dure described above, the reaction with vinylcyclopropane gave, after routine isolation and purification (silica gel, 4:1 hexane/ethyl acetate), the title compound in 64% yield. The ^{1}H NMR spectrum obtained was identical with that reported above.

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Registry No. 1, 23649-17-4; **2**, 90991-96-1; ethene, 74-85-1; 1-hexene, 592-41-6; styrene, 100-42-5; 3,3-dimethyl-1-butene, 558-37-2; methyl acrylate, 96-33-3; acrylonitrile, 107-13-1; *cis*-2-butene, 590-18-1; cyclohexene, 110-83-8; (2-carboxy-5-chlorophenyl)bis(trifluoroacetate)thallium, 90991-93-8; (2-carboxy-5-methylphenyl)bis(trifluoroacetate)thallium, 90991-94-9; (2-carboxy-3-methoxyphenyl)bis(trifluoroacetate)-thallium, 90991-95-0; isocoumarin, 491-31-6; 2-ethylbenzoic acid, 612-19-1; methylenephthalide, 3453-63-2; 3-*n*-butylisocoumarin, 30531-69-2; 3-phenylisocoumarin, 4809-08-9; 3-(carbomethoxymethyl)phthalide, 3453-60-9; 3-(cyanomethyl)phthalide, 18327-98-5; 3,4-dimethylisocoumarin, 20281-09-8; 3-ethylisocoumarin, 26477-57-6; 1,3-dihydrospiro[isobenzofuran-1-one-3,1′-cyclohex-3′-ene], 90991-97-2; 1,2,3,4-tetrahydro-4*H*-dibenzo[*b*,*d*]pyran-6-one, 90991-98-3; 3-*tert*-butyl-7-chloroisocoumarin, 90991-99-4; 3-*tert*-butyl-5-chloroisocoumarin, 90992-00-0; 3-*tert*-butyl-7-methylisocoumarin, 90992-01-1; 3-*tert*-butyl-5-methylisocoumarin, 90992-02-2; 3-*tert*-butyl-5-methoxyisocoumarin, 90992-03-3; 3-*tert*-butyl-7-methoxyisocoumarin, 90992-04-4; vinyl bromide, 593-60-2; *cis*-1-bromo-1-propene, 590-13-6; *cis*-1-bromo-1-hexene, 13154-12-6; *trans*-1-bromo-1-hexene, 13154-13-7; *cis*-1-iodo-1-hexene, 16538-47-9; α-bromostyrene, 98-81-7; vinyl acetate, 108-05-4; isopropenyl acetate, 108-22-5; 4-methylisocoumarin, 68944-81-0; 3-methylisocoumarin, 29539-21-7; 4-*n*-butylisocoumarin, 90992-05-5; 1,3-butadiene, 106-99-0; *trans*-1,3-pentadiene, 2004-70-8; *cis*-1,3-pentadiene, 1574-41-0; isoprene, 78-79-5; 1,3-cyclohexadiene, 592-57-4; 1,2-butadiene, 590-19-2; 3-vinyl-3,4-dihydroisocoumarin, 90992-06-6; 3-(*trans*-1′-propenyl)-3,4-dihydroisocoumarin, 90992-07-7; 3-isopropenyl-3,4-dihydroisocoumarin, 90992-08-8; 3-methyl-1-vinyl-3,4-dihydroisocoumarin, 90992-09-9; *cis*-1,2,4a,10b-tetrahydro-4*H*-dibenzo-[*b*,*d*]pyran-6-one, 90992-10-2; 3-methyl-4-methylene-3,4-dihydroisocoumarin, 90992-11-3; 1-phenyl-1,2-propadiene, 2327-99-3; 3-methyl-1,2-butadiene, 598-25-4; vinylidenecyclohexane, 5664-20-0; 1,2-cyclononadiene, 1123-11-1; 1,4-pentadiene, 591-93-5; 4-methylene-3-phenyl-3,4-dihydroisocoumarin, 90992-12-4; *cis*-(4-phenylmethylene)-3,4-dihydroisocoumarin, 90992-13-5; *trans*-(4-phenylmethylene)-3,4-dihydroisocoumarin, 90992-14-6; 3,3-dimethyl-4-methylene-3,4-dihydroisocoumarin, 90992-15-7; 4-methylenespiro[1*H*-2-benzopyran-1-one-3,1′-cyclohexane], 90992-16-8; 2a*H*-3,4,5,6,7,8-hexahydrocyclonana[2,3-*c*]-1*H*-2-benzopyran-1-one, 90992-17-9; 4,5-dihydro-3-vinyl-2-benzoxepin-1(3*H*)-one, 90992-18-0; vinylcylcopropane, 693-86-7; isopropenylcyclopropane, 4663-22-3; *trans*-(2-phenylisopropenyl)cyclopropane, 41577-94-0; *cis*-(2-phenylisopropenyl)cyclopropane, 91050-50-9; 1-methyl-1-vinylcyclopropane, 16906-27-7; 3-methyl-3-(1′-propenyl)-3,4-dihydroisocoumarin, 90992-19-1; 3-methyl-3-(3′-phenylpropenyl)-3,4-dihydroisocoumarin, 90992-20-4; (*E*)-3-(2′-butenyl)-3,4-dihydroisocoumarin, 90992-21-5; (*Z*)-3-(2′-butenyl)-3,4-dihydroisocoumarin, 90992-22-6; thallium(III) trifluoroacetate, 23586-53-0; benzoic acid, 65-85-0; *m*-methoxybenzoic acid, 586-38-9; *m*-chlorobenzoic acid, 535-80-8; *m*-methylbenzoic acid, 99-04-7; allyl chloride, 107-05-1; 1-hexyne, 693-02-7; 1-iodo-1-hexyne, 1119-67-1; *trans*-1-bromo-1-propene, 590-15-8; *cis*-1,2,3,4,4a,10b-hexahydro-6*H*-dibenzo[*b*,*d*]pyran-6-one, 72331-10-3; 3-chloro-3-methyl-1-butyne, 1111-97-3; 3-butyn-2-ol 4-methylbenzenesulfonate, 53487-52-8; 3-chloro-1-butyne, 21020-24-6; 1-chloro-1-ethynylcyclohexane, 6209-75-2; acetylenic alcohol, 32038-79-2.

Friedel–Crafts Alkylation of Anisole and Its Comparison with Toluene. Predominant Ortho–Para Substitution under Kinetic Conditions and the Effect of Thermodynamic Isomerizations[1]

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Abstract: The $AlCl_3$ and BF_3, as well as 65% HPF_6, catalyzed Friedel–Crafts alkylation of anisole with alkyl halides and alcohols was investigated. The alkylation of anisole with lower catalyst concentrations under mild conditions shows predominant ortho/para directing effect generally with a ratio of ~2:1, with the amount of meta isomer uniformly less than 3%. With "swamping" catalyst conditions the amount of meta substitution in methylation and ethylation can substantially increase. The isomer distribution in tert-butylation changes with time due to rapid ortho–para interconversion. Consequently, the $AlCl_3$-catalyzed isomerization of isomeric alkylanisoles was also studied. In case of *tert*-butylanisoles, the ortho isomer shows relatively rapid conversion into para followed by much slower isomerization to meta. The para and meta isomers show isomerization to meta–para mixtures. Isomerization of ethyl-, isopropyl-, and benzylanisoles is generally slow whereas methylanisoles do not isomerize. Comparing results of the alkylation of anisole with toluene leads to the conclusion that the latter are readily affected by concurrent (and in some cases consecutive) isomerization. As the barrier for isomerization in the benzenium ion intermediates of the alkylations is higher in the case of CH_3O- than CH_3-substituted systems, anisole tends to give the kinetically controlled ortho–para alkylation products and the amount of meta isomer is low. Study of alkylation of 3,5-di- and 2,4,6-trideuteriated toluene and anisole and comparing retained deuterium contents with isomer distributions shows that alkylated product formation in case of toluene, but not of anisole, is proceeded by intramolecular, 1,2-alkyl, and hydrogen–deuterium shifting resulting also in increased meta substitution. This effect is most predominant in methylation and ethylation where the alkyl shifts are intramolecular but not in tert-butylation and benzylation, where alkyl transfer is intermolecular. Isopropylation is intermediate in nature. No simple selectivity–reactivity relationship is indicated in the studied alkylation reactions. As shown in benzylations with increasingly electron-donating and -withdrawing substituted benzyl chlorides overall rate (i.e., substrate selectivity) and isomer distributions (i.e., regioselectivity) are not determined in the same step as significantly decreased substrate selectivity is not accompanied by loss of positional selectivity. Previously reported alkylations showing high degree of meta substitution, therefore, must have been affected by thermodynamically controlled rearrangement processes, including intramolecular alkyl and hydrogen shifts in the arenium ion intermediates of the alkylation reactions. These are to be differentiated from possible subsequent product isomerizations. Under predominantly kinetic conditions anisole as well as toluene are substantially ortho–para directing in alkylations, as in other electrophilic aromatic substitutions.

Until the 1950s, it was generally accepted that electron-donor substituents, such as a methyl group on the benzene ring, lead to predominant ortho–para substitution.[2] Extending the Hammett $\rho\sigma$ relationship to aromatic substitutions and introducing a new

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σ^+ substitution constant Brown, in his selectivity relationship,[3] suggested that in these substitutions a simple linear relationship exists between the reactivity of the reagent and its selectivity (both substrate and positional). With increasing reactivity of the reagent, a decrease of discrimination between the ortho, meta, and para positions of alkylbenzenes was observed, showing a trend toward the statistical 40% ortho, 40% meta, and 20% para limit. In Friedel–Crafts alkylations of toluene Brown et al. obtained 10% meta substitution in methylation,[4a] 21% in ethylation,[7a] 27% in isopropylation,[4b] 32% in *tert*-butylation,[4c] and 21% in benzylation.[4d] At the same time, the alkylations showed low substrate selectivity (k_T/k_B = 1.5–3.5).

The suggestion that electrophilic substitution reactions of monosubstituted benzenes obey a simple linear free energy relationship was criticized on the basis that resonance (conjugative) contributions to the electron-deficient transition state would not remain constant.[5] Recognizing this point Brown et al. undertook a study of the electrophilic substitution of anisole, a monosubstituted benzene with a strongly electron-donating substituent. Mercuration was studied as an example of a reaction of relatively low selectivity.[6a] Difficulties, however, of isomerizing conditions accompanying mercurations were pointed out.[6b] Noncatalytic bromination was studied as an example of a highly selective reaction.[7] The latter reaction gave an isomer distribution of 1.6% *o*- and 98.4% *p*-bromoanisole, with k_{An}/k_B = 1.7.10,[9] whereas the former gave 14% ortho and 86% para substitution with k_{An}/k_B = 4.48.10[2] (mercuric acetate in acetic anhydride).

We have in our preceding work studied the electrophilic nitration of anisole with nitronium salts and other reagents.[8] Despite varying reactivity of the reagents, even with the most reactive nitrating agent ortho–para substitution was found to be less than 1% meta. There was never observed significant increase of meta substitution, which would be expected if the Brown selectivity–reactivity relationship would be operative. Gold and Riley[9] studied the 60% perchloric acid catalyzed alkylation of anisole with alcohols. They reported with isopropyl alcohol the formation of 45% *o*- and 55% *p*-isopropylanisole. With *tert*-butyl alcohol 20% *o*- and 80% *p*-*tert*-butylanisole was obtained. No meta isomers were observed.

Kovacic and Hiller[10] studied aluminum trichloride catalyzed alkylations with alkyl halides. They found what they considered anomalously increased ortho/para isomer ratios. Methylation of anisole with methyl chloride in nitromethane solution at ~20 °C for 3 h gave 61% ortho, 7% meta, and 32% para isomer, whereas methyl bromide with 6-h reaction time gave 56% ortho, 12% meta, and 32% para. Isopropylation with isopropyl chloride gave 60% ortho, <2% meta, and 38% para isomer, whereas *tert*-butyl chloride gave 6% meta and 94% para isomer. Kovacic explained the observed greatly "increased" ortho substitution by the linear coordination effect of oxygen, i.e., initial O-alkylation followed by intramolecular O–C_{ortho} and O–C_{para} alkyl migration preferring the ortho position.

Stang and Anderson[11] studied the alkylation of anisole with vinyl triflates, very reactive electrophiles with a ρ value of −2.57. In a typical reaction they obtained 11% ortho and 89% para isomer, with no meta isomer observed. The relative reactivity of anisole over benzene k_A/k_B was 118. Comparative alkylation of toluene gave 28% ortho, 8% meta, and 64% para isomer, with k_T/k_B of 7.

In the gas-phase reaction of 720 torr of pressure of anisole with isopropyl cation Cacace et al.[12] found 85% ortho, 5% meta, and 10% para isomer, a remarkable high regioselectivity for reaction of the highly reactive free isopropyl cation.

No systematic study of the alkylation of anisole was, however, yet reported. Consequently we undertook such a study and report our results.

Results and Discussion

We have previously pointed out that the isomer distributions in alkylation of aromatics, such as toluene, can be affected by concurrent or consecutive thermodynamically controlled alkyl shifts in the arenium ion intermediates of the alkylations.[8] Intramolecular shifts within the arenium ion intermediates, i.e., prior to their deprotonation to alkylated products, can readily take place as shown in studies of stable alkylarenium ions.[13] At the same time, the alkylation conditions do not necessarily lead to isomerization of the alkylated products themselves. Lack of product isomerization, thus, cannot be used to establish "nonisomerizing" conditions. Our data on the alkylation of toluene, under conditions where product isomerization was decreased or eliminated, but intramolecular alkyl shifting in the alkylation intermediates is still possible, gave in typical alkylations the following degree of meta substitution: methylation 12–18%, ethylation 14–24%, isopropylation 14–17%, *tert*-butylation 5–7%, benzylation 4–6%.[14] We have further shown that, in reactions of reactive electrophiles with aromatics, substrate and positional selectivity is determined in two distinct steps.

Any linear relationship between reactivity and selectivity in electrophilic aromatic substitutions should be equally applicable not only to toluene, but also to anisole, a typical substituted benzene containing a much increased electron-donating substituent. Surprisingly, however, no systematic study of alkylation of anisole has yet been reported, partly because of the suggestion that the alkylation of anisole is complex, proceeding through initial attack on the ether oxygen atom, which can subsequently lead to preferential *ortho* substitution via intramolecular O → C alkyl migration (Kovacic's "linear coordination effect"[10]). We have previously shown in the case of methylation of anisole with methyl fluoride–antimony pentafluoride at low temperature that the dimethyl phenyloxonium ion, $C_6H_5O^+(CH_3)_2$, can indeed be

(1) (a) Presented at the Seventh Conference on Structure and Reactivity Relationships, Asilomar, CA, March 1983. (b) Aromatic Substitution. 51. For part 50, see: Olah, G. A.; Krishnamurthy, V. V.; Narang, S. C. *J. Org. Chem.* **1982**, *49*, 596–598.

(2) See, for example: Ingold, C. K. "Structure and Mechanism in Organic Chemistry"; Cornell University Press: Ithica, NY, 1953; pp 221–305.

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Table I. $AlCl_3$- and BF_3-Catalyzed Alkylation of Anisole with Alkyl Halides and Comparison with Related Alkylation of Toluene

alkyl halide	catalyst	solvent	reaction conditions time/°C	anisole % alkylanisoles ortho	meta	para	toluene % alkyltoluenes[a] ortho	meta	para
CH_3F	BF_3	anisole	30 min/25	75	<1	25	54	18	28[b]
		CH_3NO_2	15 min/25	55	<1	45			
CH_3Cl	$AlCl_3$	CH_3NO_2	5 min/25	68	2	30	52	17	31
CH_3Br	$AlCl_3$	CH_3NO_2	30 min/25	67	2	31	54	17	29[c]
CH_3I	$AlCl_3$	CH_3NO_2	1 h/25	67	<1	32	57	12	31
C_2H_5F	BF_3	anisole	10 min/25	47	2	51			
		CH_3NO_2	15 min/25	39	3	58	54	24	22[b]
C_2H_5Cl	$AlCl_3$	CH_3NO_2	2 min/25	69	3	28	62	18	20[d]
C_2H_5Br	$AlCl_3$	CH_3NO_2	2 min/25	67	<1	33	56	14	30[e]
C_2H_5I	$AlCl_3$	CH_3NO_2	5 min/25	50	3	47	56	15	29
i-C_3H_7F	BF_3	anisole	5 min/25	59	3	38			
		CH_3NO_2	15 min/25	58	3	39	51	14	35[b]
i-C_3H_7Cl	$AlCl_3$	CH_3NO_2	5 min/25	64	2	34	47	17	36
i-C_3H_7Br	$AlCl_3$	CH_3NO_2	10 min/25	71	2	27	47	15	38
t-C_4H_9F	BF_3	anisole	5 s/25	43		57		5	95[b]
t-C_4H_9Cl	$AlCl_3$	CH_3NO_2	5 min/25		3	97		6	94
t-C_4H_9Br	$AlCl_3$	CH_3NO_2	1 min/25			~100		7	93
$C_6H_5CH_2F$	BF_3	anisole	10 min/0	49	<0.2	51			
		CH_3NO_2					41	5	54
$C_6H_5CH_2Cl$	$AlCl_3$	CH_3NO_2	30 min/25	52	<0.5	48	44	4	52

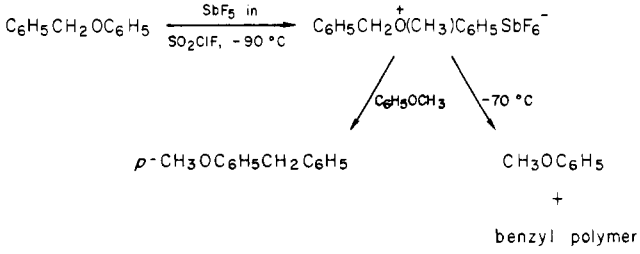
[a] Reactions generally carried out in CH_3NO_2 solutions at 25 °C. [b] In SO_2ClF, 1 min/−78 °C. [c] At 0 °C, 1 min. [d] 5 min reaction in CH_3NO_2 at 30 °C. [e] With $FeCl_3$–CH_3NO_2 catalyst.

Table II. 65% HPF_6-Catalyzed Alkylation of Anisole and Toluene with Alcohols

alcohol	temp, °C	reaction time	% alkylanisoles ortho	meta	para	% alkyltoluenes ortho	meta	para
methyl	80	6 h	51.5	1.5	47			
ethyl	80	4 h	32.0	0.5	67.5	42	28	30
isopropyl	25	15 min	49.0	2.0	49.0	57	18	25
tert-butyl	25	15 min	41.0	<0.2	59.0		7	93
benzyl	25	30 min	41.0	0.5	58.5	44	6	48

formed.[15] Subsequent methyl migration to the ring was found, however, to be an exclusively intermolecular process. The methylanisoles obtained showed a distribution of 17% ortho, 3% meta, and 80% para isomer. The intramolecular $O \rightarrow C_{ortho}$ reaction is, incidentally, also forbidden by orbital symmetry rules, as it would involve a highly unfavorable four-centered transition state. In independent work, Beak et al.[16] came to a similar conclusion in the study of the methylation of anisole with methyl chloroformate.

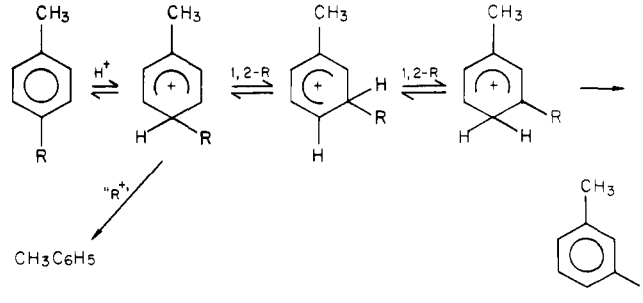
That no linear coordination effect is operative enhancing selectively ortho alkylation was now further demonstrated by reacting benzyl phenyl ether with CH_3F in SbF_5–SO_2ClF solution at −90 °C.[17] The NMR spectra of the solution show that besides ring metylation benzylmethylphenyloxonium ion, $C_6H_5CH_2O^+(CH_3)C_6H_5$, is formed (the expected ion of benzylation of anisole on oxygen), similarly to the previously described dimethylphenyloxonium ion.[15]



When the temperature of the solution was allowed to rise to above −70 °C, the ion rapidly decomposes with formation of anisole and a benzyl polymer. No (*o*-methoxyphenyl)phenylmethane is formed, the expected product of an intramolecular O → C benzyl shift. When excess anisole is added to the solution transbenzylation (but not methylation or phenylation) occurs, giving nearly exclusively (>98%) *p*-(methoxyphenyl)phenylmethane. This indicates the intermolecular nature of transbenzylation and also that the ion is a selective benzylating agent giving predominantly para substitution.

Having established that no specific ortho effect influences isomer distributions in the methylation and benzylation of anisole, a systematic study of the electrophilic alkylation of anisole was possible. We carried out such a study including the aluminum chloride or boron trifluoride catalyzed alkylations with alkyl halides in nitromethane solution (or in case of BF_3-catalyzed alkylations with alkyl fluorides also in neat anisole (Table I)). We also studied the novel and effective alkylation with alcohols in 65% hexafluorophosphoric acid (Table II). For comparison data of similar alkylations of toluene are also shown side by side in the tables.

In the acid-catalyzed isomerization of alkyltoluenes the essential step involves ipso protonation of the carbon atom to which the alkyl group is attached,[13] as shown in the case of the para isomers.



The ipso arenium ion is the same that is formed during the alkylation reactions of toluene in the para position. This arenium ion is more energetic than its isomeric forms and therefore can undergo before deprotonation rearrangement via 1,2-hydrogen or alkyl shifts to its more stable 2,4-dialkyl isomers. In study of protonation of dialkylbenzenes under stable ion conditions, the

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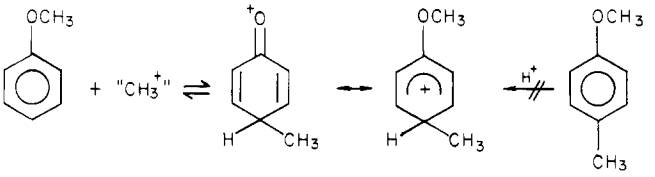
(17) Preparation of the ion was carried out using conditions similar to those described in ref 14. ^1H NMR of $C_6H_5CH_2O^+(CH_3)C_6H_5$ show δ_{CH_2} 4.1, δ_{CH_3} 3.9, and the aromatic protons at δ_{CH_2} 7.8–8.1. Details are reported separately.

ipso protonated forms are generally not observed. Such ipso ions, however, were observed in case of polyalkylbenzenes and showed ready rearrangements.[13a]

Considering isomer distributions in the alkylation of anisole whereas with relatively low catalyst concentration (0.02 mol of alkyl halide, 0.02 mol of Lewis acid halide, 0.1 mol of anisole) in dilute nitromethane solution the amount of meta isomer is low (<3%), with substantially higher catalyst concentrations the amount of meta isomer can be much higher. In ethylations and methylations with ethyl and methyl bromide or chloride, respectively, when using excess of aluminum chloride ("swamping" conditions similar to those used in isomerization of methylated phenols[18]), the amount of the meta isomer increases considerably. For example, with 5-fold of $AlCl_3$, the ethylation of anisole with ethyl bromide in nitromethane solution of 25 °C gives 46% meta isomer. Methylation of anisole with methyl bromide in the presence of similar excess of $AlCl_3$ catalyst gives 26% of meta isomer. Similar results were also obtained with methyl chloride and ethyl chloride. In these reactions it is possible that the anisole–$AlCl_3$ complex itself is also substituted in the meta position. Alternatively the "swamping" conditions increase catalyst coordination with the other oxygen. They thus also decrease the barrier for intramolecular 1,2-alkyl and hydrogen shifts. Significantly methylation and ethylation show the most significantly increased meta substitution (as is the case with toluene), as alkyl shifts in these cases tend to be intramolecular. As these reactions are complex not necessarily homogeneous systems, the data are informative but cannot be considered in a quantitative way. In contrast attempted isomerization of methylanisoles was unsuccessful and that of ethylanisoles only very limited. This is readily explained by the fact that in the alkylation reactions the corresponding ipso (to entering alkyl) benzenium ions must be formed whereas protonation of methylanisoles does not necessarily give the ipso protonated ions.



The most significant difference between the alkylation of anisole and that of toluene is the significantly lower degree of meta substitution observed in the former. Charge distribution calculations[13] of toluene and methylbenzenium ions, as well of anisole and methoxybenzenium ions, as models for "early" or "late" transition states indicate no reason to expect meta substitution in excess of 5% in either case, regardless of the nature of the transition states. The experimental data suggest that in the alkylation of anisole, in contrast to that of toluene, electrophilic attack by the alkylating agent at the ortho–para positions is less readily or not at all followed by thermodynamically controlled alkyl and hydrogen shifts, which could lead to increased meta substitution. The reason for the diminished migratory aptitude of alkyl groups is the higher activation energy of these processes in the highly stabilized para and ortho alkylmethoxybenzenium ions, as compared to the corresponding dimethylbenzenium ions.

Alkyl and polyalkylbenzenes are well-known to undergo acid-catalyzed isomerization. Friedel–Crafts isomerizations were extensively studied on dialkylbenzenes, such as xylenes, ethyltoluenes, cymenes, and *tert*-butyltoluenes.[17] Xylenes and ethyltoluenes isomerize by an intramolecular mechanism, whereas *tert*-butyltoluenes isomerize by intermolecular *tert*-butyl group migration. Isopropyl group migrations are considered to be intermediate in nature, including both intra- and intermolecular processes.

It was argued that in Friedel–Crafts alkylations nonisomerizing conditions are demonstrated if pure isomeric dialkylbenzenes, added in advance to the reaction mixtures, are recovered unchanged after the alkylations.[4] However, this approach only proves that dialkylbenzenes, once formed, are not further isomerized in consecutive reactions. It does not disprove the possibility of concurrent isomerizations, taking place during the course of the alkylations, which by necessity must involve common arenium ion intermediates with isomerizations.

Table III. Time Dependence of the BF_3-Catalyzed tert-Butylation of Neat Anisole with *tert*-Butyl Fluoride at 25 °C

	% *tert*-butylanisoles		
reaction time	ortho	meta	para
5 s	43.0		57.0
10 s	41.5		58.5
15 s	30.7		69.7
30 s	29.9		70.1
1 min	29.5		70.5
2 min	22.0		78.0
5 min	13.6		86.4
10 min	8.9		91.1
15 min	5.2		94.8
30 min	tr		100.0

That, indeed, in the reported alkylations of toluene (specifically methylations and ethylations) high meta isomer ratios were due, at least in part, to intramolecular alkyl and hydrogen shifts following the initial attack of the alkylating agent, but prior to deprotonation of the arenium ion intermediates to alkylated products, was now also tested through isotopic labeling experiments. The $AlCl_3$-catalyzed methylations of 3,5-dideuteriotoluene and 2,4,6-trideuteriotoluene were studied and compared with those of 3,5-dideuterio- as well as 2,4,6-trideuterioanisole. Deuterium label retained in combined isomeric xylene products of 3,5-dideuteriotoluene was only about 65% of that expected on the basis of comparison of deuterium content (analyzed by NMR spectroscopy and GC-mass spectrometry) with isomer distribution of the products, whereas in case of 2,4,6-trideuteriotoluene the deuterium content exceeded by about 24% that expected, assuming that no intramolecular methyl and hydrogen–deuterium shifts took place prior to product formation. In sharp contrast in the case of the deuteriated anisoles label was substantially retained as expected on the basis of isomer distributions. Although the Friedel–Crafts reaction conditions which were used do not allow quantitative evaluation of the data (as some acid-catalyzed intermolecular hydrogen deuterium exchange also can take place), the qualitative results are in accord that in the alkylation of toluene, but not of anisole, intramolecular alkyl and hydrogen (deuterium) shifting takes place within the arenium complexes prior to their deprotonation to alkylated products. This intramolecular isomerization can explain the particularly high meta isomer ratios in methylation and ethylation of toluene. These alkyl shifts are known to be intramolecular. In contrast in *tert*-butylation intermolecular transalkylation leads to fast ortho → para interconversion but only very modest increase of meta isomer (~5%). Isopropylation is intermediate in nature.

Further indication that the observed high meta substitutions in the methylation and ethylation of toluene were not affected by isomerization of the alkyltoluene products (i.e., after deprotonation of the intermediate arenium ions) was obtained when carrying out alkylations in the presence of highly hindered amines (Hunig bases) such as diisopropylcyclohexylamine or 2,4,6-tri-*tert*-butylpyridine. Neither showed any significant effect on meta substitution. As these hindered bases effectively scavange protic acids, isomerization of formed alkyltoluenes should be substantially decreased. That no difference of product distribution was observed with or without added base indicates that isomer distributions were not affected by subsequent isomerization of product alkyltoluenes.

Alkylation of anisole can also be accompanied by product isomerization, but this is less important as indicated by the generally very low degree of meta substitution. Different results are only obtained when "swamping" or more severe reaction conditions are used. In case of *tert*-butylation, however, ready ortho–para conversion is observed. In $AlCl_3$-catalyzed *tert*-butylations gen-

(18) Similar conditions were used in the isomerization of methylphenols by: Fury, L. F., Jr.; Pearson, D. E. *J. Org. Chem.* **1965**, *30*, 2301–2304.
(19) Allen, R. H.; Yats, L. D. *J. Am. Chem. Soc.* **1959**, *81*, 5289–5292. Allen, R. H.; Yats, L. D.; Erley, D. S. *Ibid.* **1960**, *82*, 4853–4858. Allen, R. H.; Alfrey, T., Jr.; Yats, L. D. *Ibid.* **1959**, *81*, 42–46. Olah, G. A.; Meyer, M. W.; Overchuk, L. A. *J. Org. Chem.* **1964**, *29*, 2310–2312.

Table IV. $AlCl_3$-Catalyzed Isomerization of *tert*-Butylanisoles

time	solvent	temp, °C	% *tert*-butylanisoles ortho	meta	para
		Ortho			
5 s	nitromethane	25	100		
10 s			64		36.0
20 s			25		75.0
40 s			54		99.5
1 min					100
24 h				37	63
72 h				65	35
		Para			
0	neat	80			100
10 min				15	85
30 min				39	61
1 h				45	55
2 h				51	49
3 h				55	45
4 h				58	42
5 h				59	41
24 h				65	35
		Meta			
1 h	neat	80		96	4
2 h				90	10
3 h				87	13
4 h				86	14
5 h				81	19
24 h				77	23
72 h				68	32

Table V. $AlCl_3$-Catalyzed Isomerization of Ethylanisoles

temp, °C	time, h	solvent	% ethylanisole ortho	meta	para
		Ortho			
25	1	CH_3NO_2	100		
25	5	CH_3NO_2	75	2	23
25	16	CH_3NO_2	62	3	35
25	40	CH_3NO_2	33	4	63
25	110	CH_3NO_2	32	8	60
65	0	CH_3NO_2	100		
65	3	CH_3NO_2	25	7	68
65	6	CH_3NO_2	41	7	68
65	8	CH_3NO_2	42	7	51
65	16	CH_3NO_2	33	17	50
100	3	neat	22	46	33
		Meta			
25	50	CH_3NO_2		100	
65	20	CH_3NO_2		100	
100	3	neat		64	36
25	1	CH_3NO_2			100
		Para			
25	1	neat			100
25	3	neat	10	1	89
25	5	neat	23	3	74
25	24	neat	26	6	68
25	52	neat	27	7	66
25	72	neat	27	11	62
65	0	CH_3NO_2			100
65	1	CH_3NO_2	32	4	64
65	3	CH_3NO_2	32	5	63
65	4	CH_3NO_2	29	6	65
65	6	CH_3NO_2	29	6	65
65	8	CH_3NO_2	26	9	65
65	16	CH_3NO_2	23	9	68
100	3	neat	11	28	61
140	0.25	neat	14	3	83
	8	neat	39	44	22

erally high proportions of *p-tert*-butylanisole were obtained. When the reaction was carried out, however, with *tert*-butyl fluoride catalyzed by BF_3 with short reaction times, 43% ortho and 57% para substitution was observed. Similarly, alkylation with *tert*-butyl alcohol in 65g HPF_6 gave ~41% ortho and 59% para isomer

Table VI. $AlCl_3$-Catalyzed Isomerization of Isopropylanisoles

temp, °C	time, h	solvent	% isopropylanisoles ortho	meta	para
		Ortho			
60	1	CH_3NO_2	99	<0.1	0.5
60	3	CH_3NO_2	97	<0.1	3
60	5	CH_3NO_2	85	3	12
60	24	CH_3NO_2	82	5	13
80	0	neat	97		3
80	1	neat	90	1	
80	2	neat	82	6	12
80	4	neat	73	8	19
80	10	neat	66	10	24
		Meta			
60	24	CH_3NO_2	tr	99.0	tr
110	3	neat		80	20
110	5	neat		77	23
		Para			
60	1	CH_3NO_2	tr		100
60	3	CH_3NO_2	3	tr	96
60	8	CH_3NO_2	8	1	91
60	24	CH_3NO_2	8	2	90
80	48	neat	34	13	53

Table VII. $AlCl_3$-Catalyzed Isomerization of *o*-Benzylanisole

solvent	temp, °C	time, h	% ortho	% meta	% para
heptane	60	0	81	2	17
heptane	60	0.5	74	4	22
heptane	60	1	68	5	27
heptane	60	2	64	6	30
heptane	60	3	63	6	31
heptane	60	5	59	8	33
heptane	60	10	55	10	35
neat	100	1	52	10	38
neat	100	3	38	17	45

(see subsequent discussion). Following the time dependence of the BF_3-catalyzed *tert*-butylation of anisole with *tert*-butyl fluoride at 25 °C (Table III) shows the dramatic shift of the ortho isomer into the para. Meta isomer is observed only after prolonged reaction time (24 h). Some changes, although generally less spectacular, were observed in isopropylation and ethylation, in agreement with decreasing migratory aptitude going from *tert*-butyl to ethyl.

Whereas alkyltoluenes isomerize with ease, alkylphenols show drastically reduced ability for isomerization.[20] The possible acid-catalyzed isomerization of alkylanisoles was not yet studied probably because alkylanisoles also were expected to show decreased ability for isomerization. In order to obtain experimental

Whereas alkyltoluenes isomerize with ease, alkylphenols show drastically reduced ability for isomerization.[20] The possible acid-catalyzed isomerization of alkylanisoles was not yet studied probably because alkylanisoles also were expected to show decreased ability for isomerization. In order to obtain experimental data we have undertaken a study of their aluminum trichloride catalyzed isomerization. The results (vide infra) are shown in Tables IV–VII. Only *tert*-butylanisoles show ready isomerization with fast initial ortho–para conversion (indicative of intermolecular reaction) followed by slower para → meta isomerization.

Isopropylanisoles isomerize verly slowly. At 25 °C the reaction is negligible. At 60 °C in nitromethane solution or at 80 °C the neat isomers show ortho ⇌ para conversion which is followed by very slow and incomplete ortho ⇌ meta and para ⇌ meta isomerization. No equilibrium is reached and much decomposition is observed. The results are thus only qualitative indication of the trend of isomerization. Benzylanisoles show somewhat similar behavior to isopropylanisoles. In case of *o*-benzylanisole, ortho ⇌ para conversion again predominates over slower ortho ⇌ meta and para ⇌ meta isomerization. Ethylanisoles show similar

(20) Buraev, V. I.; Isaev, I. S.; Koptyung, V. A. *J. Org. Chem. USSR (Engl. Transl.)* **1979**, *15*, 697–703; *Zh. Org. Khim.* **1979**, *15*, 782–789.

Table VIII. $TiCl_4$-Catalyzed Benzylation of Anisole and Toluene with Benzyl Chlorides

	anisole				toluene[14a]			
	k_A/k_B	% ortho	% meta	% para	k_T/k_B	% ortho	% meta	% para
$4\text{-}CH_3OC_6H_4CH_2Cl$	15542	30		70	97	28.5	1.5	70
$3,4\text{-}(CH_3)_2C_6H_3CH_2Cl$	260	32		68	35	29	2	69
$4\text{-}CH_3C_6H_4CH_2Cl$	148	38		62	29	31	2	67
$4\text{-}ClC_6H_4CH_2Cl$	16	42		58	7	40	4	56
$C_6H_5CH_2Cl$	14	47	<0.3	53	6	41	4	55
$3\text{-}CF_3C_6H_4CH_2Cl$	11	49	<0.5	51	5	49	4	47
$4\text{-}NO_2C_6H_4CH_2Cl$	7	54	<0.5	46	3	59	5	36[14b]

behavior, but the isomerizations are even slower. Large excess (up to 5-fold) of aluminum trichloride causes limited isomerization, again showing ortho ⇌ para interconversion followed by even slower conversion giving meta. Again no apparent equilibrium is reached, and extensive decomposition with eventual solidification of the reaction mixtures takes place. Methylanisoles show no detectable isomerization even when treated neat with large excess of aluminum chloride at reflux temperatures resulting eventually in extensive decomposition.

All results of studied and attempted isomerizations of alkylanisoles indicate that, in sharp contrast to the ready isomerization of alkyltoluenes, they isomerize much slower, if at all, and predominantly by intermolecular processes (as indicated by observed initial ortho ⇌ para conversions). The complete lack of isomerization of methylanisoles further emphasizes this point, as the methyl group has extremely poor intermolecular transfer ability. The high barrier for intramolecular, 1,2-alkyl, or hydrogen shifts in the alkylation intermediates (identical with those needed in the isomerizations of alkylanisoles) is also in accord with these findings.

In our present alkylation study no systematic effort was made to compare quantitatively the overall reactivity of anisole with that of benzene or toluene by competitive rate determinations. Fast substitutions can be affected by mixing difficulties, although alkylations of toluene seem not to be.[21] DeHaan et al.[22] raised justified questions about the need to establish truly homogeneous reaction conditions in any kinetic studies of Friedel–Crafts alkylations which can readily be affected by the presence of even trace amount of moisture or other impurities. The question of homogenity is less of a problem, however, in the case of anisole than toluene. Taking into account the above mentioned difficulties and emphasizing the qualitative nature of the data, we compared the reactivities in the $AlCl_3$-catalyzed competitive alkylation of 10-fold excess of equimolar anisole and benzene. The results indicate generally low substrate selectivity. $k_{anisol}/k_{benzene}$ was found to be about 7 in isopropylation, 18 in case of benzylation, and 130 in *tert*-butylation (with 2% or less meta isomer formed in all reactions). In contrast some highly selective reactions of anisole show k_A/k_B rate ratios as hish as 10^9.[7]

In the case of the titanium tetrachloride catalyzed benzylation of anisole and benzene with substituted benzyl chlorides, we undertook a more detailed comparison of their relative reactivities, as well as the related positional selectivity (isomer distributions) as a consequence of the nature of electron-withdrawing or -donating substituents in the benzyl chlorides. The reaction conditions were similar to those used previously in our related studies of the alkylation of toluene,[14] reacting 10-fold excess of equimolar anisole and benzene with the substituted benzyl chloride at 25 °C. We followed the change of the regioselectivity (isomer distribution) using substituted benzyl chlorides containing from strongly electron-donating (*p*-methoxy, 3,4-dimethyl, *p*-methyl) to electron-withdrawing (3-CF_3, 4-nitro) substituents. Data are summarized in Table VIII together (for comparison) with those of our previous study of the related benzylations of toluene. The similarities are quite striking. The $k_{anisole}/k_{benzene}$ rate ratio significantly increases with the increasing electron-releasing ability of the substituents. At the same time the ortho/para isomer ratio rapidly decreases but no meta substitution is observed (<0.5%). The opposite trend is observed with electron-releasing sbustituents. The increasingly more electrophilic benzylating agents show lower substrate selectivity and higher ortho–para rate ratios. Significantly, however, even the lowest substrate selectivities are not accompanied by increase in meta substitution. The only explanation we can offer, as suggested before[23] and also concluded by Stang and Anderson,[11] is that substrate and positional selectivities in reactions with reactive electrophiles are not determined in the same reaction step. They must be determined in separate steps, involving distinctly different intermediates. The nature of the methoxyarenium ion intermediates of the second step (σ-complexes) is well established by the direct observation of related ions under stable ion conditions. The nature of the interaction in the first step is still debated. We originally suggested π-complex-type interaction,[24] whereas Schofield et al.[25] indicated encounter complexes for related nitrations. These differ, however, only concerning the nature of bonding interaction, and both clearly necessitate a distinctly separate step. Kochi's recent studies strongly indicate initial charge transfer in some aromatic electrophilic substitutions.[26] Regardless of the exact nature of the first reaction intermediate, substrate and positional selectivity must be determined in two distinctly separate steps.

In conclusion the high degree of meta substitution reported in some "low" selectivity alkylations of toluene[4] is generally not observed in alkylations of anisole. It is a consequence of not kinetically but thermodynamically controlled processes, i.e., intra- as well as intermolecular isomerizations. We also need to differentiate isomerizations of already formed alkylation products from isomerization occurring during alkylation within the arenium ion intermediates prior to their desprotonation to products. These effects are less significant in the case of alkylation of anisole, although more severe "swamping" catalyst conditions can affect isomer distributions for similar reasons. Anisole, not unlike toluene, is ortho–para directing even in reactions with the most highly reactive reagents. No simple selectivity–reactivity relationship is apparent in the studied alkylations as was the case in previously studied nitrations and other substitutions[23a] as substrate and positional selectivities are determined in separate steps. Rather than being "anomalous"[27] our data after nearly 3 decades of considerable confusion restore the long recognized ortho–para directing effect of electron-donating substituents such as methyl and methoxy to their original status in electrophilic aromatic substitutions.

The Hammet $\rho\sigma$ relationship is well adaptable to electrophilic aromatic substitutions, as shown by Brown in his Selectivity Relationship[3] using σ^+ constants. For more accurate treatment multiparameter substituent constants are preferred, as used for example by Yukawa and Tsuno.[28] It is necessary, however, to

(21) Olah, G. A.; Overchuk, N. A. *J. Am. Chem. Soc.* **1965**, *87*, 5786–5788.
(22) DeHaan, F. P.; Miller, W. D.; Pace, S. A.; Pilmer, S. L.; Sollenberger, M. J.; Wolf, D. S. *J. Am. Chem. Soc.* **1978**, *100*, 5944–5948.
(23) For summaries see, for example: (a) Olah, G. A. *Acc. Chem. Res.* **1971**, *4*, 240–248. (b) "Friedel–Crafts Chemistry", Wiley-Interscience: New York, 1973; pp. 500-518 and references given therein.
(24) Olah, G. A.; Kuhn, S. J.; Flood, S. H. *J. Am. Chem. Soc.* **1961**, *83*, 4571–4580 and subsequent publications in this series.
(25) Schofield, K. "Aromatic Nitration"; Cambridge Univ. Press: 1980; pp 44-53 and references therein.
(26) Fukuzumi, S.; Kochi, J. K. *J. Am. Chem. Soc.* **1981**, *103*, 7240–7252; **1982**, *104*, 7599–7609.
(27) Santiago, C.; Houk, K. N.; Perrin, C. L. *J. Am. Chem. Soc.* **1979**, *101*, 1337–1340.
(28) Yukawa, Y.; Tsumo, Y. *Bull. Soc. Chem. Jap.* **1959**, *32*, 971.

emphasize that data used must be obtained under kinetic conditions free of thermodynamic contributions (isomerization) to avoid obvious misunderstanding of directing effects and selectivities.

Experimental Section

Alkyl halides, anisole, methylanisoles, *p-tert*-butylanisole, and alkylphenoles were commercially available in at least 98% purity. Other isomeric alkylanisoles were prepared by methylation of the corresponding potassium alkylphenolates. Anhydrous metal halides were of commercially available highest purity, purified by methods reported in earlier publications of this series. 65% aqueous HPF_6 was obtained from the Ozark-Mahoning Co.

Nitromethane was purified, as reported in our previous work[30a] based on a procedure of Winstein and Smith, representing an improvement of that of Smith and Leffer[30b] and of Thompson, Coleman, and Helm.[30c]

Efficient drybox techniques were used in handling reagents and preparing solutions. All reactions were carried out by usual protection from mositure and using well-dried apparatus. There is, however, no claim made for special efforts to achieve absolutely anhydrous conditions.

General Procedure of Alkylation of Anisole with Alkyl Halides. Anisole (10.8 g, 0.1 mol) and 2.7 g of $AlCl_3$ or 1.4 g of BF_3 (0.02 mol) were dissolved in 20 mL of nitromethane. While the solution was kept at 25 °C with good stirring, 0902 mol of alkyl halide dissolved in 10 mL of nitromethane was added. The reaction mixture was reacted at the indicated temperatures and times. It was thereafter quenched with ice water and the organic layer separated, extracted with ether, washed, dried and analyzed by gas liquid chromatograph.

Boron trifluoride catalyzed alkylations with alkyl fluorides were also carried out in neat anisole (0.25 mol).

Reactions with short reaction times were studied in the previously described flow-quenched apparatus.[29]

Alkylation of Anisole with Alcohols. To 10.8 g (0.1 mol) of anisole was added at 25 °C a solution of 0.02 mol of the corresponding alcohol dissolved in 20 mL of aqueous 65% HPF_6. The reaction mixture was stirred for the time indicated and subsequently worked up and analyzed as before.

Alkylation of Toluene. $AlCl^3$- and BF_3-catalyzed alkylation of toluene with alkyl halides in nitromethane or SO_2ClF solution were carried out as described.[14] Alkylation with alcohols with 65% HPF_6 was carried out as in the case of anisole.

Isomerization of alkylanisoles was carried out at the indicated temperatures by stirring a 10% nitromethane solution of the corresponding pure isomer with $AlCl_3$ (see Tables IV–VI) in a mole ratio of 1:1.1. When isomerizing neat alkylanisoles generally a 3:1 ratio was used, excess aromatics serving also as solvent. After usual workup isomeric compositions were analyzed by GLC.

Competitive Benzylation of Anisole and Benzene with Substituted Benzyl Chlorides. To an equimolar mixture of benzene (0.1 mol) and anisole (0.1 mol) was added 0.02 mol of titanium tetrachloride. To the resulting solution was dropwise added at 25 °C in a constant temperature bath with good stirring 0.02 mol of the corresponding substituted (or parent) benzyl chloride, and this mixture reacted for 15 min. The reaction mixture was then poured on ice water, extracted with ether, dried over Na_2SO_4, and analyzed by gas–liquid chromatography.

In the case of methyl and methoxy substituted benzyl chlorides the benzene/anisole mole ratio was raised to 5:1 and 25:1, respectively.

Preparation of 3,5-Dideuteriotoluene and -anisole. 3,5-Dibromotoluene or -anisole, respectively, were converted to their bis Grignard reagents and subsequently into the corresponding 3,5-dideuterio compounds by standard treatment with acidified D_2O.

Preparation of 2,4,6-Trideuteriotoluene and -anisole. *m*-Toluidine or anisidine was converted into its deuterium chloride salts and then reacted with excess 99.8% D_2O at 100 °C for 24 h. The 2,4,6-trideuterated salts were subsequently deaminated via diazotization with $NaNO_2$–HCl–Na_2SnO_2. 2,4,6-Trideuteriotoluene and -anisole, respectively, were isolated by standard procedures. Isotropic purity of products, as determined by GC-MS and ^1H and D^2 NMR, was 96%.

Methylation of 3,5-Dideuteriotoluene and -anisole and 2,4,6-Trideuteriotoluene and -anisole. To a solution of 0.005 M of $AlCl_3$ in 5 mL of nitromethane was added 0.025 M of the corresponding deuteriated toluene or anisole. While vigorously stirring 0.005 M methyl iodide, 5 mL of nitromethane was added keeping the reaction temperature at 20 °C. After 15 min of reaction time the mixture was quenched with ice water, washed with 5% sodium hydroxide solution, extracted with ether, dried, and analyzed by GC-MS using a packed column (Poropak Q) allowing analysis of the combined xylenes, but not individual isomers. Retained deuterium content was calculated on the basis of isomer distributions established from analytical GC analyses with capillary columns, which, however, were not adaptable to our GC-MS instrumentation.

Analysis. GLC analyses were carried out on a Varian Associates Model 3700 gas–liquid chromatograph, using a 50-m glass column coated with OV101, oven temperature from 130–180 °C, pressure 30 psi, and an FID detector. Peak areas were obtained by the use of a Varian CDS III data system.

GC-MS analyses were carried out using a Hewlett-Packard Model 5985A GC-MS spectrometer.

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Registry No. CH_3F, 593-53-3; CH_3Cl, 74-87-3; CH_3Br, 74-83-9; CH_3I, 74-88-4; C_2H_5F, 353-36-6; C_2H_5Cl, 75-00-3; C_2H_5Br, 74-96-4; C_2H_5I, 75-03-6; *i*-C_3H_7F, 420-26-8; *i*-C_3H_7Cl, 75-29-6; *i*-C_3H_7Br, 75-26-3; *t*-C_4H_9F, 353-61-7; *t*-C_4H_9Cl, 507-20-0; *t*-C_4H_9Br, 507-19-7; $C_6H_5CH_2F$, 350-50-5; $C_6H_5CH_2Cl$, 100-44-7; BF_3, 7637-07-2; $AlCl_3$, 7446-70-0; 4-$CH_3OC_6H_4CH_2Cl$, 824-94-2; 3,4-$(CH_3)_2C_6H_3CH_2Cl$, 102-46-5; 4-$CH_3C_6H_4CH_2Cl$, 104-82-5; 4-$ClC_6H_4CH_2Cl$, 104-83-6; 3-$CF_3C_6H_4CH_2Cl$, 705-29-3; 4-$NO_2C_6H_4CH_2Cl$, 100-14-1; anisole, 100-66-3; toluene, 108-88-3; methyl alcohol, 67-56-1; ethyl alcohol, 64-17-5; isopropyl alcohol, 67-63-0; *tert*-butyl alcohol, 75-65-0; benzyl alcohol, 100-51-6; *o-tert*-butylanisole, 2944-48-1; *p-tert*-butylanisole, 5396-38-3; *m-tert*-butylanisole, 33733-83-4; *o*-ethylanisole, 14804-32-1; *m*-ethylanisole, 10568-38-4; *p*-ethylanisole, 1515-95-3; *o*-isopropylanisole, 2944-47-0; *m*-isopropylanisole, 6380-20-7; *p*-isopropylanisole, 4132-48-3; *o*-benzylanisole, 883-90-9; 3,5-dideuteriotoluene, 16954-38-4; 3,5-dideuterioanisole, 55415-90-2; 2,4,6-trideuteriotoluene, 513122-37-7; 2,4,6-trideuterioanisole, 2567-25-1; HPF_6, 16940-81-1.

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