Electrophilic Reactions at Single Bonds. XIV.[1] Anhydrous Fluoroantimonic Acid Catalyzed Alkylation of Benzene with Alkanes and Alkane–Alkene and Alkane–Alkylbenzene Mixtures

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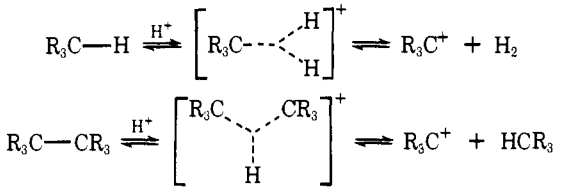
Abstract: Benzene was alkylated with C_1–C_5 alkanes in the presence of anhydrous fluoroantimonic acid (HF–SbF_5), showing the ability to ionize alkanes to alkylcarbenium ions even in the presence of benzene. The reactions are accompanied by acid-catalyzed side reactions, such as isomerization and disproportionation. When alkenes are added to the reaction mixture, alkylation products show increased alkylation by the alkanes, as well as competing alkylation by the alkenes, indicating that rapid hydrogen transfer also takes place between alkylcarbenium ions and alkanes in the presence of benzene. When *tert*-alkylbenzenes were reacted with benzene and isoalkanes under the same conditions, transalkylation as well alkylation by the alkanes is observed, further indicating the suggested reaction mechanism.

We have reported our observations relating to the protolytic behavior of alkanes with superacids.[2] Tertiary, secondary, and even primary C–H, as well as C–C bonds, were shown to undergo protolysis, in which the bound electron pairs of the σ bonds act as electron donors and lead to the formation of two-electron, three-center bonded carbonium ion transition states. Carbonium ion formation is followed by cleavage of the three-center bond to give the related carbenium ions and either hydrogen or a lower homolog alkane as cleavage products.



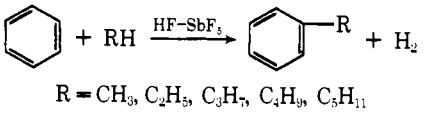
Since alkanes thus were shown capable of forming the related carbenium ions, we felt it to be of interest to extend these investigations and determine if alkanes could be utilized as alkylating agents in typical electrophilic aromatic alkylations.

Schmerling[3] has reported that isopentane and related isoalkanes when reacted with benzene in the presence of $AlCl_3$ and $CuCl_2$ gave alkylbenzenes. $AlCl_3$ or $CuCl_2$ alone does not catalyze the reaction. Schmerling suggested that the isoalkane is converted to a tertiary alkyl cation but did not discuss the way in which this process could occur, other than to suggest a hydrogen transfer reaction whereby $CuCl_2$ is reduced to CuCl and the alkyl cation is formed. Based on our experience with superacidic Friedel–Crafts catalyst systems, we felt that Schmerling's observations could be more explicitly explained as resulting from the protolysis of isopentane forming the corresponding *tert*-amyl cation (with protic impurities in the system acting as co-acids for the $AlCl_3$ initiated cleavage reaction). $CuCl_2$ then could act as an oxidant for the hydrogen formed in the protolysis. Its role thus would be that of a hydrogen scavenger being reduced in the process to CuCl. The HCl formed in this process would thus provide additional protic acid to complex with $AlCl_3$ and effect subsequent protolytic processes.

Because π-aromatic substrates, which normally undergo alkylation in typical electrophilic aromatic substitutions, are protonated much more readily than the σ-donor alkanes, it was considered appropriate to study primarly benzene as the aromatic substrate. In this case, since the protonation of benzene in superacidic media is known to be reversible,[3] the system would be expected at ambient temperatures to contain in equilibrium a sufficiently high concentration of unprotonated benzene as substrate for the alkylation process. Furthermore, benzene itself can not be affected by disproportionation.

Results and Discussion

In our studies, we investigated the anhydrous fluoroantimonic acid HF–SbF_5 1:1 v/v induced alkylation of benzene with alkanes, such as methane, ethane, propane, butane, isobutane, and isopentane (data obtained are summarized in Table I).



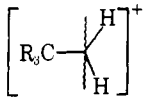
The amount of hydrogen formed in the reactions as detected by mass spectroscopy was always less than stoichiometric. In addition, it was determined by ^{19}F NMR spectroscopy that considerable reduction of SbF_5 (present in equilibrium in the fluoroantimonic acid) to SbF_3 had occurred during the course of the alkylation reactions. This is in accord with our previous findings that antimony pentafluoride can also serve as an easily reducible ("sacrificial") halide which contributes to the overall driving force of the protolytic reactions by scavenging the hydrogen formed.[2]

Moreover, it has previously been demonstrated that the reduction of SbF_5 by molecular H_2, particularly in solvent systems which coordinate with the strong Lewis acid, is relatively slow.[2] The efficient reduction of SbF_5 to SbF_3 in the presently studied systems, which contain a π-donor aromatic substrate, strongly reinforces our previous conclusion that reduction with molecular hydrogen gas may differ significantly in activity from nascent hydrogen generated in the protolysis of C–H bonds. In the protolysis of a C–H bond, a two-electron, three-center bonded carbonium ion is formed. When this three-center bond cleaves, the two hydrogen atoms have not yet reached their equilibrium ground state

Table I. Alkylation of Benzene with Alkanes

Alkane	Alkylated benzene
CH_4[a]	0.1% toluene
C_2H_6[b]	1.0% ethylbenzene 0.2% isopropylbenzene 0.1% toluene
C_3H_8[b]	1.4% isopropylbenzene 0.3% *n*-propylbenzene 0.1% ethylbenzene, traces of toluene and *tert*-butylbenzene as well of dipropylbenzenes
n-C_4H_{10}[b]	2.5–2.8% butylbenzenes (iso:sec = 1.8:1.0) approximately 0.5% dibutylbenzenes, traces of isopropylbenzene and ethylbenzene
i-C_4H_{10}[b]	2.5–2.8% butylbenzenes (tert:iso:sec = 1.0–1.9:1.0–1.8:1.0–1.2) approximately 0.5% dibutylbenzenes, traces of isopropylbenzene and ethylbenzene
i-C_5H_{12}[c]	9.6% pentylbenzenes (tert:sec:iso:neo:*n* = 16.6:13.0:7.0:4.2:1.0)

[a] At 80° for 3 hr. [b] At 25° for 24 hr. [c] At 25° for 6 hr.



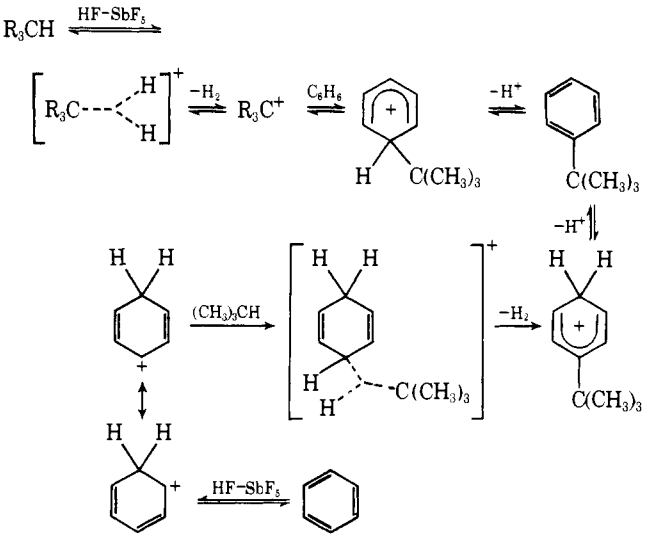
internuclear separation, and interaction with an active substrate (i.e., SbF_5) can begin prior to completion of nuclear relaxation. Hydrogen thus acts in a nascent, active form when formed via cleavage of a protonated alkane.

The alkylation reaction of benzene with C_1–C_5 alkanes gave product compositions indicating that, in the superacidic medium, protolytic cleavage of alkanes to lower molecular weight carbocationic fragments also took place, as well as expected isomerization (and disproportionation) processes of the alkylbenzenes subsequent to their formation.

The reactions with C_1–C_4 alkanes were carried out under pressure at 25° for 24 hr or, in the case of methane, at 80° for 3 hr. The reaction with isopentane was carried out under atmospheric pressure at 25°. The yields (based on benzene) for these Friedel-Crafts type alkylations using alkanes in high excess (to compete with the much more basic benzene for protonation) are expectedly low. Our studies were, however, directed primarily to establish the principle of this interesting alkylation, and no attempt was made to optimize yields (as for example was achieved in Schmerling's work using a sacrificial hydrogen scavenger although, as mentioned, SbF_5 itself can act as hydrogen scavenger being reduced to SbF_3). The formation of alkylbenzenes increases with increasing molecular weight of the alkanes used. Whereas only 0.1% toluene is formed from methane and benzene, about 10% pentylbenzenes are formed using isopentane. Alkylbenzenes with shorter or longer side chains than the starting alkanes (obtained by protolysis or alkylolysis of C–C bonds of the alkanes to give reactive carbenium ions of altered chain length) could be detected only in very small amounts (less than 0.2%). In the reaction of ethane and benzene, about 1.0% ethylbenzene, 0.2% isopropylbenzene, and 0.1% toluene were obtained. Propane and benzene gave 1.4% isopropylbenzene, 0.3% *n*-propylbenzene, 0.1% ethylbenzene, and only traces of toluene and *tert*-butylbenzene. Butane and 2-methylpropane gave 2.5–2.8% butylbenzenes (iso:sec = 1.8:1 and tert:iso:sec = 1.0–1.9:1.0–1.8:1.0–1.2, respectively), about 0.5% dibutylbenzenes, and traces of isopropylbenzene and ethylbenzene. Isopentane gave at 25° a 9.6% yield of pentylbenzenes (tert:sec:iso:neo: n = 16.6:13:7:4.2:1). The reason that the observed yields of alkylbenzenes generally do not exceed 10% is in all probability a consequence of secondary reactions of the initially formed alkylbenzenes in the superacid media and of the reaction between benzene and antimony pentafluoride. It was found in our studies, reported separately,[4] that benzene and alkylbenzenes are not only protonated or undergo isomerization and disproportionation reactions in fluoroantimonic acid (HF-SbF_5) but also react with SbF_5 (present in equilibrium) to give triaryldifluoro- and diaryltrifluorostibines, as well as polycondensed and polymeric materials. Furthermore, it was found in control experiments, such as of the reaction of propane and SbF_5 in the presence of HF, that SbF_5 was partially reduced by the active hydrogen formed in the protolytic cleavage of C–H bonds.[5]

Although the alkylation of benzene with alkanes in its studied form can not be considered a suitable preparative method for the preparation of alkylbenzenes, it is, however, significant from a mechanistic point of view as it shows that alkanes, indeed, are capable of effecting the alkylation of benzene, which has a π basicity far higher than the C–H and C–C single bond σ basicity of alkanes. Since in the reactions an excess of benzene relative to the amount of superacid was used, the benzenium ion ($C_6H_7^+$) formed by protonating benzene is rapidly proton transferring with excess benzene. However, the benzenium ion $C_6H_7^+$ which itself is a secondary carbenium ion could also react with the isoalkane. Using a large excess of alkene over benzene, this reaction could become competitive (Scheme I). The self-

Scheme I



condensation of benzene[6] and reductive dissociation reactions[7] in the superacid systems are also possible side reactions, but of lesser importance under the reaction conditions used (generally at 25°).

Comparison of these presently reported alkylations with our previous observation of protolysis of alkanes in superacids (neat or diluted with solvents of low nucleophilicity,[2] such as SO_2ClF) shows that, in the alkylation of benzene with straight chain alkanes, a difference in C–H vs. C–C reactivity becomes apparent. In protolysis of these neat alkanes, significant cleavage of C–C bonds occurs. We find, however, the C–C bonds of the same alkanes less accessible in the protolytic alkylation process. For example, in the case of ethane, we find a relative ratio of C–C:C–H cleavage of 9:1 in the absence of benzene and 1:10 in the presence of benzene (based on the toluene and ethylbenzene formed). This seems to be in good agreement with the assumption that in the latter case protonated benzene is reacting with ethane via an alkylation-cleavage mechanism which, for steric reasons, obviously takes place on the more accessible C–H bond. In other words, the benzenium ion as an alkylating agent shows much higher selectivity than found in protolytic reactions with fluoroantimonic acid (i.e., HF_2^+)

Table II. Anhydrous Fluoroantimonic Acid Catalyzed Alkylation of Benzene with Alkane–Alkene Mixtures

Alkane	Alkene	Temp, °C	Reaction time, min	Alkylated benzene: % *tert*-Butylbenzene	Alkylated benzene: % pentylbenzenes (2-methyl-3-phenylbutane, and some 2-methyl-2-phenylbutane)
i-C_5H_{12}	*i*-C_4H_8	5	5	26.6	20.5
			10	28.3	20.8
			15	28.8	21.2
			30	31	22.4
			60	30.1	22.0
i-C_4H_{10}	*i*-C_5H_{10}	5	5	51.5	10.9
			10	15.0	22.2
			15	15.1	21.8
			30	15.4	21.9
			60	14.2	22.5

which attacks preferentially the more basic C–C single bonds.

An alternate mechanism of alkylation of benzene with alkanes could be the direct oxidation (via electron transfer) of the alkane by antimony pentafluoride to the corresponding carbenium ion,[8] which then could alkylate the aromatic. Experimental data in accordance with the behavior of alkanes in fluoroantimonic acid obtained previously[5] do not support this possibility which is even less probable in the presence of benzene. The preceding studies showed that alkanes in the presence of the superacid catalyst fluoroantimonic acid are able to alkylate benzene. The ability of σ bonds to undergo protolytic ionization to form alkyl carbenium ions is thus shown even in benzene solution. The well-known ability of alkylcarbenium ions to hydrogen transfer from isoalkanes to form new carbenium ions, i.e., the Bartlett-Nenitzescu-Schmerling hydride transfer reaction[9]

$$R_3C^+ + HCR'_3 \rightleftharpoons R_3CH + C^+R'_3$$

was previously studied under stable ion conditions. We also have used superacidic catalysts in alkylation of alkenes with alkanes,[10] where the protonation of the much more reactive olefinic π bond takes first place, followed by hydrogen transfer from the excess alkane.

$$R_2C{=}CH_2 \overset{H^+}{\rightleftharpoons} R_2C^+CH_3 \overset{HCR'_3}{\rightleftharpoons} R_2CHCH_3 + C^+R'_3$$

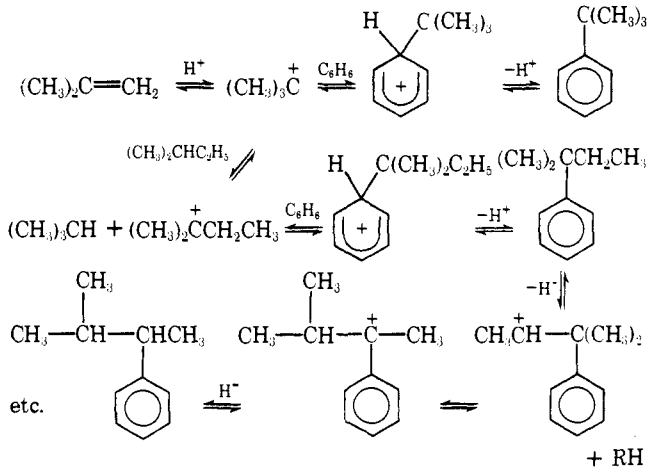
When a mixture of an isoalkane, such as isobutane or isopentane, was allowed to react in the presence of fluoroantimonic acid with benzene while introducing an alkene, such as 2-methylpropene or 2-methyl-butene-2, alkylation of benzene was observed not only by the alkene, but also the isoalkane. Table II summarizes the data obtained for the reaction of benzene with isoalkane–alkene mixtures.

It is of interest to note that, when reacting benzene with isobutane and 2-methyl-butene-2, initially substantially more *tert*-butylbenzene than pentylbenzenes (namely 2-methyl-3-phenylbutane and some 2-methyl-2-phenylbutane) are formed after 5 min reaction time at 5°; 51% *tert*-butylbenzene and 11% pentylbenzenes are found. The reaction mixture, however, readily equilibrates and, after 10 min, about 15% *tert*-butylbenzene and 27% pentylbenzenes are found, a ratio which does not change significantly further (1 hr at the same temperature). Thus, it seems that the hydrogen transfer reaction giving the *tert*-butyl cation is initially somewhat favored. The isopentane–isobutylene system shows no significant changes during the whole alkylation run.

It is also significant that, in the reactions, hydrogen formation is apparent in the systems showing that protolytic ionization also takes place.

The alkylation of benzene by both alkenes and isoalkanes shows that the alkylation of benzene by the alkylcarbenium ion formed by the protonation of the alkene is in competition with the hydrogen transfer reaction with the isoalkane present in the system. It also should be, of course, kept in mind that alkylation of benzene by the tertiary (or secondary) alkylcarbenium ions is a reversible reaction (see Scheme II). The reversibility of the alkylation of benzene

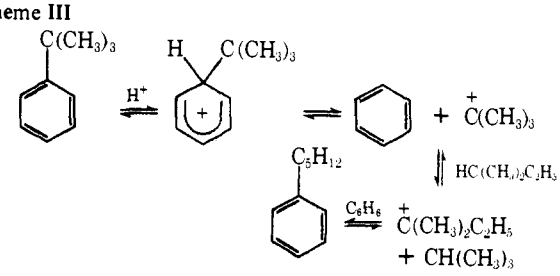
Scheme II



by the tertiary alkylcarbenium ions, indeed, seems to contribute to maintaining a suitable concentration of these carbocations allowing them to react also with the isoalkane present in the system, even if the rate of the latter reaction may be much slower. When propylene and isobutane were reacted with benzene in the presence of fluoroantimonic acid, only cumene was formed in the alkylation. The reaction of the isopropyl cation with benzene is too fast and the dealkylation of cumene formed too insignificant in this case.

To show the significance of dialkylation, we felt it of interest to study the possible alkylation of benzene with alkylbenzenes (such as *tert*-butylbenzenes and *tert*-isopentylbenzenes) and isoalkanes, such as isopentane and isobutane. In the reactions, indeed, alkylation of benzene was observed not only via transalkylation by the alkylbenzenes but also by the isoalkanes present. Data are summarized in Table III. The acid catalyst protonates the alkylbenzene forming the corresponding benzenium ion which eliminates tertiary alkylcarbenium ion to start the hydrogen transfer–realkylation sequence. Some disproportiation products (di-*tert*-butylbenzene and related pentylbenzenes) were also formed but, in benzene solution, they are only minor products (see Scheme III).

Scheme III



When the transalkylation reaction was carried out without benzene, more extensive transalkylation and disproportionation take place (up to 50–55%).

Table III. Anhydrous Fluoroantimonic Acid Catalyzed Alkylation of Benzene with Alkylbenzene–Alkane Mixtures

Alkylbenzene	Alkane	Temp, °C	Time	Alkylated benzene
tert-Butylbenzene	Isopentane	20	1 hr	18% pentylbenzenes (mostly 2-methyl-3-phenylbutane and some 2-methyl-2-phenylbutane)
2-Methyl-3-phenylbutane	Isobutane	20	30 min	7% *tert*-butylbenzene
			1 hr	8.5% *tert*-butylbenzene

Whereas our present studies were carried out, in order to be able to directly compare results of alkylation of benzene by alkanes, with alkane–alkene and tertiary alkylbenzene–alkane mixtures, with the superacidic fluoroantimonic acid as catalyst, the alkene promoted alkylations and transalkylations with alkanes can also be carried out using conventional Friedel–Crafts catalysts, such as aluminum chloride.

Experimental Section

Spectroscopic grade benzene (Mallinkrodt) was further purified by shaking with concentrated H_2SO_4, then with H_2O, dilute NaOH, and H_2O, followed by drying over 4X Linde molecular sieves and then fractionation from CaH_2. The benzene thus obtained was analyzed by gas–liquid chromatography and showed no detectable impurities. Ultra high purity methane (Matheson) was used which had a minimum purity of 99.95 mol %. Analysis by GLC showed no other detectable hydrocarbons. Ethane, propane, butane, and isobutane (Matheson) were all CP grade, i.e., >99% pure. Isopentane (Phillips) had a minimum purity of 99.5 mol %.

Gas–liquid chromatographic analyses were carried out on a Perkin-Elmer Model 226 chromatograph, equipped with 15.0 × 0.01 stainless steel open tubular Golay column, stationery phase: *m*-bis(*m*-phenoxyphenoxy)benzene + apiezon L, 100°, 30 psi helium pressure. Isolated products (Varian Aerograph Autoprep) were also identified by ^1H NMR spectroscopy (Varian A-56/60) and when needed by mass spectrometry.

Alkylation of Benzene with Alkanes. Reactions with C_1–C_4 alkanes as alkylating agents were carried out in 200-ml monel bombs, with a molar ratio of alkane:benzene:HF-SbF_5 of 20:2:1, at 25°, in case of methane, at 80°. The reaction with isopentane was carried out at atmospheric pressure at 25°. The reaction times are shown in Table I. After depressurizing, reaction mixtures were quenched with ice–water, washed with Na_2CO_3 solution, and dried over $MgSO_4$. The products were then analyzed by gas–liquid chromatography and mass spectrometry.

Alkylation of Benzene with Alkane–Alkene Mixtures. Benzene (0.2 mol) and 0.1 mol of isoalkane (isobutane or isopentane) were cooled to +5°. Anhydrous fluoroantimonic acid (0.01 mol) was added to the well-stirred mixture and then 0.1 mol of alkene (2-methylpropene or 2-methyl-butene-2) introduced while continuing the stirring. Samples were taken periodically, quenched, washed, and analyzed by gas–liquid chromatography.

Alkylation of Benzene with Alkylbenzene–Alkane Mixtures. The corresponding alkylbenzene (0.1 mol), 0.1 mol of benzene, and 0.2 mol of the isoalkane were mixed and cooled to −20°, 0.01 mol of anhydrous fluoroantimonic acid was added, and the stirred mixture was allowed to warm up to 20°, where it was stirred for 1 hr. Samples taken were quenched, neutralized, washed, and analyzed by gas–liquid chromatography.

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References and Notes

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A Chemical Model for the Cyclization Step in the Biosynthesis of L-*myo*-Inositol 1-Phosphate

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Abstract: Base treatment of D-*xylo*-hexos-5-ulose 6-phosphate (**2**) yielded, as the predominant products, two cyclose phosphates which, after reduction with sodium borohydride, gave a mixture of the cyclitol monophosphates L-*myo*-inositol 1-phosphate (**4**) and *epi*-inositol 3-phosphate (**8**). Compounds **4** and **8** were characterized as their trimethylsilyl derivatives by GC–MS. The parent cyclitols, after dephosphorylation of **4** and **8**, were identified in the same manner. The conversion of **2** to one of the cyclose phosphates, D-2,4,6/3,5-pentahydroxycyclohexanone 2-phosphate (**3**), represents a chemical model for the cyclization step in the biosynthesis of L-*myo*-inositol 1-phosphate (**4**).

The NAD-dependent conversion of D-glucose 6-phosphate (**1**) to L-*myo*-inositol 1-phosphate (**4**) has been observed in preparations from higher and lower plants as well as mammals.[1] In each system, L-*myo*-inositol 1-phosphate is considered to result from the cyclization of a δ-dicarbonyl monosaccharide derivative, D-*xylo*-hexos-5-ulose 6-phos-