-bromoanisole, 4-methylanisole, and 4-chlorophenetole form between 20% and 35% of nonaromatic product, the general structure of which is shown in eq 2. The spectral

data used to identify these nonaromatic products are presented in Table II and detailed in the Experimental Section. Samples of **2**, **9**, **10**, and **12** were isolated in a high degree of purity as seen by their spectral data and their sharp melting points. **8** was also isolated in a high degree of purity but always in mixtures with trichloroanisoles. However, its NMR (benzene-*d*₆) is distinct from these impurities. **11** was isolated with difficulty because additional impurities are present from the reaction mixture. Anisole and 3-chloroanisole do not form nonaromatic products when monochlorinated, but nonaromatic products are seen when they are dichlorinated. These products are identical with **2** and **8** and are therefore formed from 4-chloroanisole and 3,4-dichloroanisole, respectively.



The reactants that form only aromatic products are characterized by having an unsubstituted para position. These compounds chlorinate predominately in the para position since the products show high para/ortho ratios

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Table II. Summary of Physical and Spectral Properties of Tetrachloro Adducts

compd	mp, °C	mass spec	IR (C=C), ^a cm ⁻¹	NMR (benzene-d ₆), ppm				coupl const, Hz			
				OCH ₃	H(2)	H(3)	H(5) ^b	H(6) ^b	J(2,3)	J(5,6)	J(2,6)
2	75.5-76.0	M ⁺ , M ⁺ - Cl, M ⁺ - Cl - HCl, M ⁺ - 2HCl (mol ion at 126)	1648	3.02 ^c (s)	5.57 (dd)	4.09 (dd)	4.59 (d)	4.50 (ddd)	6.6	8.2	1.3
8		M ⁺ - Cl, M ⁺ - 2HCl (mol ion at 126)	1630	3.11 ^c (s)		4.73 (s)	4.65 (d)	4.54 (d)		8.5	
9	66.0-66.5	M ⁺ - 2HCl (mol ion at 179)	1648	2.99 ^{c,e} (s)	5.00 (ddd)	4.07 (dd)	4.67 (d)	4.47 (dm)	6.5	8.5	1.0
10	78.0-79.0	M ⁺ , M ⁺ - Cl, M ⁺ - 2HCl (mol ion)	1640	2.97 ^d (s)	5.73 (dd)	3.98 (d)	4.72 (d)	4.54 (dm)	6.5	8.5	1.0
11	liquid		1675	3.14, ^c (s) 1.50 ^f (s)	5.17 (dt)	4.29 (dm)	4.81 (d)	4.47 (dm)	6.0	8.5	1.5
12	64.0-65.0		1647	3.40, ^{d,g} (dq) 1.00 ^f (t)	5.62 (dd)	4.23 (d)	4.67 (d)	4.50 (dm)	6.2	8.0	1.2

^a CCl₄. ^b The absorbances assigned to H(5) and H(6) are an obvious AB quartet. ^c 100 MHz. ^d 60 MHz. ^e H-F coupling $J(2,F) = 11.5$ Hz, $J(3,F) = 4$ Hz, $J(6,F) < 1.5$ Hz. ^f CH₃. ^g OCH₂.

varying from 2.5 to 69. This is consistent with the preferred formation of benzenium ion, which one would expect from an elementary discussion on the electrophilic aromatic substitution of aromatic ethers.

This can be also be seen from the relative rates of reaction of 2- and 4-substituted anisoles. For example, it is known that in acetic acid 2-chloroanisole chlorinates 3.6 times faster than 4-chloroanisoles.⁴⁸ Even more dramatic is in bromination, where 2-chloroanisole reacts 69 times faster than 4-chloroanisole.⁴⁹ Therefore if the para position is unsubstituted, only aromatic products are formed.

4-Iodoanisole does not form a nonaromatic product, in contrast to the other 4-haloanisoles. This can be explained by iodoanisole reacting with chlorine to form iododichlorides,⁵⁰ which probably alter the course of the reaction by changing the chlorinating agent. In addition, this reaction appears to be further complicated by the formation of chloroanisoles that probably arise via ipso attack. Iodoanisoles have been shown to be unstable in their protonated form, in contrast to the other haloanisoles.⁵¹

4-Chlorophenol gives only aromatic products. This is thought to be due to less steric crowding in the transition state, thus causing the phenol molecule to be more reactive than anisole. Previous data have shown that in acetic acid phenol brominates about 100 times faster than anisole.¹⁴

2,4-Dichloroanisole, 2,6-dichloroanisole and bis(4-chlorophenyl) ether do not appreciably react with chlorine at room temperature in 2-4 h. In the case of 2,6-dichloroanisole it is clearly a case of steric inhibition of resonance as previously observed in other 2,6-disubstituted anisoles.⁵² 2,4-Dichloroanisole reacts slowly due to a similar process since it has been reported that 2,4-dimethylanisole brominates 228 times slower than the other isomeric dimethylanisoles excluding the 2,6-isomer.⁴⁹ When 2,4-dichloroanisole is chlorinated slowly over 4.5 days, no nonaromatic products were observed in the methoxy region of the NMR, although there was a singlet at 5.08 ppm (benzene-d₆). No carbonyl or double bond

Table III. Aromatization of 2

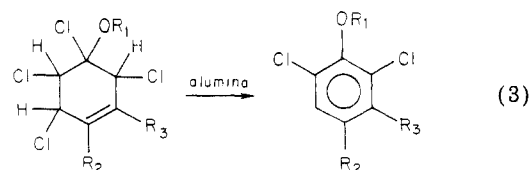
conditions	trichloroanisole, %		
	2,4,6	2,3,4	2,4,5
alumina	100		
thermal, 150 °C, N ₂	94	2	3
pyridine	92	8	tr ^a
NaOEt/EtOH	35	51	12

^a Trace.

stretches greater than 1600 cm⁻¹ were observed in the IR. Investigation of this product was not pursued. Bis(4-chlorophenyl) ether does not react appreciably due to steric factors and the deactivating effect of the 4-chlorophenyl group. It is known that in acetic acid, diphenyl ether reacts about 100 times slower than anisole.¹⁴ Similar results have been obtained in our lab for the relative rates of neat chlorination of these two compounds.⁵³

As can be seen from the data presented, a variety of simple aromatic ethers form a substantial amount of nonaromatic products when chlorinated. The spectral properties show these compounds to be 1-halo-, 1,2-dihalo-, or 1-alkyl-3,4,5,6-tetrachloro-4-alkoxycyclohexenes. The criterion for the formation of these products is that the aromatic ether must be substituted in the para position and without a substituent in the ortho positions. The group in the para position can be a halogen except iodine or an alkyl group.

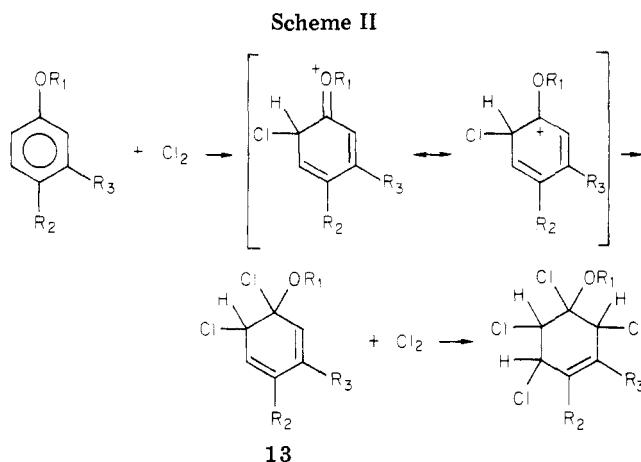
Previous work has shown that 2 decomposes over activated alumina to 2,4,6-trichloroanisole. Compounds 8-12 decompose over activated alumina to give analogous products (eq 3).



The aromatization of 2 under various conditions is shown in Table III. As conditions are changed from E1 to E2 conditions, the aromatization changes to produce

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 (49) J. E. Dubois, J. J. Aaron, P. Alcais, J. P. Doucet, F. Rothenburg, and R. Uzan, *J. Am. Chem. Soc.*, **94**, 6823 (1972).
 (50) H. H. Hodgson and A. Kershaw, *J. Chem. Soc.*, 2917 (1930).
 (51) G. A. Olah and Y. K. Mo, *J. Org. Chem.*, **38**, 2212 (1973).
 (52) L. M. Stock, "Aromatic Substitution Reactions", Prentice Hall, Englewood, NJ, 1968, p 60.

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trichloroanisoles other than 2,4,6-trichloroanisole.

Discussion

There are a variety of mechanisms that can be proposed to explain the formation of **2**. However, with the additional compounds studied, in particular 3,4-dichloroanisole and 4-methylanisole, there is only one mechanism sequence that can account for all the nonaromatic products. We propose that the predominant reaction pathway is heterolytic and consists of a 1,2-addition followed by a rapid 1,4-addition (Scheme II).

The first mole of chlorine should add by a 1,2-addition since 1,4-addition produces the wrong final product. The 1,2 chlorine addition should occur at the 1- and 6-position since attack at the 1- and 2-position is unlikely based on data presented in Table I and in the prior literature.⁵⁴ Thus we are proposing that these nonaromatic products and the normal electrophilic products arise from a common intermediate. This initial 1,2-addition is proposed to be *cis*. de la Mare has proposed an initial *cis*-1,2-addition to account for the stereochemistry found in the tetrachloro adducts of biphenyl³ and naphthalene.⁵ *Cis*-1,2-addition has been found to be significant in the halogenation of conjugated cyclic dienes such as cyclopentadiene, 1,3-cyclohexadiene,⁵⁵ and indene.⁵⁶ **13** was not detected at any time during the reaction.

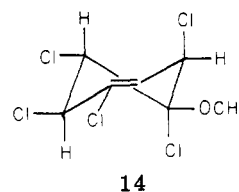
The second mole of chlorine is proposed to add rapidly in a 1,4-addition to yield the observed nonaromatic products. We propose this 1,4-addition to be predominately *cis*. The addition of DBr to 1,3-cyclohexadiene⁵⁷ and the halogenation of cyclopentadiene and 1,3-cyclohexadiene^{55,58} have been shown to occur predominately *cis*. Unfortunately, no substituted 1,3-cyclohexadienes have been studied in detail.

There appear to be other isomers present, especially in the case of **8** and **11**. Evidence is seen in the methoxy region of the NMR as well as in the melting point of the isolated product. For example, **2** containing no aromatic products as observed by NMR had a mp of 64.5–67.0 °C. Upon recrystallization from hexane the mp increased to

75.5–76.0 °C. Despite these differences in melting point, the NMR spectra were similar.

Some consideration was given to a free-radical mechanism, but several points argue against it. First the reactions are run under extremely mild conditions. Similar product distributions were observed for the chlorination of 4-chloroanisole in the dark, in the presence and absence of oxygen, and either with or without extensive reagent purification. It would be surprising if a free-radical chlorination would produce a cyclohexene since once radicals are formed the ring generally saturates to produce a chlorinated cyclohexane.⁵⁹ In addition, if chlorine radicals were present, one would expect the formation of a chloromethyl or a chloromethoxy group as has been observed for the free-radical chlorination of toluene, anisole, and 4-chloroanisole.^{60–62}

The configuration of **2**, as well as the other nonaromatic products, can be proposed on the basis of the NMR spectra in deuterated benzene and information related to the aromatization of structurally related tetrachlorocyclohexenes. Of course, the substituents at C-3 and C-6 are actually pseudoaxial and pseudoequatorial⁶³ but are represented as shown in **14** for clarity.



Model systems to compare with **14** are well-known. Kurihara and co-workers^{64–67} have examined the NMR spectra of a number of tetra-, penta-, and hexachlorocyclohexenes. In deuterated benzene coupling constants of 2.9–3.0 Hz have been observed if the allylic proton is axial and 4.0–6.0 Hz if the allylic proton is equatorial. The observed value for $J(2,3)$ of 6.6 Hz for **2** clearly places the proton at C-3 in the equatorial position. The coupling constant for H(5) and H(6), $J(5,6)$, is 8.2 Hz, which is consistent with the protons being *trans* diaxial where the proton at C-6 is in the pseudoaxial position. Kurihara values for similar coupling constants are 7.2–9.0 Hz. Coupling constants between adjacent protons involving equatorial protons are reported to be 4 Hz or less. The other coupling constants observed for **2**, i.e., $J(2,6) = 1.3$ Hz and $J(3,6) = 0.6$ Hz, are also consistent with configuration **14** and Kurihara's data. Therefore, the only part of configuration **14** where there is any doubt is at C-4.

Without a crystal structure analysis, one way to help resolve the configuration at C-4 is to examine the aromatization of related chlorinated cyclohexenes. Various isomers of 3,4,5,6-tetrachlorocyclohexene have been aromatized under E2 conditions with sodium ethoxide and ethanol.⁶⁸ Two of these isomers, α and γ , are very similar

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(64) N. Kurihara, K. Tanaka, and M. Nakajima, *Agr. Biol. Chem.*, **40**, 411 (1976).

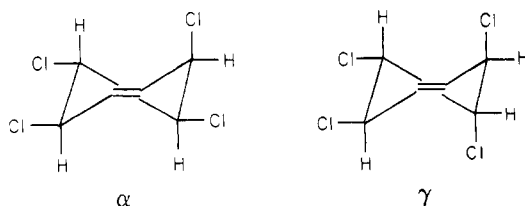
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to 14 without, or course, the chlorine attached to the double bond and the methoxy group at C-4.



The difference between the α and γ isomer is the configuration at C-4. The distribution of aromatic products obtained by the reaction of 2 with sodium ethoxide and ethanol as shown in Table III more closely resembles the products obtained from the γ isomer. The γ isomer gives a ratio of ortho/para/meta of 48:2:50 while the α isomer gives 28:29:43. Comparable isomers for 2 are 2,3,4-/2,4,5-/2,4,6-trichloroanisole, wherein the ratio is 51:12:35. On the basis of this evidence we propose that the chlorine at C-4 is axial and the methoxyl equatorial.

It should be noted that the configuration of 14 is consistent with our proposed mechanism of cis-1,2-chlorination followed by a cis-1,4-addition of chlorine.

One other point needs to be mentioned. By isomerization studies, the configuration of 14 has been shown to be the more thermodynamically stable isomer of tetra-,⁶⁹ penta-,⁶⁶ and hexachlorocyclohexenes.⁶⁴ However, under the mild conditions of our reaction it is not thought that extensive isomerization occurs.

There appears to be a discrepancy between this work and the work of de la Mare^{2,6,8} since he reports the formation of cyclohexenones and we report the formation of cyclohexenes. It should be noted, however, that de la Mare's work has been done with acetic acid as a solvent, while our work has been done neat.

In an attempt to resolve this apparent difference, 4-chloroanisole was chlorinated in acetic acid. The results show that only a trace of nonaromatic product was formed. It was not identical with 2, and because of the low yield, isolation was not attempted. It was considered that 2 might be unstable in acetic acid, but when 2 was allowed to stand in acetic acid for 24 h at room temperature, no reaction occurred. Therefore, it has been concluded that the major differences between this work and de la Mare's is his use of acetic acid. Several possible explanations could be advanced to account for this observation. One is that the chlorine reacts with acetic acid to form chlorine acetate, which is the chlorinating agent.⁷⁰ Another possibility is that either the chlorinating agent or the benzenium ion transition state is solvated by acetic acid, thereby causing a different reaction pathway.

Experimental Section

The aromatic ethers used in the experiments were obtained from Aldrich or Eastman Organic Chemicals or prepared in our laboratory by the reaction of the substituted phenol with dimethyl sulfate. All these starting materials were analyzed by GC and NMR and were found to be $\geq 99.8\%$ pure. Chlorine (99.5%) was obtained from Matheson Corp.

The chlorinated aromatic products were analyzed by GC with a column 20 ft \times 0.125 in. packed with 8% FFAP and 8% Apiezon L on 80–100 mesh Gas Chrom Q. Various temperatures and helium flow rates were used to achieve separation. Separation of all components was checked with authentic samples that were purchased, prepared, or separated from the reaction mixtures.

GC results are given in weight percent throughout this paper. NMR results were obtained on either the Varian T-60 or the Varian XL-100.

General Chlorination Procedure. A well-stirred solution of aromatic substrate was chlorinated by sparging in gaseous chlorine over a 2–4 h period at $30 \pm 5^\circ\text{C}$. Samples were analyzed by GC and NMR at regular intervals until approximately 1 equiv of chlorine was added. The final product was carefully analyzed by GC to determine the composition and by NMR to determine the presence of nonaromatic products.

If nonaromatic products were observed in the NMR, the following general procedure was used to separate them. The crude reaction sample was distilled rapidly at less than 125°C at low pressure to remove the chlorinated aromatic product. A portion of the residue (3.5 g) was eluted with hexane saturated with water through 150–175 g of deactivated neutral alumina (Fisher 80–200 mesh) containing 5.5–8% water. The chlorinated aromatic products eluted in the second or third 100-mL fractions, and the nonaromatic product (~ 1 g) eluted in the third or fourth 100-mL fraction. The crude adduct could then be recrystallized from an equal weight of hexane. NMR, mass and IR spectra and elemental analysis were done on these purified samples.

Chlorination of Anisole. Anisole (108.2 g, 1.00 mol) was chlorinated at 0.5 mol/h for 2 h at $25 \pm 5^\circ\text{C}$. The product analyzed to be 22.5% anisole, 15.4% 2-chloroanisole, 61.1% 4-chloroanisole, 0.2% 2,6-dichloroanisole, and 0.8% 2,4-dichloroanisole. At this point, only a trace of nonaromatic product was observed. The chlorination was continued for a total of 5 h. At that point, GC analysis showed 33.3% 4-chloroanisole, 3.5% 2,6-dichloroanisole, 51.3% 2,4-dichloroanisole, and 11.9% 2,4,6-trichloroanisole. The NMR, however, showed 24% nonaromatic product 2 based on the relative integration of the methoxy protons. The crude product was distilled with only a 91% recovery and with copious HCl evolution.

Chlorination of 4-Chloroanisole and Isolation of 2. 4-Chloroanisole (142.6 g, 1.00 mol) was chlorinated at ca. 0.5 mol of Cl_2/h for 4 h at $25 \pm 5^\circ\text{C}$ until no more 4-chloroanisole remained. The product analyzed to be 52.3% 2,4-dichloroanisole, 25.6% 2,4,6-trichloroanisole, and 22.1% unknown products. The NMR showed the presence of 35% nonaromatic product on the basis of the relative integration of the methoxy protons. Part of this crude product (28.1 g) was distilled at 6 mmHg. The distillate (17.8 g, bp $104\text{--}117^\circ\text{C}$) consisted of chloroanisoles. The residue (6.6 g) was ca. 70% nonaromatic. A portion of the residue (3.5 g) was eluted with hexane over neutral alumina (5.0% H_2O). The fourth 100-mL fraction (0.93 g) was pure nonaromatic product which slowly crystallized (mp $64.5\text{--}67^\circ\text{C}$). This product (2.0 g) was recrystallized twice from equal weights of hexane to produce pure 1,3,4,5,6-pentachloro-4-methoxycyclohexane, 2, as a white crystalline product (0.82 g, mp $75.5\text{--}76.0^\circ\text{C}$): mass spectrum, m/z 282 (5 Cl, M^+), 247 ($\text{M}^+ - \text{Cl} - \text{HCl}$), 210 ($\text{M}^+ - 2\text{HCl}$), 195 (3 Cl), 176 (2 Cl), 133 ($\text{C}_5\text{H}_3\text{Cl}_5^+$), 126 ($\text{CH}_3\text{OCClCHCl}^+$, most intense); infrared (film) 3080, 2950, 2840, 1645, 1455, 1440, 1420, 1330, 1300, 1280, 1240, 1210, 1160, 1140, 1105, 1040, 975, 870, 790, 745, 720, 645 cm^{-1} . Molecular weight by ebullioscopy was ca. 274. Anal. Calcd for $\text{C}_7\text{H}_7\text{Cl}_5\text{O}$: C, 29.6; H, 2.48; Cl, 62.3. Found: C, 30.0; H, 2.45; Cl, 62.7.

Chlorination of 2,4-Dichloroanisole. 2,4-Dichloroanisole (35.40 g, 0.200 mol) was chlorinated at $25 \pm 5^\circ\text{C}$ for 2 h. Essentially no reaction occurred; therefore, the temperature was increased to $55 \pm 5^\circ\text{C}$ and the chlorination continued for 4.5 days. The NMR in the methoxy region showed no indication of a nonaromatic product. However, there was a singlet due to an unknown component at 5.08 ppm. The IR spectrum showed no absorbance between 1600 and 1700 cm^{-1} . Attempted separation of this product using alumina was unsuccessful. Isolation of this product was not pursued.

Chlorination of 3,4-Dichloroanisole and Attempted Isolation of 8. 3,4-Dichloroanisole (35.41 g, 0.200 mol) was chlorinated at $25 \pm 5^\circ\text{C}$ for 4 h. The NMR showed the presence of 26% of nonaromatic products on the basis of the relative integration of the methoxy protons. After a day, crystals formed in the crude reaction mixture. These were filtered and were identified to be pure 2,4,5-trichloroanisole. The nonaromatic product was very sensitive to heat, and distillation could not be used. The crude product (3.5 g) was eluted with hexane over neutral alumina

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(7.6% H₂O). The third 100-mL fraction (1.55 g) contained ca. 40% nonaromatic product. Attempts to improve this separation were unsuccessful so that all spectral data were done on this mixture. The spectral data clearly show the nonaromatic product to be 1,2,3,4,5,6-hexachloro-4-methoxycyclohexene, 8. Mass spectrum of 8 was obtained on the MS-30 GLC/mass spectrometer with a 6-ft 10% UCW-98 glass column: 281 (M⁺ - Cl), 245 (M⁺ - Cl - HCl), 244 (M⁺ - 2HCl), 210 (C₇H₅OCl₃⁺), 201 (C₆HCl₄⁺), 195 (C₆H₂OCl₃⁺), 176 (C₇H₆OCl₂⁺), 167 (C₆H₄OCl₃⁺), 161 (C₆H₃OCl₂⁺), 133 (C₅H₃Cl₂), 126 (C₅H₄OCl₂⁺, most intense), 97 (C₅H₂Cl). The infrared spectrum of crude 8 (neat) shows a weak absorbance at 1630 cm⁻¹.

Chlorination of 4-Fluoroanisole and Isolation of 9. 4-Fluoroanisole (25.20 g, 0.200 mol) was chlorinated at 25 ± 5 °C in 2.5 h. GC analysis showed 1.3% 4-fluoroanisole, 75.7% 2-chloro-4-fluoroanisole, 16.3% 2,6-dichloro-4-fluoroanisole, and 6.7% unknown. The NMR showed 20% nonaromatic product on the basis of the relative integration of the methoxy protons. The crude products (15.0 g) were distilled to remove the aromatic products (bp 55–58 °C (1 mmHg)). The residue (8.3 g) crystallized upon cooling to room temperature. The crystals were washed with cold hexane (2 × 5 mL) to yield white crystals of 1-fluoro-3,4,5,6-tetrachloro-4-methoxycyclohexene, 9 (1.51 g, mp 66.0–66.5 °C): mass spectrum (MS-30 direct probe), *m/z* 194 (M⁺ - 2HCl), 179 (M⁺ - CH - 2HCl, most intense), 160, 151, 145, 126; IR (CCl₄) 2980, 1705, 1360, 1200, 1190, 1180, 1000, 865, 830, 730, 680, 640 cm⁻¹. Anal. Calcd for C₇H₇Cl₄FO: C, 31.4; H, 2.63; Cl, 52.9; F, 7.09. Found: C, 31.6; H, 2.69; Cl, 53.0; F, 7.5.

Chlorination of 4-Bromoanisole and Isolation of 10. 4-Bromoanisole (37.4 g, 0.200 mol) was chlorinated at 30 ± 5 °C for 3 h until the extinction of 4-bromoanisole. GC analysis showed the product to be primarily 4-bromo-2-chloroanisole and 4-bromo-2,6-dichloroanisole with lesser amounts of other components. The NMR, however, showed 34% nonaromatic product on the basis of the relative integration of the methoxy protons. The crude product was not concentrated by distillation, but some (3.5 g) was eluted with hexane over neutral alumina (160 g, 7% H₂O). The third 100-mL fraction (1.00 g) was almost pure adduct by NMR (mp 67.0–73.0 °C). This adduct (2.0 g) was recrystallized twice from hexane (2 mL) to yield pure white crystals (1.06 g) of 1-bromo-3,4,5,6-tetrachloro-4-methoxycyclohexene (10; mp 78.0–79.0 °C): mass spectrum (Atlas CH₄, direct probe); *m/z* 326 (M⁺), 291 (M⁺ - Cl), 254 (M⁺ - 2HCl), 247 (M⁺ - Br), 239 (M⁺ - 2HCl - CH₃), 205 (M⁺ - HCl₃ - CH₃), 186 (M⁺ - 4Cl), 126 (CH₃OClCHCl⁺); IR (CCl₄) 2990, 1655, 1480, 1345, 1290, 1215, 1175, 1150, 1110, 1050, 1025, 980, 965, 875, 735, 725, 645 cm⁻¹. Anal. Calcd for C₇H₇BrCl₄O: C, 25.6; H, 2.15; Br, 24.3; Cl, 43.1. Found: C, 25.8; H, 2.23; Br, 24.8; Cl, 41.4.

Chlorination of 4-Methylanisole and Isolation of 11. 4-Methylanisole (61.2 g, 0.500 mol) was chlorinated over 2.75 h at 25 ± 5 °C. The GC analysis showed 0.0% 4-methylanisole, 40.7% 2-chloro-4-methylanisole, 14.4% 2,6-dichloro-4-methoxyanisole, 26.5% 2,5-dichloro-4-methylanisole, 10.2% 2,3,5-trichloro-4-methylanisole, and 8.3% unknowns. The NMR shows the presence of 23% nonaromatic product on the basis of the relative integration of the methoxy protons. Crude product (26.3 g) was distilled to remove aromatic products (9.5 g, bp 75–88 °C (1 mmHg)). A portion of the residue (3.5 g) was eluted with hexane over neutral alumina (150 g, 10% H₂O). The third 100-mL fraction (0.62 g) was reasonably pure 1-methyl-3,4,5,6-tetrachloro-4-methoxycyclohexene, 11. No further purification was attempted. GC/mass spectrum of 11 was complicated by decomposition in the GC. IR (CCl₄) 2980, 1676, 1450, 1340, 1285, 1250, 1225, 1190, 1170, 1075, 1010, 985, 965, 885, 870, 715, 680, 640 cm⁻¹. Calcd for C₈H₁₀Cl₄O: C, 36.4; H, 3.82; Cl, 53.7. Found: C, 34.3; H, 3.65; Cl, 56.2.

Chlorination of 4-Chlorophenetole and Isolation of 12. 4-Chlorophenetole (78.3 g, 0.500 mol) was chlorinated in 2.5 h at 25 ± 5 °C. The GC analysis showed 2.6% 4-chlorophenetole, 56.9% 2,4-dichlorophenetole, 22.5% 2,4,6-trichlorophenetole, and 18% unknowns. The NMR showed the presence of 34% nonaromatic product on the basis of the relative integration of the nonaromatic protons at 4.5–6.2 ppm compared with the methylene protons. Attempts to concentrate the nonaromatic product by

distillation caused decomposition. A portion of crude product (3.5 g) was eluted with hexane over neutral alumina (175 g, 6.7% H₂O). The third 100-mL fraction (97 g) was significantly enriched with nonaromatic product. This was repeated three times, and the combined crude product (3.5 g) was passed through neutral alumina. The fifth 50-mL fraction (1.00 g) was reasonably pure 1,3,4,5,6-pentachloro-4-ethoxycyclohexene, 12 (mp 53.0–60.0 °C). This product was recrystallized from hexane (1 mL) to give white crystals of 12 (0.12 g, mp 64.0–65.0 °C): mass spectrum was not obtained; IR (CCl₄) 2995, 1645, 1330, 1280, 1235, 1220, 1195, 1160, 1105, 1010, 910, 865, 645 cm⁻¹. Anal. Calcd for C₈H₉Cl₅O: C, 32.2; H, 3.04; Cl, 59.4. Found: C, 32.3; H, 3.07; Cl, 58.9.

Chlorination of 4-Chloroanisole in Acetic Acid. 4-Chloroanisole (28.52 g, 0.200 mol) in glacial acetic acid (245 mL) was chlorinated for 2 h at 25 ± 5 °C. GC analysis showed 1.3% 4-chloroanisole, 93.8% 2,4-dichloroanisole, and 4.9% 2,4,6-trichloroanisole, the NMR showing only a trace of nonaromatic product that was not identical with 2. 2 (0.10 g) was dissolved in acetic acid (0.90 g) and the reaction monitored by NMR to determine stability. After 24 h, no reaction was observed.

Aromatization of 2 and 8–12 over Alumina. 2 (0.40 g, 1.41 mmol) was eluted through neutral alumina (20 g, 0.0% H₂O) with hexane (200 mL). Evaporation of hexane resulted in a white solid (0.19 g, 0.90 mmol, 64%) identified as 2,4,6-trichloroanisole.

Crude 8 (0.50 g) was eluted through neutral alumina (20 g, 0.0% H₂O) with hexane (100 mL). Evaporation of the hexane resulted in a liquid (0.39 g). The original mixture contained 26% 8 by NMR. The sample treated with alumina did not contain 8 but only aromatic products. The only peak in the NMR that increased after aromatization was that for 2,3,4,6-tetrachloroanisole, which increased from 13.4% to 49%.

9 (0.30 g, 1.12 mmol) was eluted through neutral alumina (20 g, 0.0% H₂O) with hexane (100 mL). Evaporation of hexane yielded pure 2,6-dichloro-4-fluoroanisole (0.09 g, 0.30 mol, 27%). GC analysis showed the sample to be 99.3% pure.

10 (0.46 g, 1.40 mmol) was eluted through neutral alumina (50 g, 0.0% H₂O) with hexane (300 mL). Evaporation of hexane yielded pure 2,6-dichloro-4-bromoanisole (0.26 g, 1.02 mmol) 72.9%.

11 (0.25 g, 0.95 mmol) was eluted through neutral alumina (20 g, 0.0% H₂O) with hexane (100 mL). Evaporation of the hexane yielded 2,6-dichloro-4-methylanisole (0.07 g, 0.37 mmol, 39%). GC analysis showed the sample to be 92.1% pure.

12 (0.39 g, 1.31 mmol) was eluted through neutral alumina (20 g, 0.0% H₂O) with hexane (100 mL). Evaporation of the hexane yielded 2,4,6-trichlorophenetole (0.26 g, 1.15 mmol, 88%).

Aromatization of 2 at 150 °C. 2 (0.10 g, 0.35 mmol) was heated at 150 °C for 24 h in the presence of N₂ to give the isolated product (0.07 g, 0.331 mmol, 94.0%).

Aromatization of 2 in Pyridine. 2 (0.10 g, 0.352 mmol) was mixed with pyridine (1.0 g) for 17 h. The mixture was mixed with an equal volume of CH₂Cl₂, and the insoluble crystals of Py·HCl were filtered. After evaporation of the solvent, the crystals were slurried with benzene (1.5 g) and refiltered, and the benzene was evaporated to yield a white solid (0.05 g, 0.236 mmol, 76.0%). 2 (0.20 g, 0.703 mmol), benzene-*d*₆ (0.80 g), and pyridine (0.06 g, 0.70 mmol) were mixed in an NMR tube, and the reaction was followed by NMR to determine if any intermediates formed. After 3 days, the only observable change in the NMR was the formation of 2,4,6-trichloroanisole (ca. 15%).

Aromatization of 2 in NaOEt/EtOH. 2 (0.20 g, 0.703 mmol) was dissolved in absolute ethanol (2.0 mL). Sodium ethoxide (0.49 g of 20.4 wt % in EtOH, 1.47 mmol) was added, whereupon an instantaneous reaction occurred with the evolution of heat (~35–40 °C) and an immediate precipitation of NaCl. The NaCl (0.07 g) was filtered and the ethanol evaporated to yield a liquid (0.16 g, 0.756 mmol, 100%).

Supplementary Material Available: Figures 1–3 containing NMR spectra of 4-chloroanisole plus chlorine, 2 in CCl₄, and 2 in benzene-*d*₆ (3 pages). Ordering information is given on any current masthead page.