252. Site Selectivity in the Gas-Phase Ionic Phenylation of Alcohols and Alkyl Chlorides

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Dedicated to Prof. Dr. *Tino Gäuman* on the occasion of his 60th birthday

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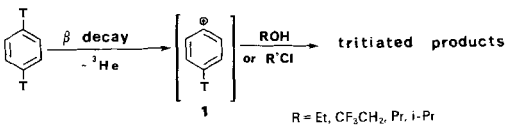
Free, unsolvated phenylium ions formed by the spontaneous β decay of [1,4-$^3H_2$]benzene have been allowed to react with gaseous alcohols (ROH: R = Et, CF_3CH_2, Pr, or *i*-Pr; partial pressure: 3–56 Torr) and alkyl chlorides (R'Cl: R' = Pr, *i*-Pr, or Bu; partial pressure: 20–450 Torr), in the presence of a thermal radical scavenger (O_2: 4 Torr). Phenylium ion confirms its considerable site selectivity, demonstrated by the distinct preference toward the *n*-centre of the substrate (46–100%), although significant insertion into the alkyl group of alcohols is observed as well. Phenylium ion displays significant positional selectivity even between different *n*-type sites in a bidentate molecule such as CF_3CH_2OH. An affinity F < O < Cl trend is observed, which indicates a direct relationship between the polarizability of the *n*-centre of the molecule and its orienting properties toward phenylium ion. The stability features of the ionic intermediates from addition of phenylium ion with ROH or R'Cl have been evaluated, as well as their fragmentation and isomerization mechanisms. The behaviour of phenylium ion toward the selected substrates in the gas phase is discussed and compared with previous mechanistic hypotheses from related nuclear-decay studies.

Introduction. – Radiochemical techniques, currently available for the production of unsolvated cations of defined structure in both gaseous and condensed phases [1] proved very useful in the understanding of the intrinsic reactivity properties of highly reactive species, such as the phenylium $C_6H_5^+$ ion **1** *(Eqn. 1)*, involved as elusive transient in solvolytic reactions [2]. Essential information on the tendency of **1** to undergo unimolecular automerization [3] as well as on its reactivity and selectivity toward representative *n*- [3] [4] and σ-type acceptors [5], has been obtained by this approach. Gaseous phenylium ion **1** displayed an exceedingly high reactivity toward both classes of nucleophiles, which contrasts with a remarkable site selectivity. Thus, for instance, a distinct preference of **1** for the C–H bonds of an hydrocarbon molecule has been observed [5], which well compares with a marked affinity for the lone-pair electrons when a *n*-centre is present in the substrate molecule [4].

We now report the extension of the study to the gas-phase ionic phenylation of aliphatic alcohols ROH, with R = Et, Pr, *i*-Pr, and CF_3CH_2, and alkyl chlorides R'Cl,



(1)

with R = Pr, *i*-Pr, Bu. The investigation has been primarily undertaken to bring to a sharper focus the site selectivity of **1** toward substrates containing both *n*- and σ-type reaction centres, where the ratio of the σ- and *n*-type sites is progressively increased. In one case (CF_3CH_2OH), we expect to gain a direct insight into the site selectivity of phenylium ion between two different *n*-type centres within the same molecule (F- and O-atoms). Additional interest is attached to CF_3CH_2OH, since this alcohol is often used as solvent of low nucleophilicity in the solvolytic formation of arylium ions by heterolytic dediazoniation of arenediazonium salts [6].

Experimental. – *Materials.* 1,4-Ditritiobenzene, used as a precursor of the phenylium cations, was synthesized according [3]. Aliphatic alcohols ROH (R = Et, Pr, *i*-Pr, CF_3CH_2), alkyl chlorides R'Cl (R' = Pr, *i*-Pr, Bu), and the aromatic compounds employed either as substrates or as standards in the GC analyses were research-grade chemicals from *Merck AG* and were used without further purification. Other aromatic compounds not commercially available, such as isomeric phenyl propyl ethers [4a], phenyl vinyl ether [4b], trifluoroethyl phenyl ether [4c], and trifluoromethyl phenyl ketone [4d] were prepared according to established synthetic procedures.

Procedure. The decay samples were prepared by introducing sealed glass capillaries containing *ca.* 1 mCi of tritiated benzene (specific activity: 90 mCi $mmol^{-1}$) into 300-ml *Pyrex* ampoules. The ampoules were then connected to a vacuum line and thoroughly degassed. The org. substrate (ROH or R'Cl) was then introduced, together with minor amounts (at *ca.* 4 Torr) of O_2, which was used as a scavenger of the radical species that could be formed by the passage of the β-particle from the nuclear decay of the tritiated benzene through the gaseous mixture. The ampoules were finally sealed and the capillary tube containing the benzene broken with a glass hammer.

The decay mixtures were then stored for 12–14 months in the dark at r.t. The vessels were then opened under airtight conditions and their contents analyzed by radio GLC, using a *Carlo Erba Fractovap 4200* gas chromatograph equipped with a high-sensitivity hot-wire detector (HWD), coupled in series with a *Berthold* proportional counter tube, kept at 180°. The identity of the tritiated products was established by coincidence of the radiochemical peaks with the HWD signals from authentic reference compounds on the following columns: *i*) 3.5 m bentone 3,4-diisodecylphthalate 5%:5% on *Chromosorb W-AW*, operated at temp. ranging from 50 to 130°; *ii*) 8 m dimethylsulfolane 25% on *Chromosorb W*, operated at 90°; *iii*) 6 m silicone oil *E301* 25% on *Chromosorb W*, operated at 130°; *iv*) 5 m silicone grease *QF1* 10% on *Chromosorb W*, operated at 170°. Over 40 reference compounds were tested, including those described in the previous section, substituted arenes (*e.g.* propyl- and propenylbenzenes), phenyl-substituted alcohols and alkyl chlorides (*e.g.* phenylethanol), carbonyl compounds (*e.g.* acetophenone), phenols (*e.g.* 2-isopropylphenols), and their ether derivatives (*e.g.* methylanisole).

Results. – *Tables 1–4* show the relative yield of tritiated products recovered from the gas-phase attack of the 1,4-ditritiobenzene decay ions on ROH (R = Et, Pr, *i*-Pr, and CF_3CH_2). Reaction conditions were chosen to span a factor of *ca.* 10 for the alcohol partial pressure in the CH_3CH_2OH and CF_3CH_2OH systems, whereas in the PrOH experiments the lower volatility of the alcoholic substrates sets an upper limit at *ca.* 14 Torr. The tritiated product distribution from ionic phenylation of alkyl chlorides R'Cl

Table 1. *Tritiated-Product Distribution from Gas-Phase Attack of Phenylium Ions on EtOH*

EtOH Pressure [Torr][a])	Relative yields of products [%][b])			
	PhOEt	PhOH	PhEt	PhCOMe
6	30	16	20	34
8	38	12	13	37
44	51	4	12	33
56	69	2	n.d.[c])	29

[a]) All gaseous mixtures contained O_2 (4 Torr) and tritiated benzene (*ca.* 1 mCi).

[b]) Expressed as a percentage of the total activity of the recovered products; standard deviation of data, *ca.* 10%.

[c]) Below detection limit: *ca.* 1%.

Table 2. *Tritiated-Product Distribution from Gas-Phase Attack of Phenylium Ions on CF_3CH_2OH*

CF_3CH_2OH Pressure [Torr][a])	Relative yields of products [%][b])			
	$PhOCH_2CF_3$	PhOH	PhF	$PhCOCF_3$
4	44	5	19	32
8	46	5	28	21
33	60	3	19	18
42	68	2	20	10

[a]) See *Footnote a, Table 1.* [b]) See *Footnote b, Table 1.*

Table 3. *Tritiated-Product Distribution from Gas-Phase Attack of Phenylium Ions on PrOH*

PrOH Pressure [Torr][a])	Relative yields of products [%][b])					
	PhOPr	PhOH	PhOEt	$PhOCH{=}CH_2$	PhEt	PhCOEt
4	12	27	12	24	14	11
10	19	19	12	22	18	10
14	36	18	8	16	14	8

[a]) See *Footnote a, Table 1.* [b]) See *Footnote b, Table 1.*

Table 4. *Tritiated-Product Distribution from Gas-Phase Attack of Phenylium Ions on* i-*PrOH*

i-PrOH Pressure [Torr][a])	Relative yields of products [%][b])					
	PhO(*i*-Pr)	PhOH	PhOEt	$PhOCH{=}CH_2$	PhEt	$PhCH_2COMe$
3	7	31	18	17	13	14
10	26	29	12	15	14	4
14	33	27	9	20	11	n.d.[c])

[a]) See *Footnote a, Table 1.* [b]) See *Footnote b, Table 1.* [c]) See *Footnote c, Table 1.*

Table 5. *Tritiated-Product Distribution from Gas-Phase Attack of Phenylium Ions on Alkyl Chlorides (R'Cl)*

R'	Pressure[a])	Relative yields of products[b])		
	[Torr]	PhCl	PhR'	Unknown
i-Pr	20	93	n.d.[c])	7
i-Pr	450	100	n.d.	n.d.
Pr	20	91	5	4
Pr	450	98	2	n.d.
Bu	20	91	4	5
Bu	80[d])	95	2	3

[a]) See *Footnote a, Table 1.* [b]) See *Footnote b, Table 1.* [c]) See *Footnote c, Table 1.* [d]) 4 Torr NH_3 added to the gaseous system.

(R' = *i*-Pr, Pr, Bu) is shown in *Table 5*. The absolute yields of the listed aromatic products, expressed as the ratio of their total activity to the activity originally contained in the decay-produced phenylium ion, were well reproducible, amounting to 40 ± 5% for the ROH systems and to 50 ± 5% for the R'Cl systems. Furthermore, the total activity of the crude reaction mixture, measured by liquid scintillation spectrometry, closely matched the combined activity of the individual products identified by GLC. This showed that high-boiling labeled products, *i.e.* polymers, are not formed in appreciable

yields. The activity balance must, therefore, be accounted for by some low-boiling fragmentation products and by the formation, *via* hydride-ion transfer from ROH or R'Cl to **1**, of monotritiated benzene, whose activity cannot be discriminated from that contained in the undecayed 1,4-ditritiobenzene. The identity of a few radioactive products is left undefined, since it could not be safely assessed by comparison with authentic standard compounds. However, according to their retention volumes on the selected GLC columns, these unknown products are most likely phenyl derivatives of the substrate, which underwent alkyl-chain skeletal isomerization and unimolecular fragmentation.

Analysis of *Tables 1–4* reveals that alkyl phenyl ethers are major products in all alcoholic systems investigated, whose combined yields range from 30 to 69% of the recovered tritiated products. Minor amounts of fluorobenzene (19–28%) are produced together with 2,2,2-trifluoroethyl phenyl ether in the CF_3CH_2OH systems *(Table 2)*. Formation of alkyl aryl ether in the ROH decay experiments is accompanied by variable amounts of phenol and of oxidation products, *i.e.* aromatic ketones, whose formation implies a complex reaction mechanism.

While phenetole and 2,2,2-trifluoroethyl phenyl ether represent the only ethers produced in EtOH *(Table 1)* and CF_3CH_2OH *(Table 2)*, respectively, formation of phenyl propyl ether in the corresponding propanol systems is flanked by the presence of variable amounts of PhOEt and $PhOCH{=}CH_2$, whose relative yields depend upon the total pressure of the system (*Tables 3* and *4*). In particular, the yields of PhOEt and $PhOCH{=}CH_2$ increase at low pressure, where instead formation of PhOPr appears depressed (*Tables 3* and *4*). A similar behaviour is observed with respect to the pressure dependence of the PhOH yield in all alcoholic systems. The R'Cl decay systems are instead invariably characterized by the predominant formation of tritiated chlorobenzene (relative yields: 91–100%) *(Table 5)*.

Discussion. – The nature and the properties of free phenylium ion **1** produced by nuclear decay in tritiated benzene *(Eqn. 1)* and used in the present study as the electrophilic reactant have been previously described in detail [3–5].

The present results confirm the remarkable affinity of **1** toward the *n*-centre of the substrate, as inferred from the relatively high yields of alkyl phenyl ethers (30–69%) and phenol (2–31%) from ROH *(Tables 1–4)* and of halogenobenzenes from CF_3CH_2OH (19–28%) and R'Cl (91–100%) (*Tables 2* and *5*). It is, therefore, suggested, in analogy with the conclusion reached in previous studies [3] [4], that the phenylation process occurring in the selected decay systems involves competitive attack of **1** on the *n*- and σ-centres of the substrate, to give the corresponding onium intermediate **2** in predominant yields *(Eqn. 2a)* and minor amounts of the arenium ion **3** *(Eqn. 2b)*, respectively, both excited by the exothermicity of their formation processes[1]).

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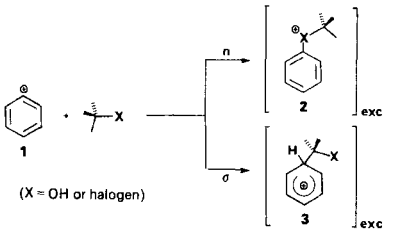
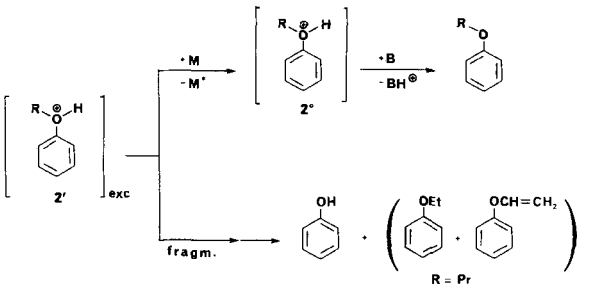
[1]) An enthalpy change ranging around -293 kJ mol^{-1} is estimated for the formation of oxonium ion **2** (X=OH) *(Eqn. 2a)* from the selected alcohols, using a value of $H_f^\circ = 1129$ kJ mol^{-1} for **1** (H.M. Rosenstock, J.T. Larkins, J.A. Walker, *Int. J. Mass Spectrom. Ion Phys.* **1973**, *11*, 309) and approximate values ranging between 782 and 865 kJ mol^{-1} for the proton affinities of the O centre of the alkyl phenyl ethers. Formation of halonium ions **2** (X=F or Cl) *(Eqn. 2a)* appears equally exothermic from rough calculations [3c]. The lack of reliable thermochemical data concerning the arenium ions **3** *(Eqn. 2b)* prevents even a rough estimate of their formation processes. However, since the insertion of **1** in a C–H bond of ethane and propane is computed to be *ca.* 263 kJ mol^{-1} exothermic [5a], it is likely that the corresponding insertion into a C–H bond of ROH and R'Cl to give **3** is almost equally exothermic.



(2a)

(2b)



(3a)

(3b)

In the case of ROH, collisional stabilization of the excited oxonium ions **2'** *(Eqn. 3)* followed by proton transfer to a gaseous base provides a direct route to PhOR. This process is efficiently contrasted by unimolecular fragmentation of the excited intermediate **2'**. Under the conditions prevailing in the present experiments, *i.e.* low pressures, absence of added bases, *etc.*, route 3a appears to be a rather slow process[2]), and, therefore, the large excitation energy of **2'** allows its extensive fragmentation to give eventually phenol in all systems, together with phenetole and phenyl vinyl ether in the propanol samples *(Eqn. 3b)*.

This view provides a plausible rationale for the opposite pressure dependence observed for the relative yields of PhOR and of the companion fragmentation products, *e.g.* PhOH *etc. (Tables 1–4)*. The relative extent of the unimolecular fragmentation channel of **2'** *(Eqn. 3b)* appears rather sensitive to the nature of the alkyl group of the ROH substrate, increasing in the order: R = CF_3CH_2 < Et < Pr < *i*-Pr. This behaviour finds a complete correspondence with previous gas-phase studies, on unimolecular fragmentation of alkyl phenyl oxonium ions [4] [7].

In contrast to the oxonium ions **2'**, the only route available to the halonium ions **2** from the attack of **1** on R'Cl or CF_3CH_2OH *(Eqn. 2a,* X = Cl or F) to collapse into isolable neutral derivatives, *i.e.* the corresponding halogenobenzenes, necessarily involves cleavage of their C_{sp^3}–X bond.

The relatively high yields of halogenobenzenes in R'Cl and CF_3CH_2OH systems and their limited sensitivity to the experimental conditions (*Tables 2* and *5*) suggest simple C_{sp^3}–X bond fission as the most favoured reaction path available to the excited halonium ions **2**, with respect to other conceivable processes. In the adduct between **1** and the

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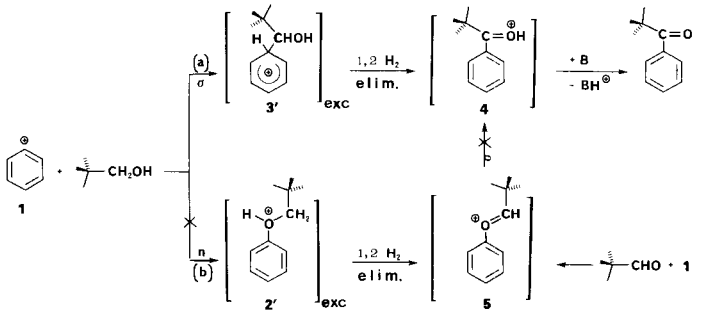
[2]) Proton transfer from ground-state oxonium ions **2°** to the parent alcohol ROH, *i.e.* the major component of the gaseous mixture, is a process several kcalories *per* mol endothermic. However, the process may occur, if excited oxonium ions are involved. Other gaseous bases available to the ground-state ions **2°** could be formed by self-radiolysis of the gaseous sample.

F-atom of CF_3CH_2OH, the C_{sp^3}–F cleavage may be further promoted by neighbouring OH-group participation [8].

Direct insertion of **1** in a σ bond of the selected substrates, followed by loss of an oxygenated or halogenated moiety from the ensuing excited adduct (*e.,g.* **3**, *Eqn. 2b*), accounts for the formation of alkylbenzenes in all systems investigated. Similarly, establishment of a C–C-bonding interaction and elimination of a H_2 molecule from the addition complex between **1** and ROH represent events necessary to the formation of ketones in the decay systems *(Tables 1–4)*. Here, however, the question immediately arises as to the priority of the two events in the ketone-formation mechanism. In other words, the purposes of the discussion require discrimination between a mechanism involving primary insertion of **1** in the α-C–H bond of the alcohol followed by 1,2-H_2 elimination (path *a*, *Eqn. 4*) and a mechanism involving primary attack of **1** on the O-atom of ROH to give excited **2′**, which then undergoes 1,2-H_2 elimination and Ph-group transfer from O to C-atom (path *b*, of *Eqn. 4*).



(4)

The latter mechanism appears unfavoured in the formation of aryl ketones in the decay systems on the grounds of independent evidence. In fact, when intermediate **5** is directly formed by addition of **1** on the O-atom of aliphatic aldehydes, it does not evolve to **4**, but rather it simply loses a proton to give the corresponding alkenyl phenyl ether [9]. It is, therefore, concluded that formation of alkyl phenyl ketones involves as the first step the direct insertion of **1** in the σ-C–H bond in α to the OH group of EtOH, CF_3CH_2OH, and PrOH. Similarly, direct insertion of **1** in the C_β–H bonds of *i*-PrOH followed by H_2 elimination accounts for the formation of benzyl methyl ketone in the *i*-PrOH samples. At any rate, a general aspect of path *a* of *Eqn. 4* is that fragmentation of the relevant excited intermediates **3′** is fast with respect to their quenching by proton transfer to a suitable acceptor, as shown by the lack of *C*-phenylated alcohols among the tritiated products from ROH.

Once the nature of the tritiated products recovered in the decay mixtures is clearly established, it is possible to link their distribution to the site selectivity of **1** on the selected substrates. However, even under such circumstances, deducing the site selectivity of **1** toward ROH and R′Cl from the relevant product distribution may be deceptive, since the latter can be affected by structural reorganization within the excited ionic precursors, which alters the initial orientation of attack. Nevertheless, if analysis is restricted to product distributions observed at high pressures and in the presence of added bases, *i.e.* under conditions minimizing secondary isomerization and fragmentation processes, it

Table 6. *Site Selectivity of Gaseous Phenylium Ion toward Some Alcohols and Alkyl Chlorides*

Substrate	Dipole moment, μ [Debye]	Site selectivity [%]	
		n-centre	σ-CH
MeOH	1.70	95 (O)[a])	5[a])
EtOH	1.69	71 (O)	29
CF_3CH_2OH	2.03	70 (O); 20 (F)	10
PrOH	1.68	78 (O)	22
i-PrOH	1.66	89 (O)	11
MeCl	1.87	90 (Cl)[b])	10[b])
PrCl	2.05	98 (Cl)	2
i-PrCl	2.17	100 (Cl)	–
BuCl	2.05	95 (Cl)	5

[a]) [3b]. [b]) [3c].

can be assumed that the relevant product compositions reflect satisfactorily the intrinsic orientation of the electrophile **1** toward the substrate *(Table 6)*.

On these grounds, the remarkable affinity of **1** toward the Cl-atom of the alkyl chloride results directly proportional to the dipole moment of the substrate and rather insensitive to the σ/n electrons ratio, increasing in the order: MeCl < PrCl ≈ BuCl < *i*-PrCl. In the case of the selected alcohols, instead, the hydrocarbon character of the substrate appears to predominate over its dipole moment in determining the positional selectivity of the gaseous electrophile. Indeed, extent of n-phenylation is observed to decrease in passing from MeOH (μ = 1.70D) to EtOH (μ = 1.69D), and PrOH (μ = 1.68D). However, an additional selectivity factor appears to be the number of C–H bonds in α to the OH group of the alcohol, as shown by the significant increase of n-phenylation observed for *i*-PrOH (89%; μ = 1.66D) with respect to PrOH (78%; μ = 1.68D).

Gaseous phenylium ion **1** is found to sharply discriminate even between different n-type centres within the same molecule such as the O- and F-atoms of CF_3CH_2OH. Taking into account statistical factors, a k_O/k_F ratio of *ca.* 10 can be calculated for the attack of **1** on the O and F sites of the substrate. From the above considerations, the site selectivity of **1** toward the n-centres of a gaseous aliphatic molecule follows a trend, *i.e.* F < O < Cl, which points to a direct correspondence between the polarizability of the heteroatom and its intrisic directive properties toward gaseous **1**.

In conclusion, the present investigation of the gas-phase reaction of phenylium ion with aliphatic alcohols and chlorides has not only extended our knowledge on the nature and the reactivity of the ionic reactant, but has also provided a more complete view of the intrinsic factors determining site selectivity in the intimate complex formed by the interaction of the electrophile with the substrate in the gas phase.

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