Friedel–Crafts Ethylation in Nonpolar Solvents

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Abstract: Competitive Friedel–Crafts ethylations of benzene and toluene were carried out at 25° in homogeneous solutions of excess aromatics, nonpolar organic, or basic organic solvents. The rate of boron fluoride catalyzed ethylation with ethyl fluoride in *n*-hexane or chloroform was also measured under noncompetitive reaction conditions. Ethylation in nonpolar organic solvent shows an anomalous substrate selectivity. Benzene is more reactive than toluene. The isomer distributions of ethyltoluene formed in nonpolar organic solvents are not statistical. Aluminum bromide catalyzed ethylation of benzene with ethyl-2-^{14}C iodide was carried out in *n*-hexane solution. Oxidation of the ethylbenzene obtained with nitric acid gave radioactive *p*-nitrobenzoic acid, indicating migration of radioactivity from the β- to the α-carbon atom of the ethyl group. It is suggested that the electrophile in ethylation is either an ethyl carbonium ion in the nonpolar organic solvent or a nonionized ethyl halide–metallic halide complex in the basic organic solvent, and that the substrate and positional selectivities in all Friedel–Crafts alkylations are determined by an activation energy of the formation of σ complex.

The electrophilic character of the following alkyl carbonium ions increases in the order: $(CH_3)_3C^+ < (CH_3)_2CH^+ < C_2H_5^+ < CH_3^+$. If Friedel–Crafts alkylation proceeds by means of an ionization mechanism, the partial rate factor for alkylation would be expected to decrease in the reverse order.[1] However, the *ortho* and *para* partial rate factors for gallium bromide catalyzed alkylation with alkyl bromide in excess aromatics were found to vary in the order: methylation > ethylation > isopropylation < *t*-butylation.[2] Brown concluded, therefore, that the electrophile in methylation or ethylation is not the carbonium ion but the nonionized alkyl bromide–gallium bromide complex, and that the methylation or ethylation reaction involves an S_N2 displacement reaction with the aromatic component which contributes to the breaking of the carbon–halogen bond. Until now there has been no evidence of the formation and role of methyl- or ethylcarbonium ions in the Friedel–Crafts alkylation.

Results

Competitive Ethylation. The competitive ethylation of benzene and toluene at 25° was carried out in excess aromatics, basic organic, or nonpolar organic solvents. Nitromethane or chloroform was used as the basic organic solvent. Carbon tetrachloride, cyclohexane, or *n*-hexane was used as a nonpolar organic solvent. Boron fluoride or aluminum bromide was used as a catalyst. Ethyl fluoride or ethyl iodide was used as an ethylating agent. All reactions were homogeneous.[3] An equimolar mixture of the aromatic components was used. The mole ratio of the solvent to ethyl halide was 30:1 or 100:1. The mole ratio of ethyl halide to catalyst changed from 1:0.6 to 1:2. The mole ratio of aromatics to ethyl halide was 10:1. Some boron fluoride catalyzed ethylations proceeded under high pressure. Details of the procedures of ethylation are described in the Experimental Section. The data obtained are summarized in Table I. A practical constant excess of aromatics always remained during the reaction. The amount of detectable di- or higher ethylate did not exceed 5% of monoethylate. Aluminum bromide catalyzed ethylation proceeds much faster than boron fluoride catalyzed ethylation in *n*-hexane solution.

The relative rate of toluene to benzene was lower in nonpolar organic solvents than in basic organic solvents. An anomalous substrate selectivity was found in all nonpolar organic solvents. Benzene was more reactive than toluene. Ethylation was insensitive to change in polarity of the basic organic solvent. The concentration of *meta* isomer in the nonpolar organic solvent was much lower than the statistical value (40% *meta* isomer).[4]

Noncompetitive Ethylation. The rate of boron fluoride catalyzed ethylation of benzene or toluene was also measured in separate runs under identical conditions. Boron fluoride fairly readily dissolves in *n*-hexane. The solubility of boron fluoride in *n*-hexane is higher than in other nonpolar solvents and is nearly equal to that in chloroform.[3] *n*-Hexane was used as a nonpolar organic solvent. Chloroform was used as a basic organic solvent. The mole ratio of solvent to aromatics, ethyl fluoride, and boron fluoride in the solution was always 100:10:3:0.6. The reaction was allowed to proceed at 25°. Aliquots were analyzed periodically. Details of the procedures of ethylation are described in the Experimental Section. The obtained results are shown in Figures 1 and 2. Pseudo-

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(1) H. C. Brown and K. L. Nelson, *J. Am. Chem. Soc.*, **75**, 6269 (1953).

(2) H. C. Brown and C. R. Smoot, *ibid.*, **78**, 6255 (1956).

(3) The solubility of Friedel–Crafts catalyst in nonpolar organic solvents is low at room temperature. Therefore there is always the possibility that the catalyst is not soluble in the nonpolar organic solvent when Friedel–Crafts reactions are carried out. The critical temperature of boron fluoride is −12.25° (H. S. Booth and J. M. Carter, *J. Phys. Chem.*, **36**, 1359 (1932)). When boron fluoride is insoluble, undissolved boron fluoride may exist as a gas. The vapor pressure of solutions of constant mole ratio of boron fluoride to the solvent will be constant, if boron fluoride is not entirely soluble and the vapor pressure of the solvent is zero. However, the vapor pressure of the *n*-hexane solution is much lower than that of the carbon tetrachloride solution. When the mole ratio of solvent, benzene, ethyl fluoride, and boron fluoride is 100:10:1:1, the vapor pressure of the *n*-hexane solution at 25° is about 650 mm and that of the carbon tetrachloride solution about 2000 mm. This means that the quantity of boron fluoride existing as a gas is much smaller in the *n*-hexane than in the carbon tetrachloride solution and hence the solubility of boron fluoride is much higher in *n*-hexane than in carbon tetrachloride. The solubility of boron fluoride in the following solvents increases in the order: $CCl_4 < C_6H_{12} < n\text{-}C_6H_{14} \approx CHCl_3 < CH_3NO_2$. Boron fluoride is fairly soluble in *n*-hexane. Aluminum bromide is also soluble in *n*-hexane.

(4) L. M. Stock and H. C. Brown, *Advan. Phys. Org. Chem.*, **1**, 45 (1963).

Table I. Friedel–Crafts Ethylation of Benzene and Toluene at 25°

Catalyst	Ethyl halide	Solvent	k_T/k_B	Ethyltoluenes, % ortho	meta	para	Partial rate factors o_f	m_f	p_f
BF_3	C_2H_5F	Excess aromatics	2.26[a,c]	46.2	28.7	25.1	3.13	1.95	3.40
		CH_3NO_2	2.66[a,d]	43.8	24.2	32.0	3.50	1.93	5.11
		$CHCl_3$	1.95[a,e]	46.3	27.2	26.5	2.71	1.59	3.10
			2.50[b]	48.6	23.7	27.7	3.65	1.78	4.16
		CCl_4	0.70[a,e]	46.0	29.7	24.3	0.97	0.62	1.02
		C_6H_{12}	0.57[a,e]	45.5	29.2	25.3	0.78	0.50	0.87
		n-C_6H_{14}	0.56[a,e]	45.3	29.2	25.5	0.76	0.49	0.86
			0.61[b]	49.2	27.1	23.7	0.90	0.50	0.87
$AlBr_3$	C_2H_5I		0.63[f]	44.8	10.9	44.3	0.85	0.20	1.67

[a] Competitive ethylation. [b] Noncompetitive ethylation. [c] Mole ratio of reactants, aromatics:C_2H_5F:BF_3 = 10:1:1. [d] Mole ratio of reactants, solvent:aromatics:C_2H_5F:BF_3 = 30:10:1:0.6. [e] Mole ratio of reactants, solvent:aromatics:C_2H_5F:BF_3 = 100:10:1:1. [f] Mole ratio of reactants, solvent:aromatics:C_2H_5I:$AlBr_3$ = 100:10:1:2.

second-order rate plots were obtained in both systems assuming

$$\frac{d[\text{product}]}{dt} = k'[\text{aromatic}][\text{ethyl fluoride}]$$

where $k' = k[BF_3]$.

The aromatics react slowly with ethyl fluoride in each solution. The reactivity of benzene was lower in n-hexane than in chloroform. The relative rate of toluene to benzene, k_T/k_B, which was calculated from the slope of the kinetic curve, was 0.61 in the n-hexane solution, whereas it was 2.50 in $HCCl_3$. Orientation in ethylation of toluene was 49.2% o-, 27.1% m-, and 23.7% p-ethyltoluene in n-hexane and 48.6% o-, 23.7% m-, and 27.7% p-ethyltoluene in chloroform. The partial rate factors together with the relative rate and isomer distributions are summarized in Table I. The *ortho*, *meta*, and *para* partial rate factors in n-hexane solution are slightly larger than those obtained by the competitive procedure. The o_f in the chloroform solution was nearly equal to the o_f in the nitromethane solution.

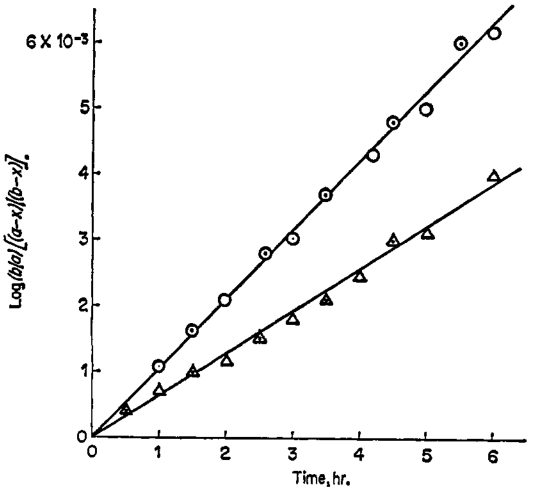

Figure 1. Ethylation of benzene and toluene in n-hexane solution: benzene, (○) experiment 1, (⊙) experiment 2; toluene, (△) experiment 1, (◬) experiment 2.

Ethylation with Radioactive Ethyl Iodide. Aluminum bromide catalyzed ethylation of benzene was carried out at 25° with ethyl-2-^{14}C iodide in n-hexane. Ethylation proceeded in the purple solution, in which the mole ratio of n-hexane to benzene, ethyl-2-^{14}C iodide, and aluminum bromide was 100:10:1:7. After 30 sec the solution was quenched in water. A large amount of n-hexane was separated from the extracted organic layer by fractional distillation. The remaining solution was oxidized with nitric acid according to the procedure of Roberts, *et al.*[5] About 20% of the radioactivity of ethyl-2-^{14}C iodide was found in the p-nitrobenzoic acid obtained.

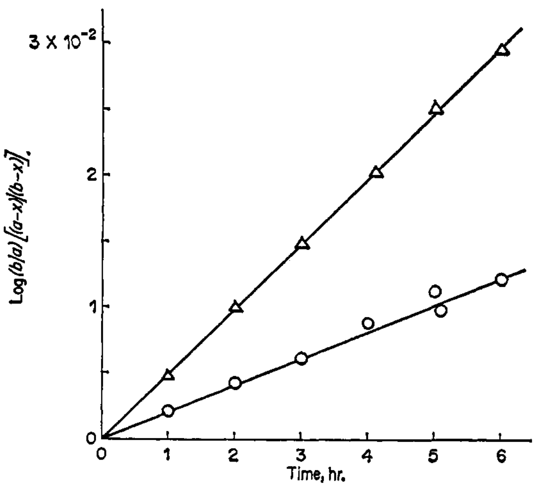

Figure 2. Ethylation of benzene and toluene in chloroform solution: benzene, ○; toluene, △.

Discussion

On the bases of the *ortho* and *para* partial rate factors for gallium bromide catalyzed ethylation with ethyl bromide in excess aromatics, Brown, *et al.*,[2] suggested that the electrophile is the nonionized ethyl bromide–gallium bromide complex and that ethylation is an SN2 displacement reaction. Roberts, *et al.*,[5] found that the aluminum chloride catalyzed ethylation of benzene with ethyl-2-^{14}C chloride in excess benzene gave no rearranged product. This finding also supports the concept of the SN2 displacement mechanism for alkylation with primary alkyl halide. However, ethyl halide in contact with the Friedel–Crafts catalyst in the absence of aromatics for many hours shows complete equilibration of the α- and β-carbon positions of the

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(5) R. M. Roberts, G. A. Ropp, and O. K. Neville, *J. Am. Chem. Soc.*, 77, 1764 (1955).

ethyl group occurred, suggesting the formation of the ethyl carbonium ion.[5,6] Aluminum bromide catalyzed ethylation of benzene with ethyl-2-^{14}C iodide was carried out in *n*-hexane and oxidation of the ethylbenzene obtained with nitric acid gave radioactive *p*-nitrobenzoic acid, indicating the formation of ethyl-1-^{14}C-benzene and hence the migration of radioactivity from β- to α-carbon positions of the ethyl groups. These results suggest that the ethyl carbonium ion is an electrophile in ethylations carried out in nonpolar organic solvents and an internal hydride shift occurs in part of ethyl group before the ethyl carbonium ion combines with the benzene ring.

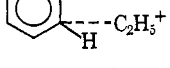
The Friedel–Crafts ethylation of aromatics with ethyl halide proceeds by one of two mechanisms. In basic organic solvents or in excess aromatics, the ionization of ethyl halide is not favored because of the competing donor effect of the solvent. Ethyl halide forms a nonionized complex with metallic halide and reacts by the SN2 displacement. In nonpolar organic solvents ethyl halide can be ionized directly to the ethyl carbonium ion. The rupture of the C–X bond is probably complete before reaction.

Brown[4] suggested that an ultimate powerful electrophile could not distinguish the difference between benzene and toluene or among the available sites in a substituted benzene, and moreover, that the relative rate, k_T/k_B, would be 5/6, and the orientation in alkylation of toluene would be 40% *ortho*-, 40% *meta*, and 20% *para* isomer (the statistical value). All partial rate factors are 1. In ethylations carried out in nonpolar organic solvents, the very reactive ethylcarbonium ion is the electrophile. If Brown's proposal is correct, the relative rate will be nearly equal to or slightly larger than 5/6, and the isomer distributions will approach the statistical value. In the boron fluoride catalyzed ethylation, however, the relative rate is smaller than 5/6 and the concentration of *meta* isomer is much lower than the statistical value. All partial rate factors are smaller than 1. According to Allen[7] the isomerization of ethyltoluene takes place 84% by intramolecular and 16% by intermolecular isomerization. During the boron fluoride catalyzed ethylation in *n*-hexane, only a little intermolecular isomerization and transalkylation take place, because the relative rate, k_T/k_B, obtained in the competitive ethylation is slightly smaller than obtained in separate runs which shows the true value. However, the concurrent intramolecular isomerization would be difficult to exclude and would affect the observed isomer ratio. The concentration of the *meta* isomer formed in the direct, kinetically controlled ethylation would be lower than the spontaneously observed *meta* isomer. In the ethylation of toluene steric hindrance is not of major importance. If direct, kinetically controlled ethylation in the *meta* position and the concurrent isomerization do not take place, m_f will be zero and o_f as well as p_f will be 1.22, because k_T/k_B is 0.61. Accordingly, o_f and p_f for the direct, kinetically controlled ethylation in *n*-hexane will be larger than the spontaneously observed one, which is approximately 0.9, and smaller than 1.22. The m_f will be smaller than 0.50. The o_f and p_f observed in *n*-hexane are not greatly different from those observed in other nonpolar organic solvents. Therefore, o_f and p_f for ethylation, in which the ethylcarbonium ion is an electrophile, are nearly equal to or larger than 1, but are smaller than those for ethylation in which the nonionized complex is an electrophile, and those for isopropylation, in which an isopropyl carbonium ion or its ion pair is an electrophile.[8,9] The m_f for ethylation, in which the ethyl carbonium ion is an electrophile, is much smaller than 1.

Olah[8,10] suggested that the rate-determining transition state for the Friedel–Crafts reaction with a powerful electrophile correlates well with π complex stability. The stability of the π complex does not change greatly with increasing number of alkyl substituents, but the stability of the toluene complex is slightly greater than for the benzene complex.[10] If Olah's proposal is correct, all relative rates of toluene to benzene should not be smaller than 1. However, contrary to Olah's proposal the relative rate of toluene to benzene for the ethylation in the *n*-hexane solution was determined in separate runs to be much smaller than 1.

In all Friedel–Crafts alkylations, the substrate and positional selectivities seem to be determined by the activation energy of formation of the σ complex. The transition states of the σ complex are always composed of the separate transition states corresponding to the *meta*, *para*, and *ortho* positions among which the *meta* position is the highest energy barrier. The complex cation passes over the lower energy barrier leading to the σ complex.[8] Hence, all electrophiles distinguish the difference between the *ortho* or *para* and the *meta* sites in toluene. A powerful electrophile like ethyl carbonium ion can distinguish slightly the difference between each site in benzene and the *ortho* or *para* site in toluene, but readily the difference between each site in benzene and the *meta* site in toluene. Accordingly, in the ethylation carried out in nonpolar organic solvents, o_f and p_f are slightly larger than 1 and m_f is much smaller than 1. This fact explains why the isomer distributions do not reach the statistical values but the relative rates of toluene to benzene are smaller than 5/6. On the other hand, a weak electrophile readily distinguishes the difference between each site in benzene and the *ortho* or *para* site in toluene, and hence the o_f and m_f become much larger than 1.

When the electrophile is an ethyl carbonium ion, it attacks the aromatic ring to form the oriented π complex, *viz.*



and then the σ complex, the formation of which determines the rate of ethylation and the orientation in ethylation.

At low temperatures a termolecular oriented π complex is formed with toluene and the nonionized complex.[11-13] When boron fluoride is withdrawn from

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(6) C. C. Lee, M. C. Hamblin, and N. James, *Can. J. Chem.*, **36**, 1957 (1958).

(7) R. H. Allen, *J. Am. Chem. Soc.*, **82**, 4856 (1960).

(8) G. A. Olah, S. H. Flood, S. J. Kuhn, M. E. Moffatt, and N. A. Overchuck, *ibid.*, **86**, 1046 (1964).

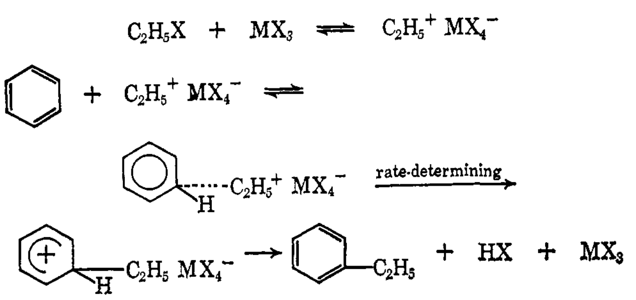
(9) G. A. Olah and N. A. Overchuck, *ibid.*, **87**, 5786 (1965).

(10) G. A. Olah, S. J. Kuhn, and S. H. Flood, *ibid.*, **83**, 4571 (1961); **84**, 1688 (1962).

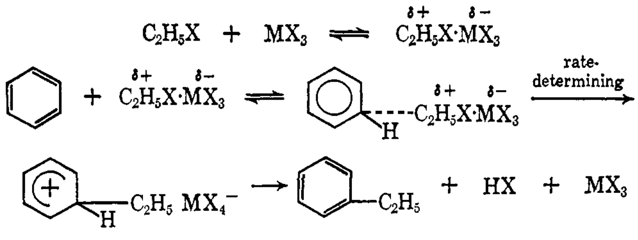
(11) R. Nakane, A. Natsubori, and O. Kurihara, *J. Am. Chem. Soc.*, **87**, 3597 (1965).

(12) R. Nakane, T. Oyama, and A. Natsubori, *J. Org. Chem.*, **33**, 275 (1968).

(13) T. Ōyama and R. Nakane, *ibid.*, **34**, 949 (1969).



the termolecular oriented complex, ethylation proceeds. The transformation from the termolecular oriented π complex to the σ complex determines the rate of the ethylation at low temperatures. Also when the nonionized complex is the electrophile of ethylation at room temperature, it seems probably that the termolecular oriented π complex becomes the unstable intermediate and transformation from the termolecular oriented π complex to the σ complex determines rate and orientation.



Experimental Section

Materials. Toluene, ethyl fluoride, and boron fluoride were prepared and purified by previously described methods.[11,14] Ethyl-2-^{14}C iodide was obtained from The Radiochemical Centre (Amersham, England). Ethyl iodide was obtained from Yanagishima Chemical Co. (Tokyo, Japan) and was the purest material available commercially. It was used without further purification. Anhydrous aluminum bromide was prepared from aluminum metal (Junsei Pure Chemical Co., Tokyo, Japan) by reaction with bromine (Junsei Pure Chemical Co.) according to the method of Winter, *et al.*,[15] and purified by distillation. Benzene was Dotite Spectrosol (Dojin Chemical Co., Tokyo, Japan) for absorption spectrum measurement. It was fractionated through a glass column (length 50 cm; i.d. 10 mm) packed with no. 3012 Helipack. *n*-Hexane was also Dotite Spectrosol. It was used without further purification. Chloroform, carbon tetrachloride, cyclohexane, and nitromethane were obtained from Junsei Pure Chemical Co. and were the purest materials available commercially. They were purified by distillation. The average purity of all organic materials was more than 99% by gas chromatographic analysis.

Competitive Ethylation. An apparatus made of stainless steel was used in the boron fluoride catalyzed ethylations. When competitive ethylation of benzene and toluene was carried out in solutions containing aromatics as solvent, benzene (0.05 mol) and toluene (0.05 mol) were charged in the reaction flask. The flask was then placed in a constant-temperature bath at 25 ± 0.1°. From high pressure reservoirs gaseous ethyl fluoride (0.01 mol) and gaseous boron fluoride (0.01 mol) were introduced into the flask. The valve connected to the flask was closed. The vapor pressure of the solution was 22 atm. The flask with the valve was detached from the line and was shaken for 1.5 hr. Then the flask was again connected to the line and the valve opened. The vapor was introduced into an evacuated reservoir. After ammonia was introduced in the flask, the organic liquid was separated from the white solid and analyzed by gas chromatography. As solvent nitromethane (0.30 mol), chloroform (0.18 mol), carbon tetrachloride (0.14 mol), cyclohexane (0.12 mol), or *n*-hexane (0.10 mol) was charged in the flask. The required amounts of aromatics, ethyl fluoride, and boron fluoride were added to them and the vapor pressure of the nitromethane solution, chloroform solution, carbon tetrachloride solution, cyclohexane solution, or *n*-hexane solution was determined to be ~0.1, ~0.9, ~2.5, ~1.4, or ~0.9 atm, respectively. During the competitive ethylation in the nitromethane solution, the organic liquid separated after quenching of ammonia was washed with 5% NaOH solution and water.

A glass flask was used in the aluminum bromide catalyzed ethylation. Ethyl iodide (0.005 mol) and anhydrous aluminum bromide (0.010 mol) were added and the flask was placed in a constant-temperature bath at 25 ± 0.1°. Thereafter, benzene (0.025 mol) and toluene (0.025 mol), in *n*-hexane (0.5 mol), were added with vigorous stirring. A purple solution was formed immediately. It was quenched in water after 30 sec, extracted with ether, dried over calcium chloride, and analyzed by gas chromatography.

Kinetic Measurements. All of the kinetic experiments were carried out in a 225-ml, two-necked glass flask. A greaseless vacuum valve (Fisher and Porter Co., Warminster, Pa.) was joined to one neck. A Perflone sheet was set in a flanged end of another neck and secured in position by a washer. The end was then closed. The flask was evacuated. *n*-Hexane or chloroform (each 0.72 mol) and benzene or toluene (each 0.12 mol) were added to the flask. After the valve was connected to the vacuum line, the flask was immersed in liquid nitrogen and evacuated. Boron fluoride (0.0072 mol) was introduced through the valve into the flask and condensed. The valve was closed and the flask was separated from vacuum line, and then placed in the constant-temperature bath at 25 ± 0.1°. A magnetic stirrer was put into place. The reactant in the flask began to melt. After equilibration, ethyl fluoride (0.036 mol) was dissolved in the solvent (0.48 mol), and introduced into the flask through the valve. A part of the solution in the flask was immediately withdrawn with an injector through the Perflone sheet. This moment was taken as a starting point of the reaction. The sample was quenched in water, extracted with ether, dried over calcium chloride, and analyzed by gas chromatography. The quantity of unreacted aromatic in the sample was taken as an initial concentration (*a*). The initial concentration of ethyl fluoride (*b*) was calculated from the quantities of unreacted aromatics and ethylated product. The magnetic stirrer was then started and aliquots were analyzed periodically. The vapor pressures of benzene–*n*-hexane, toluene–*n*-hexane, benzene–chloroform, and toluene–chloroform mixtures are *ca.* 700, 750, 690, and 740 mm respectively.

Ethylation with Ethyl-2-^{14}C Iodide. Benzene (1.0 mol), ethyl-2-^{14}C iodide (0.1 mol) (1.00 μCi/mmol), and *n*-hexane (10 mol) were charged in the flask. With vigorous stirring anhydrous aluminum bromide (0.7 mol) was added to the solution. The solution immediately became purple. After the reaction which continued 30 sec, the solution was quenched in water. In a preliminary experiment with nonradioactive ethyl iodide it was confirmed that about 5% ethyl iodide was consumed after the purple solution had stood for 30 sec. The organic layer was washed with 4% NaOH solution and then five times with water. The organic solution was dried over calcium chloride and subjected to fractional distillation. A large amount of *n*-hexane was removed. The remaining solution was treated in accordance with the procedure of Roberts, *et al.*[5] The solution was mixed with 60 ml of concentrated nitric acid and heated at 100° for 40 hr. The solution was washed with water and extracted with ether. The ethereal layer was extracted with sodium bicarbonate solution. The *p*-nitrobenzoic acid which precipitated on acidification was crystallized from water four times to give light yellow crystals. The nonradioactive *p*-nitrobenzoic acid, prepared by a similar method in a preliminary experiment, was analyzed by a mass spectrometer and its purity was checked. The yield was about 10%. *p*-Nitrobenzoic acid (8 mg) was dissolved in a liquid scintillator (10 ml), and the radioactivity of the solution was counted. The solution had a radioactivity of 0.15–0.25 μCi/mmol.

Gas Chromatographic Analysis. Analyses were carried out with a Hitachi Perkin-Elmer gas chromatograph Model F6D using a hydrogen flame ionization detector. A stainless steel column (length 4 m, i.d. 3 mm) packed with Benton 34 and DDP supported on Chromosorb W was used. The column temperature was 70°. Dry nitrogen (12 cc/min) was used as carrier gas. The accuracy of measurements concerning *ortho*, *meta*, and *para* isomers of methylethylbenzene was checked against the analytical data of the standard samples of isomers obtained from Tokyo Kagaku Seiki Co.

Radioactivity Measurements. Radioactivity measurement was carried out with a Beckman LS-150 liquid scintillation system at

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(14) R. Nakane and T. Ōyama, *J. Phys. Chem.*, **70**, 1146 (1966).

(15) P. K. Winter and P. L. Cramer, *Ind. Eng. Chem.*, 32, 856 (1940).

room temperature by an external channel ratio method. Dioxane containing the usual scintillators was used as solvent. A counting efficiency of about 85% with a background of about 50 cpm was obtained.

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A New Phosphorylating Reagent. I. The Preparation of Alkyl Dihydrogen Phosphates by Means of 2-Chloromethyl-4-nitrophenyl Phosphorodichloridate

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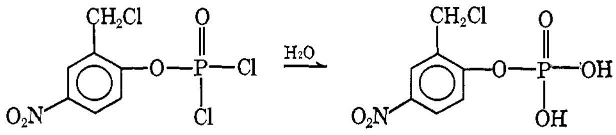
Abstract: A convenient method for the preparation of alkyl dihydrogen phosphates was investigated. 2-Chloromethyl-4-nitrophenyl phosphorodichloridate (**2**), a phosphorylating agent having a new protecting group, was prepared from 2-chloromethyl-4-nitrophenol (**1**) and phosphoryl chloride. It reacts smoothly with alcohols in the presence of tertiary amines to give the corresponding alkyl 2-chloromethyl-4-nitrophenyl phosphorochloridates (**3**), which were in turn converted by hydrolysis into alkyl 2-chloromethyl-4-nitrophenyl hydrogen phosphates (**4**). When the phosphates **4** are treated with pyridine, they change to inner salts of 1-(2′-alkyl hydrogen phosphoroxy-5′-nitrobenzyl)pyridinium hydroxide (**7**). The inner salts **7** readily underwent hydrolysis to yield the corresponding alkyl dihydrogen phosphates (**8**) and inner salt of 1-(2′-hydroxy-5′-nitrobenzyl)pyridinium hydroxide (**9**) in good yields.

A considerable number of phosphorylation methods have been investigated and successfully applied to the syntheses of various phosphates and pyrophosphates. However, there are few reports dealing with general methods of the preparation of alkyl dihydrogen phosphates except those concerned with phosphorylation of alcohols by means of β-cyanoethyl phosphate and dicyclohexylcarbodiimide (DCC),[1] trichloroacetonitrile and inorganic phosphoric acid,[2] or dibenzyl phosphorochloridate.[3] Recently it has been demonstrated in this laboratory that inorganic phosphorous acid reacts with mercuric chloride to give an intermediate complex, from which alkyl dihydrogen phosphates can be obtained by further reaction with alcohols.[4]

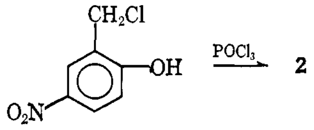
In the present study, a convenient method for the syntheses of alkyl dihydrogen phosphates by the use of 2-chloromethyl-4-nitrophenyl phosphorodichloridate (**2**), a phosphorylating reagent having a new protecting group, was investigated. The phosphorodichloridate **2** was chosen on the following assumptions; first, one of the two chlorine atoms of **2** would exclusively react with 1 equiv of alcohol to give alkyl 2-chloromethyl-4-nitrophenyl phosphorochloridate (**3**). Second, alkyl 2-chloromethyl-4-nitrophenyl phosphate (**4**) derived from **2** would yield, when treated with a tertiary amine, the inner salt of 1-(2′-alkyl hydrogen phosphoroxy-5′-nitrobenzyl)trialkylammonium hydroxide (**6**), an active phosphorylating reagent. This reasoning is based on the facile generation of a phosphoryl cation by the elimination of a phenoxy group when activated by two electron-withdrawing groups, $-NO_2$ and $-CH_2N^+<$.

Thus the 2-chloromethyl-4-nitrophenyl group acts as a protecting group in the first stage of this process and, in the next stage, it functions as a strongly electron-withdrawing group, activating the phosphate to generate an active phosphoryl cation. Therefore, this group may be called an "activatable protecting group."

The phosphorylating reagent **2**[5,6] was readily prepared in 71% yield by refluxing 2-chloromethyl-4-nitrophenol (**1**) and 2.5 mol of phosphoryl chloride for 6 hr. In this reaction, the yield of **2** decreased considerably when a large excess of phosphoryl chloride was used. This is probably due to the lower reaction temperature.



2 **12**



1

Alcohols were selectively phosphorylated with **2** to give the corresponding alkyl 2-chloromethyl-4-nitrophenyl phosphorochloridates (**3**) by the reaction of 1 mol of **2** and 1 mol of an alcohol in the presence of

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(1) G. M. Tenner, *J. Am. Chem. Soc.*, **83**, 159 (1961).

(2) F. Cramer and G. Weimann, *Chem. Ind.* (London), 46 (1960).

(3) F. R. Atherton, H. T. Openshaw, and A. R. Todd, *J. Chem. Soc.*, 382 (1945).

(4) T. Obata and T. Mukaiyama, *J. Org. Chem.*, **32**, 1063 (1967).

(5) The preparation of compound **2** was first carried out in the laboratory of Professor F. Cramer, Max-Planck-Institut für experimentelle Medizin in Göttingen.

(6) The structure of **2** was supported by the elemental analysis and was further confirmed by derivating to 2-chloromethyl-4-nitrophenyl dihydrogen phosphate (**12**) by hydrolysis.