round-bottom flask was chilled in an ice bath. About 20 g (0.25 mol) of dry hydrogen selenide (hydrogen selenide was generated from aluminum selenide by addition of water and passed through the calcium chloride tube) was passed through the solution. In the course of time the elemental selenium precipitated at the bottom of the flask. After 10 days at room temperature, the elemental selenium was removed by filtration. The filtrate was poured into cold water and diselenide was collected by filtration, treated with dilute hydrochloric acid, and washed with water. Recrystallization from ethanol provided 1 (76%), mp 92 °C. The solid diselenides listed in Table II were recrystallized from absolute alcohol to afford analytically pure products.

Method B. Liquid Diselenides. The following synthesis of dipropyl diselenide (Table II, expt 6) will serve as general procedure for the preparation of liquid diselenides. Following the general procedure described above (method A) with the slight modification, a mixture of 5.8 g (0.1 mol) of propionaldehyde, 25 mL of anhydrous pyridine, and 10 mL of triethylamine in a 100-mL flask was chilled in an ice bath. About 20 g (0.25 mol) of dry hydrogen selenide was passed through the solution. After 10 days at room temperature, and elimination of elemental selenium as described in method A, the solution was poured into cold water and extracted with three 50-mL portions of diethyl ether. The extracts were combined, treated with dilute hydrochloric acid, and washed with water. The ether solution was dried over anhydrous sodium sulfate. Evaporation of the solvent left a liquid which on distillation gave 5.8 g (48%) of **6**, bp 92 °C (10 mm).

Registry No.—Benzaldehyde, 100-52-7; 4-chlorobenzaldehyde, 104-88-1; 4-methoxybenzaldehyde, 123-11-5; 4-ethoxybenzaldehyde, 10031-82-0; 1-naphthalenecarboxaldehyde, 66-77-3; propanal, 123-38-6; 2-propanone, 67-64-1; butanal, 123-72-8; pentanal, 110-62-3; 3-pentanone, 96-22-0; hexanal, 66-25-1; 2-ethylbutanal, 97-96-1; cyclopentanone, 120-92-3; cyclohexanone, 108-94-1; hydrogen selenide, 7783-07-5.

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A Reinvestigation of Nitration in Aqueous Sulfuric Acid of Benzene and Halogenobenzenes

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The nitration of benzene in aqueous sulfuric acid is a matter of interest because its reaction mechanism appears to be affected by an encounter rate-determining step.[1,2] Evidence for this circumstance comes from the estimated rate coefficient at 68% H_2SO_4. The value appears to be close to the rate coefficient for encounter between two species, under the same conditions.[1,2] Also a limiting rate of nitration, reached with sufficiently reactive aromatics, has been regarded as an important source of information, in connection with the influence of encounter upon the benzene.[1,2]

Concerning the acidity dependence of the rate profile, two different slope values have been observed in the range 63–82% H_2SO_4 on the plot log $k_{2(\mathrm{obsd})}$ vs. $(H_R + \log a_w)$.[1,2] The behavior of the rate profile prompted us to extend previous kinetic data for benzene.[2,3] This was during the attempt to determine whether the observed deviation from linearity is significant evidence of the interference of different rate-determining steps upon the benzene. For comparative purposes, the nitration of some deactivated compounds, such as halogenobenzenes, has been reinvestigated.[3,4]

Table I. Second-Order Rate Coefficients for Nitration in Aqueous Sulfuric Acid at 25 °C

H_2SO_4, %[a]	$[HNO_3]$, mol/L	[AcOH], mol/L	Log $k_{2(\mathrm{obsd})}$, L mol^{-1} s^{-1} [c]
	Benzene[b]		
71.77	4.24×10^{-3}		0.24
70.97	3.72×10^{-3}		−0.328
70.97	3.26×10^{-3}		−0.328
69.87	3.47×10^{-3}		−0.775
69.87	3.76×10^{-3}		−0.787
69.87	3.98×10^{-3}		−0.779
69.87	4.15×10^{-3}		−0.791
69.87	4.39×10^{-3}	3.80×10^{-4}	−0.810
69.20	4.12×10^{-3}		−0.997
68.22	5.74×10^{-3}		−1.335
68.18	2.37×10^{-3}		−1.369
67.71	4.06×10^{-3}		−1.577
66.95	4.57×10^{-3}		−1.775
66.95	3.53×10^{-3}	1.69×10^{-3}	−1.793
66.78	2.37×10^{-2}		−1.849
66.08	4.25×10^{-3}		−2.096
66.04	2.37×10^{-2}		−2.173
65.41	1.02×10^{-2}		−2.364
64.79	3.33×10^{-3}		−2.587
64.68	1.69×10^{-2}		−2.534
64.68	1.69×10^{-2}	5.12×10^{-4}	−2.553
63.91	3.07×10^{-3}		−2.848
62.37	9.43×10^{-3}	6.01×10^{-4}	−3.422
	Fluorobenzene[b]		
69.91	1.08×10^{-2}		−1.613
69.43	4.27×10^{-2}	3.99×10^{-3}	−1.801
67.69	1.31×10^{-2}		−2.409
67.11	1.94×10^{-2}		−2.609
65.76	1.27×10^{-1}		−3.049
	Chlorobenzene[b]		
73.37	7.71×10^{-3}		−0.497
71.42	6.73×10^{-3}		−1.259
69.43	1.39×10^{-2}		−2.060
69.43	8.86×10^{-2}	3.52×10^{-3}	−2.064
67.11	8.93×10^{-2}		−2.902
65.76	1.099×10^{-1}		−3.378
	Bromobenzene[b]		
73.37	5.201×10^{-3}		−0.576
71.42	1.67×10^{-2}		−1.296
69.43	1.13×10^{-1}		−2.087
69.43	1.07×10^{-1}	3.99×10^{-3}	−2.105
67.11	7.66×10^{-2}		−2.981
65.76	1.62×10^{-1}		−3.567
	Iodobenzene[b]		
73.37	4.586×10^{-3}	1.998×10^{-3}	−0.097
71.21	1.691×10^{-3}	1.998×10^{-3}	−0.970
70.57	4.722×10^{-3}	1.998×10^{-3}	−1.150
67.65	1.173×10^{-1}	1.998×10^{-3}	−2.153
67.11	7.687×10^{-2}		−2.343
65.81	2.873×10^{-1}	1.998×10^{-3}	−2.698

[a] ±0.1%. [b] [Aromatic] = $10^{-4}/10^{-5}$ mol L^{-1}. [c] Estimated percentage of standard error of the mean ±2.5%.

Results and Discussion

Rate coefficients for the nitration of benzene and halogenobenzenes in the range 62–74% sulfuric acid are in Table I.

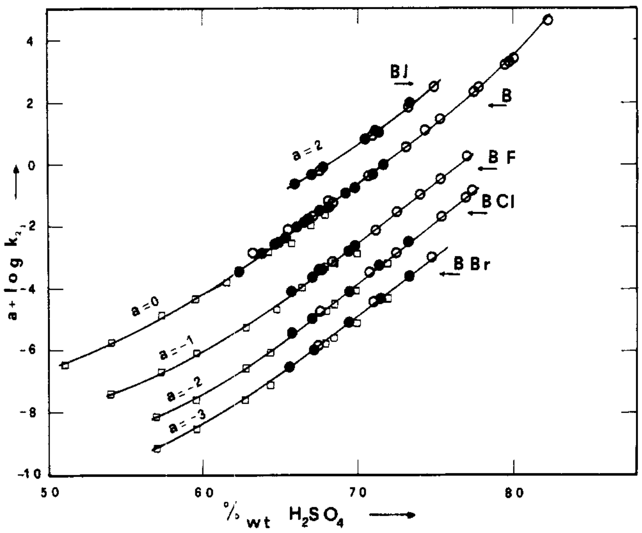

Figure 1. Plots of [a + log $k_{2(\mathrm{obsd})}$] vs. percentage of nitration at 25 °C in aqueous sulfuric acid: (B) benzene; (BF) fluorobenzene; (BCl) chlorobenzene; (BBr) bromobenzene; (BJ) iodobenzene (○, data of ref 2, 11; □, data of ref 8; ●, present work).

Because of the limited solubilities of aromatic compounds in aqueous acids, the influence of acetic acid added to acid solutions has been also investigated (Table I). Kinetic runs with and without AcOH, performed under conditions otherwise the same, show that addition of ca. 10^{-3} M AcOH increases appreciably the solubility of aromatic substrates, without affecting the rate values. Although this feature cannot be generalized, it assures, in this case, the satisfactory utilization of the results which come from the work of Deno,[3] obtained in the presence of a small amount of AcOH.

The kinetic data reported in this paper, combined with extant data of the literature, permit us to obtain the rate profiles given in Figure 1. It can be seen that the results of each data set show good agreement among them; the spread of experimental points is not greater than expected from experimental errors. The figure, then, provides evidence of the influence of medium acidity upon the nitration, when a wide range of acid concentration is investigated (51–82% H_2SO_4).

The significant feature observed on the plots log $k_{2(\mathrm{obsd})}$ vs. percentage acid concentration is the curvature of rate profiles of halogenobenzenes, compared to the known curvature of benzene.[1,2] The analysis of the plots of log $k_{2(\mathrm{obsd})}$ vs. (H_R + log a_w) gives the same results[5] (Figure 2) using either the H_R values of Cook et al.[6] or those of Deno.[7] It follows that the previous observed linearity of rate profiles is only apparent, arising from the shortness of the acidity range examined.

Concerning the halogenobenzenes, independent evidences[4,8] show that concentrations of reagents, nitration products, and isomeric compositions are not significantly affected by side reactions in the whole acidity range examined. Their curved lines then, do not appear a result of specific interactions or variations of mechanism, since the encounter rate should not affect these deactivated compounds.[4]

These reasons make it impossible to relate the curvature of the plots for benzene to some changeover of mechanism even if its influence were important. Such a behavior also suggests that the curved lines are a consequence of the specific criteria of analysis already discussed and usually applied to nitration. Evidence for this suggestion in sulfuric acid comes from the plots[9a] of log $k_{2(\mathrm{obsd})}$ vs. H_0 acidity function, since linear rate profiles are now observed for benzene and halogenobenzenes in the whole acidity range (51–82% H_2SO_4).[9b] The results of nitrations carried out in perchloric acid[10] also support the above conclusions.

In the range 59–68% $HClO_4$, isomeric compositions and relative reactivities of halogenobenzenes are as observed in sulfuric acid. It follows from this analysis that the rate profiles which have been examined are of little value for understanding mechanistic problems and appear in some cases not related to chemical behavior of compounds.

Experimental Section

Materials. Benzene and halogenobenzenes (R. P. Carlo Erba) were each distilled several times and their purity was checked by gas–liquid chromatography. The purified halogenobenzenes were stored in the dark. Nitric acid purified by vacuum distillation from concentrated sulfuric acid (1:2 v/v) was used and stored at −40 °C. Sulfuric acid was Analar grade and percentage composition of solutions was determined

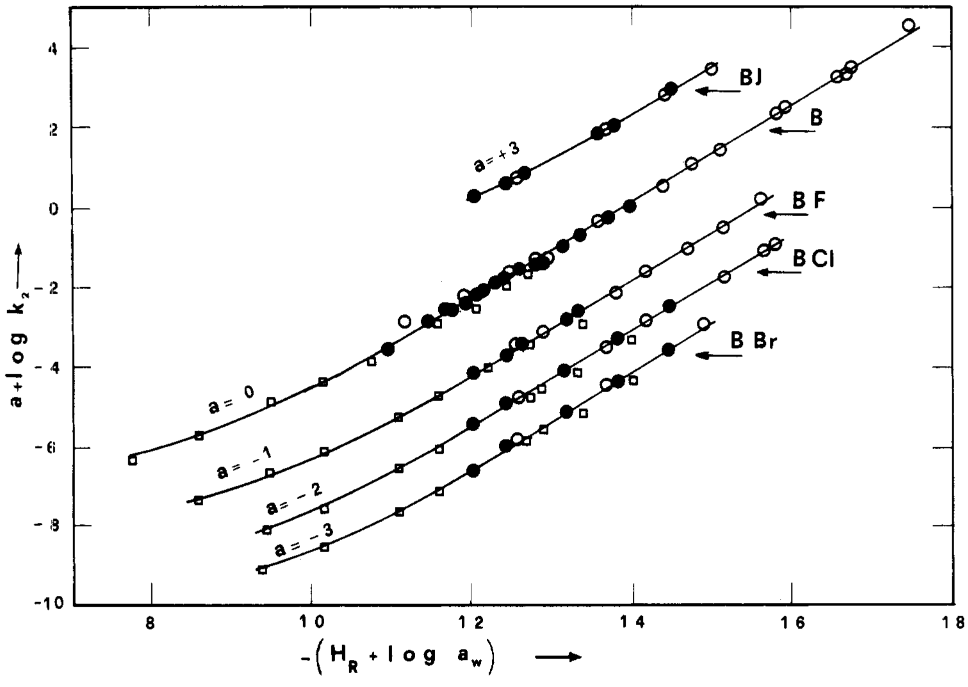

Figure 2. Plots of [a + log $k_{2(\mathrm{obsd})}$] vs. (H_R + log a_w) for nitration at 25 °C in aqueous sulfuric acid: (B) benzene; (BF) fluorobenzene; (BCl) chlorobenzene; (BBr) bromobenzene; (BJ) iodobenzene (○, data of ref 2, 11; □, data of ref 8; ●, present work; H_R values of ref 7).

by automatic potentiometric titrations of weighted samples against standard solutions of sodium hydroxide. Titrations were performed on an Amel 235 instrument, using a motorized buret (Model 232–233). Each percentage value is the average of at least ten titrations and the estimated error is ±0.1%. Two different normal solutions of HCl were used for the standardization of normal solutions of NaOH.

Kinetic Measurements. Separate solutions of aromatic compounds (with and without added AcOH) and nitric acid in the appropriate concentration of sulfuric acid were prepared and thermostated at 25 °C. Equal volumes of solutions of both reagents were rapidly mixed by syringes in a thermostated silica cell and the changes of absorbance with time, at selected wavelengths, were obtained on Perkin-Elmer EPS-3T and CGA PM5 spectrophotometers. Because of the limited solubilities of aromatic compounds in sulfuric acid, preliminary experiments were carried out using aromatic solutions in acid solutions kept for different times before use. The rates were independent of time. By using nitric acid concentrations at least ten times those of the substrates, good linear pseudo-first-order kinetic plots were obtained and $k_{2(\mathrm{obsd})}$ values were calculated from the stoichiometric concentration of nitric acid. Guggenheim's method was used in a few cases. Second-order rate constants for the nitration at 25 °C of the substrates are given in Table I.

Acknowledgments. We are grateful to Professor J. H. Ridd and Professor K. Schofield for helpful discussions. We thank the Consiglio Nazionale delle Ricerche (Roma) for financial support.

Registry No.—Benzene, 71-43-2; fluorobenzene, 462-06-6; chlorobenzene, 108-90-7; bromobenzene, 108-86-1; iodobenzene, 591-50-4; nitric acid, 7697-37-2; sulfuric acid, 7664-93-9.

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m-Nitrophenyl D-Glucose and D-Galactose Ethers via Alkoxide Displacement of a *m*-Nitro Group

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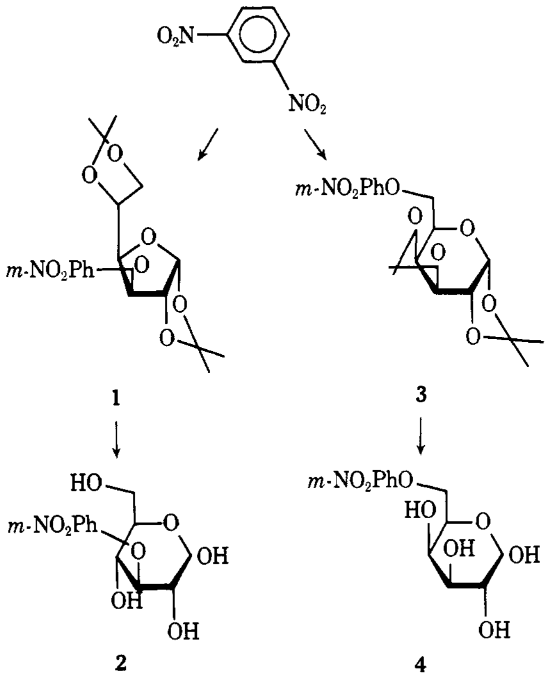
Our interest in the design and synthesis of carbohydrate derivatives[2a,b] as compounds with possible application as radiocontrast agents[3] brought our attention to the feasibility of *m*-nitrophenyl sugar ether synthesis. The unusual hydrolytic stability of benzyl sugar ethers,[4] e.g., relative to glucosides, suggests high relative stability for phenyl sugar ethers.

For design reasons, precursors to benzene based radiocontrast agents must have a meta orientation of substituents.[3] Yet only *p*-nitrophenyl[5] and 2,4-dinitrophenyl[6] sugar ethers were heretofore reported. However, a recent report of the synthesis of *m*-nitroanisole by methoxide displacement of a nitro group from *m*-dinitrobenzene[7] suggested the parallel reaction with a sugar alkoxide. We wish to report the synthesis of 1,2:5,6-di-*O*-isopropylidene-3-*O*-(*m*-nitrophenyl)-D-glucofuranose (**1**) and 1,2:3,4-di-*O*-iospropylidene-6-*O*-(*m*-nitrophenyl)-D-galactopyranose (**3**) by this route. The corresponding nonsubstituted compounds **2** and **4** were also prepared (Scheme I).

Scheme I



Since benzylation of carbohydrates using a strong base in dry, aprotic media (e.g., benzylbromide/DMF/NaH[8]) proceeds with isomeric integrity, and since the use of diisopropylidene sugars precludes any isomeric products based upon the position of phenylation, it was anticipated that *m*-nitro phenylation (*m*-dinitrobenzene/HMPA/NaH) would not involve significant amounts of isomerization. This contention was borne out by the relatively high yields of isomerically pure products **1** (82%) and **3** (62%). Both crude products **1** and **3**, after decolorization on alumina columns, were readily crystallizable from cyclohexane/petroleum ether to give sharp melting points, 119–121 and 109–111 °C, respectively. Removal of the isopropylidene groups from **1** and **3** (H_2O/*p*-dioxane/H_2SO_4) was accomplished in high yields as monitored by TLC, but isolated yields were 50 and 26%, respectively, suggesting anomeric mixtures.[9]

We anticipate that this work may engender interest in pharmacophysiological investigation of meta-substituted sugar ethers as relatively stable sugar derivatives, since product **2** exhibited no apparent hydrolysis[10] (monitored by TLC) at pH 7.4 after 48 h at 75 °C in a 1% aqueous solution. Compound **4** was not sufficiently H_2O soluble to test for hydrolytic stability.

Experimental Section

Melting points were determined on a Thomas-Hoover apparatus in open capillaries and are uncorrected. Infrared spectra (KBr) were recorded on a Beckman Acculab 4 instrument. NMR spectra were recorded on a Varian EM 360 instrument using tetramethylsilane as internal reference. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Thin layer chromatograms (TLC) were performed on silica gel 60F-254 (E. Merck, Darmstadt, Germany) precoated glass plates, developed with THF (93 mL)/C_6H_{12} (7 mL)/H_2O (5 mL), and visualized with UV and/or 40% aqueous H_2SO_4 at 110 °C. Column (30 mm o.d. × 35 cm) chromatography was accomplished on aluminum oxide, activated, basic, CAMAG (Ventron, Beverly, Mass.). Reagents were obtained from the following sources: 1,2:5,6-di-*O*-isopropylidene-D-glucofuranose from Pfanstiehl Labo-