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Involvement of Dicationic Species as the Reactive Intermediates in Gattermann, Houben−Hoesch, and Friedel−Crafts Reactions of Nonactivated Benzenes

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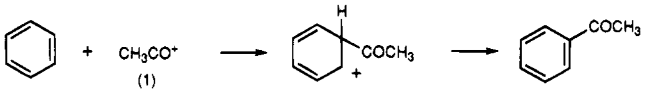
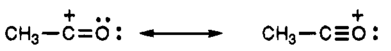
Abstract: The active electrophile involved in the Gattermann reaction of benzene with cyanide is *N,N*-diprotonated hydrogen cyanide, $HC^{+}{=}N^{+}H_2$. Similarly, Houben−Hoesch acylation by benzonitrile involves *N,N*-diprotonated nitrile as the active species. Participation of the second proton was demonstrated by kinetic measurement of the intramolecular cyclization of phenylpropionitrile. Acylation of benzene, toluene, and chlorobenzene by CH_3COSbF_6 or $C_6H_5COSbF_6$ depends strongly on the acidity of the media. The major active species are the protonated acyl cations formed in the highly acidic media. The acyl cation itself contributes only to a minor extent even in the acylation of benzene and toluene. Dications (superelectrophiles or protosolvated cations) are proposed to be the real electrophiles in these reactions of benzene and nonactivated benzenes.

Since the discovery of the aluminum trichloride-catalyzed alkylation and acylation of aromatic hydrocarbons in 1877 by Friedel and Crafts,[1] the reaction mechanism has been extensively studied by the discoverers themselves and by a number of ingenious chemists. The results were comprehensively summarized in a book, *Friedel-Crafts and Related Reactions*, in 1963.[2] Olah made a tremendous contribution to the chemistry, in particular, by employing superacids to stabilize various ions for study.[3] As a result, the alkylation of arenes is generally well-understood.[4] However, the acylation reactions, in particular, of benzene and deactivated arenes are less well-understood.

Acetylation of benzene is an example of electrophilic attack by an acyl cation on the arene, simply represented by the equation shown below. The acyl cation, represented by an acetyl cation (1), is a relatively weak electrophile because the ion is stabilized by resonance involving two structures represented by a carbenium ion (**1a**) and an oxonium ion (**1b**), with the latter being more important.[5]





$$CH_3{-}\overset{+}{C}{=}\ddot{O}: \longleftrightarrow CH_3{-}C{\equiv}\overset{+}{O}:$$

(1a) (1b)

Thus, it is curious that stable benzene reacts with a stable (nonreactive) species such as the acetyl cation. A similar situation arises in the Gattermann and Houben−Hoesch reactions,[6] where the protonated and Lewis acid-complexed nitriles should be stable. Our previous research on dications such as the iminium−benzenium dications,[7] *O,O*-diprotonated nitro olefins (*N,N*-dihydroxyiminium−carbenium dications),[8] and iminium− and oxonium−allyl dications,[9] all of which can react with benzene, suggested that benzene itself is attacked only by such activated electrophiles. Olah called similar species superelectrophiles.[10]

Friedel−Crafts type acylation reactions, under the original conditions, usually employ $AlCl_3$ and other Lewis acids. The Gattermann and Houben−Hoesch reactions also use Lewis acids or Lewis acid−Brönsted acid combinations. These media almost always contain HCl or other protonic acids or water, which makes the nature of the media complex, and probably highly acidic. The Friedel−Crafts acylation often requires a more than equivalent amount of catalyst.[11] The Gattermann and Houben−Hoesch reactions of benzene usually result in a low yield of the product. The difficulty of performing quantitative analysis of the reactions has been due, at least partially, to the uncertainty in the acidity of the reaction media. By employing superacids, which are stronger acids than sulfuric acid, we can now define the reaction medium in terms of its acidity (H_0). We usually use trifluoromethanesulfonic acid (TFSA) ($H_0 = -14.0 \pm 0.1$) and mixtures of TFSA−trifluoroacetic acid (TFA) ($H_0 = -8.0$ to -14.0).[12]

Analyses of the Houben−Hoesch and Gattermann reactions and of Friedel−Crafts acylation in TFSA-based media strongly

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(12) (a) Saito, S.; Saito, S.; Ohwada, T.; Shudo, K. *Chem. Pharm. Bull.* **1991**, *39* (10), 2718−2720. (b) Saito, S.; Sato, Y.; Ohwada, T.; Shudo, K. *J. Am. Chem. Soc.* **1994**, *116*, 2312−2317.

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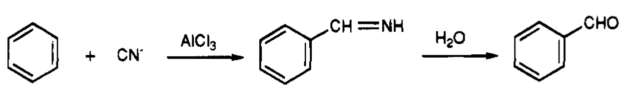
Table 1. Acid-Catalyzed Reactions of Aromatics with Cyanides

entry	aromatic	nitrile	acid	H_0	temp (°C)	time (min)	yield (%)	isomer ratio ortho	isomer ratio meta	isomer ratio para
1	benzene	NaCN	23% TFSA/77% TFA	−10.6	20	300	0			
2			55% TFSA/45% TFA	−11.8	20	300	3			
3			80% TFSA/20% TFA	−12.7	20	300	11			
4			TFSA	−14.0	20	30	44			
5			1% SbF_5/99% TFSA	−16.8	20	30	65			
6			5% SbF_5/95% TFSA	<−18	20	5	92			
7	benzene	TMS−CN	20% TFSA/80% TFA	−10.0	20	720	0			
8			55% TFSA/45% TFA	−11.8	20	300	2			
9			80% TFSA/20% TFA	−12.7	20	30	17			
10			TFSA	−14.0	20	30	55			
11			5% SbF_5/95% TFSA	<−18	20	5	99			
12	toluene	TMS−CN	5% TFSA/95% TFA	−8.5	0	120	0			
13			60% TFSA/40% TFA	−12.0	0	30	45	47	0	53
14			TFSA	−14.0	0	30	79	46	0	54
15	chlorobenzene	TMS−CN	TFSA	−14.0	20	30	2	26	0	74
16			1% SbF_5/99% TFSA	−16.8	20	30	61	24	0	76
17			5% SbF_5/95% TFSA	<−18	20	5	49	25	0	75
18			5% SbF_5/95% TFSA	<−18	20	10	93	25	0	75

suggest that the real electrophile is not the monoprotonated nitrile or the simple acetyl cation but the dicationic species formed by protonation of the monocation.

Gattermann reaction

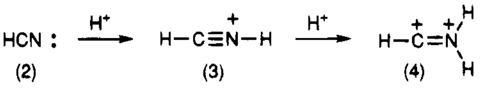
The Gattermann reaction,[6] first described in 1898,[13] is an acylation reaction of arenes using aluminum trichloride and cyanide salts. The reaction proceeds through an imine intermediate. In the reaction with benzene, the yield of benzaldimine (often isolated as benzaldehyde) was low. Hinkel *et al.*[14] improved the original reaction conditions by the use of $AlCl_3$−HCl as the catalyst at reflux temperature. The reaction in the presence of $Zn(CN)_2$−HCl−$AlCl_3$ was examined by Olah *et al.*[15] In these cases, the reaction media are complex but undoubtedly highly acidic. Is such high acidity, higher than needed for monoprotonation or monocoordination of the Lewis acid, really required? This question can be clearly answered by use of the TFSA−TFA system. In our earlier experiments, we used sodium cyanide as the cyanide source.



In 23% TFSA−77% TFA, having an acidity of $H_0 = -10.6$, benzene is not attacked by the species derived from sodium cyanide (Table 1, entry 1). An increase of the acidity by addition of increasing amounts of TFSA to the medium was required for the reaction to proceed (entries 2 and 3; yields were determined after aqueous acid hydrolysis to benzaldehyde). In TFSA, the reaction was complete within 30 min at 20 °C and the yield reached 44%. A further increase of the acidity by the addition of 1% SbF_5 to TFSA sped up the reaction. In the presence of 5% SbF_5, the reaction was instantaneous and the yield was excellent. These experiments indicate that the acidity of the media is extremely important, though the neutralizing effect of sodium cyanide needs to be considered when the acidity is high. This problem has been overcome by the use of trimethylsilyl cyanide (TMSCN) in place of the cyanide salt. TMSCN in TFA or TFA−TFSA is rapidly converted to hydrogen cyanide (in TFA) or to protonated hydrogen cyanide (in TFA−TFSA), accompanied with production of trimethylsilyl trifluoroacetate.[16] The reaction of TMSCN with benzene in media with various levels of acidity proceeded in a manner similar to the cases of sodium cyanide (Table 1, entries 7−11). In both cases, the higher the acidity is, the faster the rate and the better the yield.[17]

Even in the case of toluene, a slightly activated benzene, 5% TFSA−95% TFA is not acidic enough to allow the reaction to proceed. A higher acidity than $H_0 = -12.0$ is required (Table 1, entries 12−14). The rate is somewhat faster than that of the reaction with benzene. The reaction with chlorobenzene is also as anticipated; the reaction proceeded only slowly, even at $H_0 = -14.0$ (entries 15−18). The concentration of the active species in TFSA is still low for the detectable reaction of this nonactivated benzene.

Since the TFSA is the key acid catalyst, its reaction with HCN can be simply analyzed in terms of the protonation status.



$$\mathrm{HCN} : \xrightarrow{H^+} \overset{+}{\mathrm{H{-}C{\equiv}N{-}H}} \xrightarrow{H^+} \mathrm{H{-}\overset{+}{C}{=}\overset{+}{N}H_2}$$

(2) (3) (4)

The pK_{BH^+} of hydrogen cyanide is estimated to be between −10 and −11 (−10.5 for benzonitrile and −10.12 for acetonitrile);[18] hydrogen cyanide in TFSA−TFA with $H_0 = -12$ is more than half-protonated.[19] In spite of this significant degree of protonation, the rate of the acylation reaction is very slow. The rate increases when the acidity is further increased, implying that additional protonation of the monoprotonated species is required for the progress of the reaction.

Thus, it is concluded that the species which reacts with benzene is not the stable nitrilium ion $HCNH^+$ but the diprotonated species $HCNH_2^{2+}$. The resonance-stabilized nitrilium ion shows only limited imido carbenium ion character

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(13) Gattermann, L. *Ber. Dtsch. Chem. Ges.* **1898**, *31*, 1149−1152.

(14) Hinkel, L. E.; Ayling, E. E.; Morgan, W. H. *J. Chem. Soc.* **1932**, 2793−2798.

(15) Olah, G. A.; Ohhannesian, L.; Arvanaghi, M. *Chem. Rev.* **1987**, *87*, 671−686. Olah, G. A.; Pelizza, F.; Kobayashi, S.; Olah, J. A. *J. Am. Chem. Soc.* **1976**, *98*, 296−297.

(16) This conversion was confirmed by NMR observation of HCN (^1H at 4.1 ppm and ^{13}C at 108.5 ppm in TFA), $CF_3COOTMS$ ($CF_3{}^{13}COO$ at 161.5 ppm and $Si^{13}CH_3$ at −1.4 ppm in TFA), and $HCNH^+$ (^1H at 4.5 ppm and ^{13}C at 106.3 ppm in TFSA).

(17) Yato, M.; Ohwada, T.; Shudo, K. *J. Am. Chem. Soc.* **1991**, *113*, 691−692.

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(19) In TFSA, $HCNH^+$ is the sole product observed by NMR at −30 °C. This reacts slowly with the medium to yield the protonated triflate $CF_3SO_3CH{=}N^+H_2$ after several hours at 20 °C.

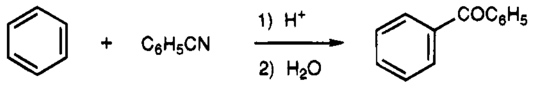
Table 2. Acid-Catalyzed Houben–Hoesch Reactions of Benzene with Nitriles

entry	aromatic	nitrile	acid	H_0	temp (°C)	time (min)	yield (%)
1	benzene	C_6H_5CN	55% TFSA/45% TFA	−11.8	20	300	11
2			TFSA	−14.0	20	120	14
3			5% SbF_5/95% TFSA	<−18	20	30	54
4	benzene	$C_6H_5CNCH_3^+TfO^-$	TFA	−2.7	20	2880	0
5			TFSA	−14.0	20	1200	3
6			5% SbF_5/95% TFSA	<−18	20	30	55

and accordingly is a mildly electrophilic agent which can only react with activated benzenes but cannot react with benzene itself or nonactivated benzenes. This interpretation is consistent with the observations by Olah *et al.*[15] In regard to the second protonation site, the planar *N,N*-diprotonated structure (**4**) is preferable to the *C,N*-diprotonated structure according to calculations for the diprotonated hydrogen cyanide H_3CN^{2+},[20] as would be intuitively expected.

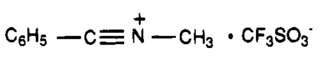
Houben–Hoesch Reaction

The Houben–Hoesch reaction is an acylation reaction initiated with nitriles and HCl (and/or Lewis acid). This reaction is also useful for the acylation of an activated arene such as phenol, polyphenols, and anilines. For nonactivated benzenes, trichloroacetonitrile works quite well.[21] Generally, a Lewis acid-coordinated nitrile or a protonated chloroimine is regarded as the electrophilic species. An *N*-protonated trichloroacetonitrile may be reactive enough because of the electron-withdrawing power of the trichloromethyl moiety. But generally, protonated nitriles are stable species which are unlikely to react with benzene. We tried to optimize the reaction of acetonitrile with benzene in TFSA–TFA media. The products were triazine derivatives or complex mixtures. Reaction of benzonitrile with benzene proceeded fairly well, however (Table 2, entries 1–3).



In a weak acid system (55% TFSA–45% TFA, $H_0 = -11.8$), the yield of benzophenone obtained after hydrolysis of the product mixture was very low, with some recovery of the starting material and the formation of 2,4,6-triphenyltriazine. In a medium of higher acidity, however, formation of benzophenone became significant. In order for benzonitrile to react with benzene, a highly acidic medium is required. The monoprotonated state of benzonitrile cannot be the responsible electrophile.[22]

N-Methylbenzonitrilium triflate (**5**)[22,23] is a good probe for examining the possible participation of nitrilium ion as the electrophile (Table 2, entries 4–6). This ion reacts with



$$C_6H_5{-}C{\equiv}\overset{+}{N}{-}CH_3 \cdot CF_3SO_3^-$$

(**5**)

activated aromatics[23] but does not react with benzene in TFA. TFSA catalyzes the reaction, but only very slowly (20 h); benzophenone is formed in a low yield (3%). The medium consisting of acid 95% TFSA–5% SbF_5 was acidic enough for the reaction to proceed; benzophenone was isolated in high yield (55%) in this case. This demonstrates that protonation of **5** is required for the reaction with benzene to occur.

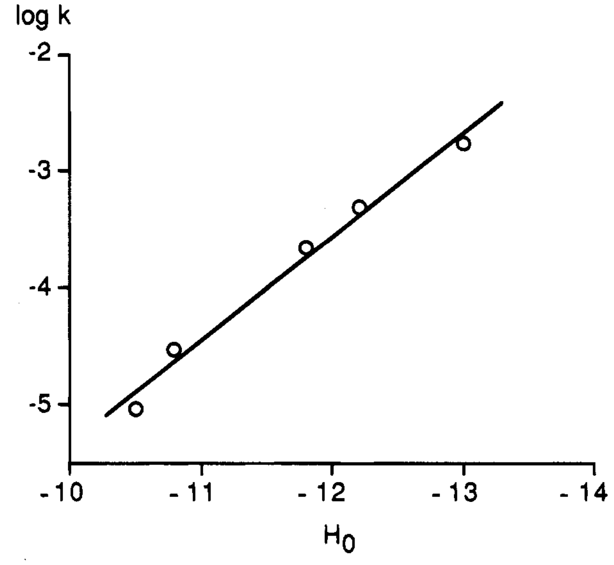
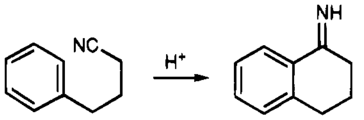


Figure 1. Acidity–rate relationship in the intramolecular Houben–Hoesch reaction of 4-phenylbutyronitrile

The importance of acidity in the reaction is best illustrated by the acid-catalyzed intramolecular cyclization of 4-phenylbutyronitrile to 1-tetralone imine (isolated as 1-tetralone) in good yield. This nitrile is stable in an acidic medium weaker than



$H_0 = -10$. In highly acidic media at 25 °C, the cyclization is clean and smooth. Since the media are homogeneous, the rate of cyclization could be plotted against the acidity of the medium; the rate is linearly proportional to the acidity H_0 (Figure 1, Table 3), satisfying the Zucker–Hammett conditions.[24] Since the pK_{BH^+} of the nitrile is −10.5 (by NMR titration at −30 °C, Figure 2), in a medium of $H_0 = -10$ to −11, the nitrilium ion should be about half-monoprotonated. Thus, the linear relation of the rate to H_0 should not hold, if the nitrilium ion participates in the rate-determing step, because the concentration of the active protonated species must be low in order to satisfy the Zucker–Hammett hypothesis. The linear increase of the rate with acidity (more than 100-fold increase of the rate from a medium of $H_0 = -10.5$ to a medium of $H_0 = -13$; the slope is 0.89) strongly supports the reversible protonation of the nitrilium ion to yield steady state amounts of diprotonated species. The fact that the slope is close to 1 may mean that the second proton transfer to the substrate at the transition state is

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[20] Koch, W.; Heinrich, N.; Schwarz, H. *J. Am. Chem. Soc.* **1986**, *108*, 5400–5403. Bouma, W. J.; Random, L. *J. Am. Chem. Soc.* **1983**, *105*, 5484–5486.

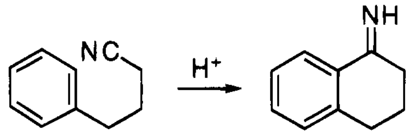
[21] Houben, J.; Fischer, W. *Ber. Dtsch. Chem. Ges.* **1931**, *64*, 2645–2653. Olah, G. A. Reference 2, Vol. 1, pp 119–120.

[22] PhCN is fully monoprotonated in TFSA. The ^{13}C-chemical shift (103 ppm) of $Ph^{13}CN$ in TFSA is close to that of $Ph^{13}CN^+CH_3$ in TFSA (103 ppm). The protonated species, $PhCNH^+$, is slowly converted to the triflate ester $CF_3SO_3C(C_6H_5){=}N^+H_2$. $PhCN^+CH_3$ is stable in TFSA.

[23] Booth, B. L.; Jibodu, K. O.; Proença, M. F. J. R. P. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1067–1073.

[24] Zucker, L.; Hammett, L. P. *J. Am. Chem. Soc.* **1939**, *61*, 2791–2798. Long, F. A.; Paul, M. A. *Chem. Rev.* **1957**, *57*, 935–1010.

Table 3. Rate Constants for the Intramolecular Houben–Hoesch Reaction of 4-Phenylbutyronitrile at 25 °C



entry	H_0	k_{obs} (s^{-1})	ratio
1	−13.0	1.74×10^{-3}	190
2	−12.2	4.82×10^{-4}	52
3	−11.8	2.23×10^{-4}	24
4	−10.8	2.92×10^{-5}	3.2
5	−10.5	9.22×10^{-6}	1

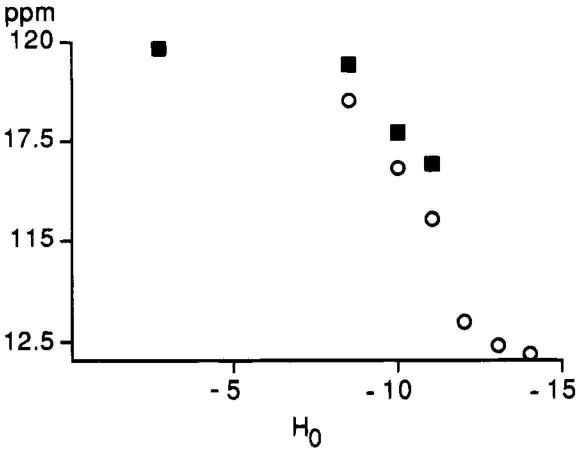
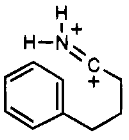


Figure 2. Protonation of 4-phenylbutyronitrile detected by ^{13}C-NMR spectroscopy in TFA–TFSA (■, 25 °C; ○, −30 °C).

nearly complete.[25] Thus, the intramolecular cyclization can be understood in terms of the involvement of a dicationic species, the *N,N*-diprotonated nitrile (**6**), as the *de facto* reagent[10] in the rate-determining step.



(**6**)

Friedel–Crafts Acylation

Experiments to test the effect of acidity on the Friedel–Crafts acylation were done with acetylium hexafluoroantimonate ($CH_3CO^+SbF_6^-$),[26] which is highly ionic, and spectrometrically studied in HF–FSO_3H by Olah.[5] The salt can be purified from nitromethane–TFA, indicating that it is stable in nitromethane or TFA or it exists at least in equilibration with any complexed or coordinated species.

The reaction characteristics are summarized in Table 4. In the reaction of CH_3COSbF_6 with benzene (entries 1–9), TFA serves as a poor medium. Even after a long reaction time, less than a 10% yield of acetophenone was formed. In the reaction of the acylium salt with toluene, the acetylated product was formed in significant yield after a long reaction time (entries 10 and 13). Chlorobenzene, on the other hand, did not react at all (entry 14).

In nitromethane and nitrobenzene, the salt acetylates benzene slowly (entries 8 and 9). These results suggest that the acetyl cation itself has the ability to acetylate benzene, but only slowly. Even in this case, a strong acid, $HSbF_6$, is formed in the reaction which can catalyze subsequent reaction.

The most noteworthy feature of these experiments is the correlation of rate with the acidity; the enhancement of the rate is roughly 10 times or more when the acidity is increased from $H_0 = -12$ to $H_0 = -14$, though quantitative estimation is difficult because of the heterogeneity of the reaction medium. NMR spectroscopy shows that, even at $H_0 = -12$, a significant amount (60%) of the added salt is detected as the acetyl cation CH_3CO^+.[27] This increases to almost 75% at $H_0 = -14$. If the acetyl cation is the active electrophile, the rate enhancement in going from a medium with $H_0 = -12$ to one with $H_0 = -14$ would be far less than 2-fold. Acetyl cation must be transformed by protonation into another more reactive species, protonated acetyl cation (**7**), in the more acidic medium.

$$CH_3-\overset{+}{C}\equiv O \xrightarrow{H^+} CH_3-\overset{+}{C}=\overset{+}{O}-H$$

(7)

This situation can be clearly observed in acetylation of chlorobenzene (Table 4, entries 14–22). Rate enhancements were apparent even at higher activity than that of TFSA. Such enhancement can only be interpreted when the Zucker–Hammett conditions[24] hold; *i.e.*, the active species is formed by protonation, and its concentration is low. This is consistent with the NMR observation that the predominant species in TFSA is the nonreactive acetyl cation, and the reactive protonated acetyl cation cannot be detected. In this case, it should be noted that the isomer ratio did not depend on the medium, indicating that the mechanisms operating at $H_0 = -10$ and at $H_0 \approx -18$ are the same.

The change of the isomer ratio in the case of toluene acetylation is significant; the relative percentage of the meta product in TFA is 6%, but it is negligible in TFSA. Even in TFA, when the reaction is run for a longer time, the percentages seem to approach that observed in TFSA. The products are stable in TFSA.[28] Therefore, the change of the isomer distribution means that the mechanisms in TFA and in TFSA are different. Because toluene is an arene having characteristics between activated arenes and nonactivated arenes, it may be reasonable that toluene can also be acetylated by the stable acetyl cation in low-acidity media. The decrease of the *meta* product as the reaction proceeds may be due to the formation of $HSbF_6$ which increases the acidity of the medium.

The benzoylation of benzene, toluene, and chlorobenzene by benzoyl hexafluoroantimonate ($C_6H_5CO^+SbF_6^-$)[26] also gave similar results (Table 5). Increase of the acidity of the media enhanced the rate of reaction and yield of benzophenones. The enhancement was observed at higher acidity than that of TFSA, though the salt in TFSA was shown spectroscopically to exist solely as the benzoyl cation.

In the case of toluene benzoylation, the isomer distribution changed in TFA and TFSA in a way similar to, but positionally different from, that in the case of acetylation of toluene.

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[25] The smaller slope (0.3) in the case of the intramolecular ketone cyclization of 1,3-diphenylpropanone (ref 12b) may mean that proton transfer at the transition state is around one-half. This may be well-understood in terms of the concept of "protosolvation". The slope may reflect the degree of tightness of the protosolvation at the transition states.

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[27] $^{13}C^+$=O at 153 ppm and ^{1}H of CH_3 at 4.5 ppm in TFSA. The protonated acetic acid $CH_3COO^+H_2$ is also detectable (^{13}COO at 194 ppm and ^{1}H of CH_3 at 3.3 ppm in TFSA).

[28] Even in the presence of toluene.

Table 4. Acid-Catalyzed Acetylation of Aromatics with CH_3COSbF_6

							isomer ratio		
entry	aromatic	solvent	H_0	temp (°C)	time (min)	yield (%)	ortho	meta	para
1	benzene	TFA	−2.7	5	720	8			
2		5% TFSA/95% TFA	−8.5	5	60	27			
3		20% TFSA/80% TFA	−10.0	5	60	35			
4		60% TFSA/40% TFA	−12.0	5	5	5			
5		60% TFSA/40% TFA	−12.0	5	60	76			
6		TFSA	−14.0	5	5	78			
7		TFSA	−14.0	5	60	97			
8		nitrobenzene	−	5	60	21			
9		nitromethane	−	5	60	3			
10	toluene	TFA	−2.7	0	30	13	1	6	93
11		TFA	−2.7	0	720	55	1	2	97
12		TFSA	−14.0	0	5	66	0.3	0	99.7
13		TFSA	−14.0	0	30	97	0.3	0	99.7
14	chlorobenzene	TFA	−2.7	5	1440	0			
15		5% TFSA/95% TFA	−8.5	5	60	0			
16		20% TFSA/80% TFA	−10.0	5	60	9 (*para*)			
17		60% TFSA/40% TFA	−12.0	5	60	21	1.2	0.8	98
18		TFSA	−14.0	5	60	32	0.7	0.3	99
19		TFSA	−14.0	5	1440	91	0.6	0.4	99
20		1% SbF_5/99% TFSA	−16.8	5	60	48	1.1	0.9	98
21		5% SbF_5/95% TFSA	<−18	5	60	82	0.6	0.4	99
22		nitrobenzene	−	5	60	0			

Table 5. Acid-Catalyzed Benzoylation of Aromatics with $C_6H_5COSbF_6$

							isomer ratio		
entry	aromatic	acid	H_0	temp (°C)	time (min)	yield (%)	ortho	meta	para
1	benzene	TFA	−2.7	5	60	1			
2		TFSA	−14.0	5	60	96			
3	toluene	TFA	−2.7	0	30	19	12	1	87
4		TFSA	−14.0	0	30	98	7	1	93
5	chlorobenzene	TFSA	−14.0	5	60	13 (*para*)			
6		1% SbF_5/99% TFSA	−16.8	5	60	32	0	1	99
7		5% SbF_5/95% TFSA	<−18	5	60	71	0	1	99

In conclusion, acetyl cation CH_3CO^+ and benzoyl cation $C_6H_5CO^+$ are relatively weak electrophiles and can react only slowly with benzene or toluene. The real or major acylating agents are the protonated acetyl and benzoyl cations.

In relation to acetylation and benzoylation, the Koch reaction in highly acidic media studied by Olah[15,36] using fluoroformic acid is fundamental and suggestive. The results can be interpreted in terms of the participation of diprotonated carbon monoxide, protoformyl dication, or an equivalent (BF_3-coordinated) species as the reactive electrophile. This is the parent protonated acyl cation and is isoelectronic with diprotonated hydrogen cyanide as discussed above.

The structure of the protonated acetyl cation was theoretically discussed, and the $C_2H_4O^{2+}$ dication was observed[29] in charge-stripping mass spectroscopic studies. Theoretical calculations on protonated formyl cations suggested that the *O*-protonated formyl cation is obligatory in the reaction.[30] The participation of the protonated acetyl cation has been demonstrated in the hydride transfer from isobutane to the acetyl cation generated from acetic acid in HF−BF_3.[31]

In general, a strong acid modifies the reactivity of the acetyl cation by generating a more reactive species, protonated acetyl cation, though the acetyl cation itself may also be involved as an electrophile in acetylation in a weakly acidic medium. An analogous situation is proposed for benzoylation; the *O*-protonated benzoyl cation is the real electrophilic species under highly acidic conditions.

Conclusion

The Gattermann and Houben−Hoesch reactions have been of less practical importance because of the poor yields when the substrates are not activated. The use of strong acids makes these reactions more useful. Analysis of the acid dependency of the reactions demonstrated that they involve diprotonated hydrogen cyanide and nitriles. These species can be categorized as activated dications.

Friedel−Crafts acylation is a general method for obtaining aromatic ketones. The results described here indicate that the major active species involved in the reaction with benzene and with deactivated benzenes in highly acidic media is the protonated acyl cation rather than the acyl cation itself. The pathway involving the dication operates exclusively in the acetylation of chlorobenzene and predominantly in the reaction of benzene. In the acetylation of an activated benzene, toluene, the dicationic electrophile also plays a significant role, though the acetyl cation itself plays a role under weakly acidic conditions. The scheme is also valid for other Friedel−Crafts acylations such as benzoylation.

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The present proposal also resolves the long-puzzling problem that Friedel–Crafts reactions often require more than 1 equiv of $AlCl_3$ or require HCl or a trace of H_2O. All these conditions increase the acidity of the media or allow a more acidic species to form, favoring the formation of protonated acyl cations or the activation of an acyl cation by further coordination of the Lewis acid as proposed by Vol'pin *et al.*[32] Participation of protonated acetyl cation or protosolvated acetyl cation in the hydride abstraction from isobutane by the acetyl cation in superacidic $HF-BF_3$ has been discussed by Olah *et al.*[33]

O-Protonated acyl cations are isoelectronic with *N,N*-diprotonated nitriles, and *N,N*-diprotonated hydrogen cyanide is isoelectronic with *C,O*-diprotonated carbon monoxide (*O*-protonated formyl cation). Thus, the active species in the Friedel–Crafts and Gattermann–Koch reactions and Gattermann and Houben–Hoesch reactions can be classified as carbocations destabilized by an onium group.

A similar concept, that destabilized cations[34,35] can be reactive toward weak nucleophiles, has been developed by Olah and coworkers, who have used the term "protosolvated cations"[36] or superelectrophiles.[10] Most superelectrophiles are dications whose dicationic centers interact.[37] Dications such as iminium–benzeniums, iminium–carbeniums, iminium–allyl, and oxonium–carbeniums are also superelectrophiles.

Experimental Section

General Methods. Proton and carbon NMR spectra were measured on a JEOL GX 400-MHz NMR spectrometer with CH_2Cl_2 (5.30 ppm for proton and 54 ppm for carbon) as an external reference for acid solutions. Gas chromatography was conducted on a Shimadzu GC-6A (FAP-S, 3 m; nitroterephthalic ester type column used at 160 °C). All operations for kinetic studies and NMR observation of acid solutions were carried out in an AtmosBag (Aldrich).

Materials. Trifluoromethanesulfonic acid (TFSA) was purchased from 3M Co. or Central Glass Co. and was purified by distillation under a nitrogen atmosphere in the presence of P_2O_5. Extreme care was required to obtain anhydrous TFSA which showed the acidity of -14.1. All operations were carried out in a dry bag flushed with dry nitrogen. Trifluoroacetic acid (TFA) was also purified as reported.[12a] The acidity (H_0) of the mixed acids was checked before use in kinetic studies. Benzene, toluene, and chlorobenzene were purified by distillation under a nitrogen atmosphere over a small amount of P_2O_5. Sodium cyanide was the commercial product and was used without further purification. Trimethylsilyl cyanide (TMSCN) was obtained from Tokyo Kasei Industry Co. and was purified by distillation under a nitrogen atmosphere (bp 117–118 °C). Acetonitrile was distilled from CaH_2 under a nitrogen atmosphere. Benzonitrile was distilled from P_2O_5 under a nitrogen atmosphere. *N*-Methylbenzonitrilium triflate was prepared as reported.[23] Commercial 4-phenylbutyronitrile was purified by distillation under a nitrogen atmosphere (bp 99–100 °C/2 mmHg). Acetyl fluoride was prepared as reported.[38] Benzoyl fluoride was a commercial product and was purified by distillation under a nitrogen atmosphere (bp 160–162 °C). Freon 113 was washed with water, dried over $CaCl_2$, and distilled under a nitrogen atmosphere (bp 47 °C). Acetyl and benzoyl hexafluoroantimonates were prepared by the method of Olah.[26] The acetylium salt was further purified by recrystallization from nitromethane–TFA under a nitrogen atmosphere.

Gattermann Reaction of Benzene with NaCN. NaCN (1.0 mmol, 1 equiv) was added to a vigorously stirred solution of 450 equiv of acid and 450 equiv (35.9 g) of benzene under a nitrogen atmosphere. After the defined reaction was complete, the mixture was poured into ice–water. The resultant mixture was heated at 40 °C for 20 min and extracted with *n*-hexane. The organic layer was dried over $MgSO_4$ and filtered. The yield of benzaldehyde was determined by gas chromatography. The identity of benzaldehyde isolated by column chromatography on silica gel was confirmed by IR and NMR spectroscopy.

Gattermann Reaction of Benzene with TMSCN. A solution of TMSCN (1.0 mmol, 1 equiv) in 10 equiv (0.80 g) of benzene was added *via* a syringe to a vigorously stirred solution of 450 equiv of acid and 440 equiv (34.6 g) of benzene under a nitrogen atmosphere. After the defined reaction, the mixture was poured into ice–water. The resultant mixture was heated at 40 °C for 20 min and extracted with *n*-hexane. The organic layer was dried over $MgSO_4$ and filtered. The yield of benzaldehyde was determined by gas chromatography. In the reaction of toluene, GC conditions for isomer analysis were the same as above. For analysis of chlorobenzaldehyde isomers, a Shimadzu FAP-S 3 m column was used at 110 °C.

Houben–Hoesch Reaction of Benzene with Benzonitrile. A mixture of benzonitrile (1.0 mmol, 1 equiv) and 10 equiv (0.80 g) of benzene was added *via* a syringe to a vigorously stirred solution of 450 equiv of acid and 440 equiv (34.6 g) of benzene under nitrogen atmosphere. After the defined reaction, the mixture was poured into ice–water. The resultant mixture was heated at 40 °C for 20 min and extracted with *n*-hexane. The organic layer was dried over $MgSO_4$ and filtered. The yield of benzophenone was determined by gas chromatography. The identity of benzophenone isolated by column chromatography on silica gel was confirmed by IR and NMR spectroscopy.

Houben–Hoesch Reaction of Benzene with *N*-Methylbenzonitrilium Triflate. *N*-Methylbenzonitrilium triflate (0.38 mmol, 1 equiv) weighed into a glass tube was directly added to a vigorously stirred solution of 500 equiv of acid and 500 equiv (14.6 g) of benzene under a nitrogen atmosphere. The exact amount of added triflate was determined from the decrease of the total weight of the glass tube–substrate. After the defined reaction, the mixture was poured into ice–water. The resultant mixture was heated at 40 °C for 20 min and extracted with *n*-hexane. The organic layer was dried over $MgSO_4$ and filtered. The yield of benzophenone was determined by gas chromatography.

Kinetics of the Intramolecular Cyclization of 4-Phenylbutyronitrile. 4-Phenylbutyronitrile (0.11 mmol, 1 equiv) was added to a mixture of acids (10.0 mL, 1000 equiv) *via* a microsyringe to start the reaction. The reaction mixture was kept at 25 ± 0.1 °C, and portions were taken at intervals into the syringe (*ca.* 0.2 mL). The reaction was quickly quenched by injecting the sample into water (2.0 mL) in a preweighed flask. The exact amount of added reaction mixture was calculated from the increase in weight of the flask. The organic layer was extracted with CH_2Cl_2, dried over $MgSO_4$, and filtered. The amount of 4-phenylbutyronitrile which had reacted was determined by gas chromatography. The data which were collected between 20% and 80% reaction of 4-phenylbutyronitrile were used for the kinetic calculation. Very good first-order kinetics were obtained.

Preparation of CH_3COSbF_6. Dry KF (0.17 mol, 1.3 equiv) was added to a dry CH_3COOH (35 mL). The mixture was stirred well and cooled to 5 °C in an ice bath. CH_3COCl (10.5 g, 1 equiv) was added dropwise to the mixture for 15 min. The reaction mixture was stirred for an additional 15 min at 5 °C and warmed to 40–45 °C. Crude CH_3COF (5.3 g) was isolated by distillation. After careful distillation under a nitrogen atmospere, 2.1 g of CH_3COF was obtained (24.5%), bp 20 °C.

A mixture of SbF_5 (2.14 g) and Freon 113 (20 mL) was dropped into a well-stirred solution of CH_3COF (675 mg) and Freon 113 (20 mL) at -30 °C under a nitrogen atmosphere. The mixture was stirred for 30 min, and then the solvent and excess CH_3COF were evaporated off under reduced pressure at -30 °C. The residual white solid was washed with Freon 113 (20 mL) five times and dried for 1 h at 25 °C and an additional 30 min at 40 °C under 1 mmHg to afford 2.15 g of CH_3COSbF_6 (78.0%).

TFA was dropped into a solution of 200 mg of CH_3COSbF_6 in CH_3NO_2 (2 mL), and soon colorless needles separated out. The crystallized salt was separated from the solution by filtration and washed with Freon 113. The salt was put into a glass tube and dried for 15 min under

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(37) Another superelectrophilic species, which is monocationic, is a carbocation bearing a trihalomethyl moiety such as CF_3. (Ohwada, T.; Shudo, K. *J. Am. Chem. Soc.* **1988**, *110*, 1862–1870. Dao, L. H.; Maleki, M.; Hopkinson, A. C.; Lee-Ruff, E. *J. Am. Chem. Soc.* **1986**, *108*, 5237–5242.) See also refs 34 and 35.

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reduced pressure, giving 160 mg of recrystallized CH_3COSbF_6 as colorless needles, mp 155−156 °C.

Acylation of Benzene with CH_3COSbF_6. The CH_3COSbF_6 (0.54 mmol, 1 equiv), weighed into a glass tube, was directly added to a vigorously stirred solution of 500 equiv of acid and 500 equiv (21.0 g) of benzene under a nitrogen atmosphere. The exact amount of added salt was calculated from the decrease of the total weight of the glass tube−salt. After the defined reaction was completed, the mixture was poured into ice−water and extracted with *n*-hexane. The organic layer was dried over $MgSO_4$ and filtered. The yield of acetophenone was determined by gas chromatography (column: Shimadzu phenylmethyl silicone type OV-17 3%, 2 m, temperature 130 °C). The identity of acetophenone isolated by column chromatography on silica gel was confirmed by IR and NMR spectroscopy.

In the reaction of toluene, GC conditions for isomer analysis were the same as for benzene. For analysis of chloroacetophenone isomers, a Shimadzu FAP-S 3 m column was used at 160 °C.

Preparation of $C_6H_5COSbF_6$. A mixture of SbF_5 (6.2 g) and Freon 113 (50 mL) was dropped into a well-stirred solution of C_6H_5COF (3.2 g) and Freon 113 (50 mL) at −30 °C under a nitrogen atmosphere. Stirring was continued for 30 min, the solvent was decanted off, and the residual white solid was washed with Freon 113 (50 mL) three times. The solvent was evaporated under reduced pressure at −30 °C. The residual white powder was washed with Freon 113 (50 mL) five times and dried for 1 h at 25 °C and for an additional 1 h at 40 °C under 1 mmHg to afford 7.1 g of $C_6H_5COSbF_6$ (80.8%): white needles; mp 138−140 °C.

Acylation of Benzene with $C_6H_5COSbF_6$. The $C_6H_5COSbF_6$ (0.44 mmol, 1 equiv) weighed into a glass tube was added directly to a vigorously stirred solution of 500 equiv of acid and 500 equiv (17.2 g) of benzene under a nitrogen atmosphere. The exact amount of added salt was calculated from the decrease of the total weight of the glass tube−salt. After the defined reaction was complete, the mixture was poured into ice−water and extracted with *n*-hexane. The organic layer was dried over $MgSO_4$ and filtered. The yield of benzophenone was determined by gas chromatography. The identity of benzophenone isolated by column chromatography on silica gel was confirmed by IR and NMR spectroscopy.

When the reactions were run with toluene or chlorobenzene, the isomeric products were analyzed under the same GC conditions.

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