Friedel−Crafts-Type Reaction of Benzaldehyde with Benzene. Diprotonated Benzaldehyde as the Reactive Intermediate

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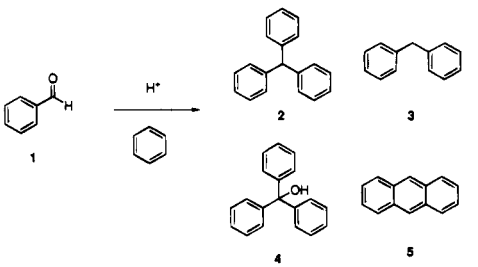
Abstract: Benzaldehyde (**1**) reacted with benzene in the presence of trifluoromethanesulfonic acid (TFSA) or a mixture of TFSA−trifluoroacetic acid (TFA) to give triphenylmethane (**2**), diphenylmethane (**3**), and triphenylmethanol (**4**). The initial formation of the intermediate **2** was followed by the formation of **3** and **4** as the final products. The total yield of the products **2**−**4** became higher in the presence of stronger acids, which indicated that the further activation of monoprotonated **1** was required in this reaction. O,O-Diprotonated benzaldehyde was proposed as the reactive intermediate, on the basis of the relationship between yield and acidity and the result of the NMR investigation.

The acid-catalyzed reaction of benzaldehydes with benzene has been known since 1886.[1] Under highly acidic conditions (for example, 2 equiv of $AlCl_3$ at 60 °C),[2] benzaldehyde (**1**) reacts with benzene to give a complex mixture of triphenylmethane (**2**), diphenylmethane (**3**), triphenylmethanol (**4**), and anthracene (**5**) (Scheme 1). The yields are generally low (total yield 30−60%).[3] Redox reactions clearly take place, but the mechanism has not been studied thoroughly.

Heteroatom-stabilized carbonium ions (e.g., monoprotonated ketones or acylium ions) are weak electrophiles, and their reactivity toward benzene is very low. In the intramolecular cyclodehydration of ketones with an aromatic ring to give indenes, the reactive intermediate is a dicationic species, rather than the monoprotonated ketone.[4] We have also shown that O-protonated acylium ions are the real reactive electrophile in the Friedel−Crafts acylation of benzene and non-activated aromatic compounds.[5] These results, together with the fact that highly acidic conditions are required for the reaction of benzaldehyde with benzene, suggest that a dicationic electrophile is also involved as the reactive intermediate in the present Friedel−Crafts-type reaction. Involvement of a dicationic species in the same reaction has been proposed by Olah et al.[6] In order to clarify the mechanism of this complex, but fundamental, reaction, we employed an acid system consisting of trifluoromethanesulfonic acid (TFSA)−trifluoroacetic acid (TFA) as the catalyst. Since the acidity (H_0, Hammett acidity function) of TFSA, TFA, and a mixture of TFSA and TFA is easily determined,[7] the reactions can be analyzed in relation to the defined acidity of the catalyst. Another advantage of employing TFSA and TFA is their stability to oxidation and reduction.

Scheme 1. Friedel−Crafts-Type Reaction of Benzaldehyde with Benzene



Results

Benzaldehyde reacted with benzene in the presence of TFSA as the acid catalyst at 50 °C to give several compounds (**2**−**5**) (Table 1, runs 1−3). When 100 equiv of benzene to 1 equiv of **1** was used in the presence of 100 equiv of TFSA, the major products were diphenylmethane (**3**), triphenylmethanol (**4**), and anthracene (**5**), while the reaction with a larger excess (500 equiv) of benzene and 100 equiv of TFSA suppressed the formation of **5** and yielded **3** and **4** as the major products. When a 1:1 mixture of diphenylmethane (**3**) and triphenylmethanol (**4**) was dissolved in a mixture of 100 equiv of benzene and 100 equiv of TFSA, a significant amount of **5** was formed. Thus, **5** is plausibly formed through stepwise reactions from the products (in particular diphenylmethane) when the excess of benzene is relatively small. Therefore, we conducted the reaction in 500 equiv of benzene and 100 equiv of TFSA hereafter to avoid the formation of anthracene via complex pathways.

In this reaction, the expected primary products are diphenylmethanol (**6**) and triphenylmethane (**2**). The formation of **3** and **4** instead of **6** and **2** suggests that redox pathways are involved in the reaction. We studied the reaction of possible intermediates in the TFSA−benzene system to understand the mechanism of this reaction in detail. As expected, the acid-catalyzed reaction of **6** with benzene proceeded smoothly and rapidly (5 °C, 10 min) to give **2** as the major product in the presence of TFSA. Compound **2**, which was rather stable, decomposed in TFSA (excess)−benzene (50 °C, 19 h) to give **3** and **4** (Scheme 2).

The formation of **2** as the early intermediate in the reaction was confirmed by examining the product distribution at a shorter

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(1) Griepentrog, H. *Ber. Dtsch. Chem. Ges.* **1886**, *19*, 1876−1877.
(2) Schaarschmidt, A.; Hermann, L.; Szemzo, B. *Ber. Dtsch. Chem. Ges.* **1925**, 1914−1916.
(3) Hofmann, J. E.; Schriesheim, A. In *Friedel−Crafts and Related Reactions*; Olah, G. A., Ed.; Wiley: New York, 1964; Vol. II, Chapter XIX pp 616−621.
(4) Saito, S.; Sato, Y.; Ohwada, T.; Shudo, K. *J. Am. Chem. Soc.* **1994**, *116*, 2312−2317.
(5) Sato, Y.; Yato, M.; Ohwada, T.; Saito, S.; Shudo, K. *J. Am. Chem. Soc.* **1995**, *117*, 3037−3043.
(6) Olah, G. A.; Rasul, G.; York, C.; Prakash, G. K. S. *J. Am. Chem. Soc.*, in press.
(7) Saito, S.; Saito, S.; Ohwada, T.; Shudo, K. *Chem. Pharm. Bull.* **1991**, *39* (10), 2718−2720.

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Table 1. Reaction of Benzaldehyde (**1**) with Benzene (50 °C)

run	compound[c]	time (h)	amt of benzene (equiv)	recovery of **1** (%)	yield (%) **2**	**3**	**4**	**5**
1[a]	**1**	19	100	*e*	0	38[f]	27	14[f]
2[a]	**1**	19	500	*e*	0	37	44	0
3[a]	**3** + **4**[d]	19	100	*e*	0	48[f]	30	8[f]
4[b]	**1**	3	500	64	27	3	6	0
5[b]	**1**	6	500	19	16	32	30	0
6[b]	**1**	15	500	12	12	44	27	0

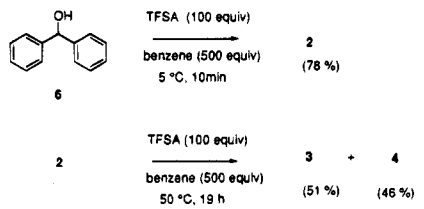
[a] Isolated yield. [b] Yields determined by GC. [c] One millimole was used, unless otherwise noted. [d] The amount of each compound used was 0.5 mmol. [e] Not detected by TLC. [f] Yields estimated by NMR.

Table 2. Relationship between the Yield and Acidity in the Reaction of Benzaldehyde (**1**) with Benzene (500 equiv of Benzene, 100 equiv of Acids, 50 °C, 15 h)

run	acid	H_0[a]	recovery of **1**(%)	yield (%) **2**	**3**	**4**	total yield (**2** + **3** + **4**, %)
1	TFA	−2.6	92	*b*	*b*	*b*	*b*
2	5% (w/w) TFSA−95% TFA	−9	82	4	*b*	*b*	4
3	21% (w/w) TFSA−79% TFA	−10	84	13	*b*	2	15
4	50% (w/w) TFSA−50% TFA	−12	56	39	1	*b*	40
5	80% (w/w) TFSA−20% TFA	−13	14	30	29	18	77
6	TFSA	−14	12	12	44	27	83

[a] See ref 7. [b] Less than 1%.

Scheme 2. Reactions of Possible Intermediates



reaction time. It was shown that triphenylmethane is initially formed in the reaction mixture, prior to the formation of diphenylmethane (**3**) and triphenylmethanol (**4**) (Table 1, runs 2 and 4−6).

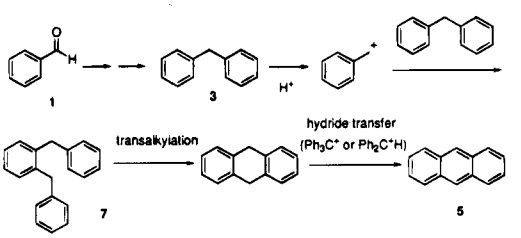
We investigated the effects of the acidity on the yield in order to deduce the protonated state of the reactive intermediate in the rate-determining step (Table 2). It is clear that a highly acidic condition is required for facile reaction. The pK_{BH^+} value of **1** is estimated to be −6.8[8] : **1** is almost completely monoprotonated in 5−21% (w/w) TFSA−95−79% TFA (H_0 = −9 to −10; see runs 2 and 3). In spite of the presence of monoprotonated benzaldehyde as the predominant species, a further increase of the acidity enhanced the formation of the products **2**−**4** (runs 4−6).

The results shown in Table 2 suggested that further addition of a proton to the monoprotonated **1** is essential to the reaction. Therefore, an NMR investigation was carried out to specify the position of protonation. Benzaldehyde (**1**) was dissolved in 100 equiv of TFSA-*d*, heated to 50 °C, and the integrations of every proton of **1** were monitored by means of NMR spectroscopy. No exchange of protons of **1** with deuterium was observed after 19 h. We also heated 4-fluoro- or 2-fluorobenzaldehyde in TFSA (50 °C, 19 h) to know whether transformylation took place, and found that no isomerized products or deformylated products were detected by NMR.

Discussion

The reaction of **1** with benzene usually gave compounds **2**−**5** as products, and the formation of multiple products made the analysis of the reaction difficult. We succeeded in reducing the number of products: the formation of anthracene (**5**) was not observed in the reaction using a large excess of benzene (500 equiv). This observation is consistent with the reports that the concentration of **1** was higher in cases where **5** was formed.[3] In such cases, the product **3** would react with another molecule of **3** (transalkylation) to give *o*-dibenzylbenzene (**7**), which would then undergo intramolecular transalkylation followed by hydride transfer involving a triphenylmethyl cation to give **5**. The increase of the yield of **5** in the presence of a lower excess of benzene (higher concentration of the phenylated products) can be well understood in terms of the mechanism in Scheme 3.[9]

Scheme 3. A Possible Mechanism of the Formation of Anthracene



In the presence of a large excess of benzene (500 equiv), the major products of this reaction were **3** and **4**, instead of the expected product **2**. We found that **2** was oxidized to give triphenylmethyl cation (and diphenylmethyl cation was reduced to diphenylmethane) in TFSA−benzene solution. The formation of **2** in the reaction as an intermediate was demonstrated at a shorter reaction time: the formation of the final products **3** and **4** followed the formation of **2**.

Compound **1** reacts slowly with benzene, followed by a quick second substitution to give **2**. By hydride transfer, **2** reduced the diphenylmethyl cation to give diphenylmethane. The diphenylmethyl cation could be formed by the elimination of benzene from **2** under a highly acidic condition, or by elimination of water from diphenylmethanol. It is less likely that the hydride acceptor is monoprotonated **1** instead of the diphenylmethyl cation, since monoprotonated **1** is a very weak hydride acceptor.[10] Though diprotonated benzaldehyde is a strong hydride acceptor, it would react with benzene (solvent), rather than **2**.

(8) Greig, C. C.; Johnson, C. D. *J. Am. Chem. Soc.* **1968**, *90*, 6453−6457.

(9) Full details will be published separately.

(10) (a) Olah, G. A. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 767−788. (b) Brouwer, D. M.; Kiffen, A. A. *Recl. Trav. Chim. Pays-Bas* **1973**, *92*, 809−813.

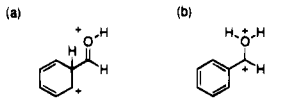
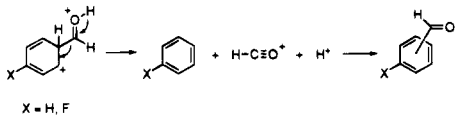


Figure 1. Possible structures of the diprotonated **1**.

Scheme 4. Possible Reactions of O,*ipso*-C-Diprotonated Benzaldehydes

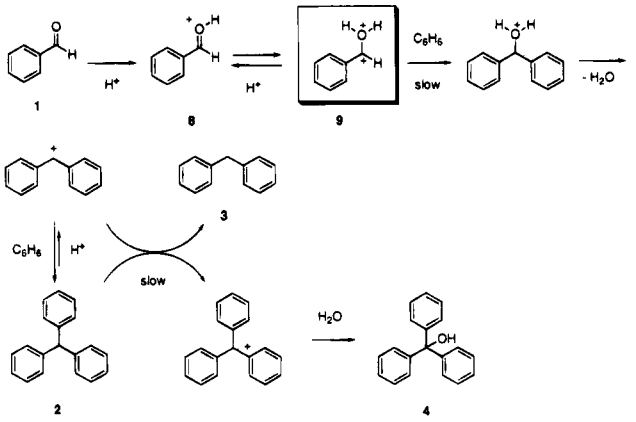


Under Friedel–Crafts conditions, some ketones and aldehydes react with aromatics to give disubstituted products. For example, cyclohexanone reacts with 2 equiv of phenol to give 1,1-bis(4-hydroxyphenyl)cyclohexane in good yield in the presence of concentrated HCl.[3] This result can be readily understood in terms of the high nucleophilicity of phenol, which can attack monoprotonated ketones (weak electrophiles). The reaction of trichloroacetaldehyde with benzene can be understood in terms of the destabilizing effect of the trichloromethyl group, which makes the protonated ketone highly electrophilic.[3]

On the other hand, the reaction of **1** with benzene is the reaction of a nonactivated aldehyde with a nonactivated aromatic compound. It is difficult to explain the results of the reaction of **1** with benzene, by supposing that a monoprotonated benzaldehyde is the reactive intermediate. The pK_{BH^+} of **1** is −6.8, and therefore benzaldehyde is almost completely monoprotonated in 5% (w/w) TFSA–95% TFA solution ($H_0 = -9$). If monoprotonated benzaldehyde was the reactive intermediate, the rate of the reaction would remain constant when more highly acidic solutions were used as catalysts, but this is not the case. The total yield of **2**–**4** increased with the use of catalysts with higher acidity. Though we were not able to measure the rate constants because of the heterogeneity of the reaction medium, this result strongly suggests that the rate of the reaction increased significantly under highly acidic conditions. Therefore, the reactive intermediate in this reaction should be a further activated species rather than the monocation.

The second protonation of the monoprotonated benzaldehyde (diprotonated benzaldehyde, **8**) or a protosolvated monoprotonated benzaldehyde is a straightforward explanation to the enhanced reactivity. The second protonation could take place at several positions of **8**, though the concentration of the diprotonated species must be very low. The results of NMR experiments limited the possible positions of protonation. It is not likely that the second protonation takes place in the *ortho*-, *meta*-, or *para*-position of the aromatic ring, because any protons of the aromatic ring did not exchange with deuterium of TFSA-*d*, when **1** was heated in TFSA-*d*. C-protonation on the carbonyl group is negative, since no exchange of the −C*H*O proton with deuterium was observed. The remaining possibilities are the protonation on (a) the *ipso*-position of the aromatic ring or (b) the oxygen atom of the carbonyl group (Figure 1). O,*ipso*-C-diprotonation of an aromatic ketone was reported (type a, Figure 1).[11] The protonation of the *ipso*-position of the aromatic ring should be followed by the formation of (protonated) formyl cation, which would recombine with the aromatics (Scheme 4). We favor that the intermediate is formed by the second protonation of the oxygen atom, since no isomerized fluorobenzaldehyde was detected in the presence of TFSA. Thus, the experimentally possible structure for the diprotonated species is the O,O-diprotonated species (type b, Figure 1). The

Scheme 5. Proposed Mechanism of the Reaction of Benzaldehyde with Benzene



structures of some O,O-diprotonated carbonyl compounds have been deduced by calculations.[6,10a,12] We propose the mechanism of the whole reaction as presented in Scheme 5. Olah et al. proposed O,*meta*-C-diprotonated benzaldehyde whose structure was deduced from molecular orbital calculation as the reactive species.[6] This proposal seems to contradict our experimental results, and we need to investigate further the nature of the real active species by experimental and computational methods.

Conclusion

O,O-diprotonated benzaldehyde (**9**) is the key electrophile in the reaction of benzaldehyde with benzene under highly acidic conditions. This reaction is another example of the reaction of carbonyl compounds which have been converted to superelectrophiles by diprotonation. The mechanism of the whole reaction involves hydride transfer, alkylation, and transalkylation. The present results contribute to the establishment of the concept of the superelectrophile,[10a] which is becoming a key idea in various fields of chemistry.

Experimental Section

General Methods. All the melting points were measured with a Yanagimoto hot-stage melting point apparatus (MP-500) and are uncorrected. Proton NMR spectra were measured on a JEOL GX 400 MHz NMR spectrometer with tetramethylsilane as an internal reference in $CDCl_3$, unless otherwise noted. Flash column chromatography was performed on silica gel (Kieselgel 60, 230–400 mesh, Merck) with the specified solvent. Gas chromatography was performed on a Shimadzu GC6A gas chromatograph (column OV-17, 2 m). Combustion analyses were carried out in the microanalytical laboratory of this faculty.

Materials. Trifluoromethanesulfonic acid (TFSA) was purchased from Central Glass Co. (Japan) and was purified as reported.[7] Trifluoroacetic acid (TFA) and the indicators were also purified as reported.[7] CF_3SO_3D (TFSA-*d*) was prepared by the reaction of triflic anhydride with D_2O, and purified by distillation. Benzaldehyde (**1**), 2-fluorobenzaldehyde, and 4-fluorobenzaldehyde were purified by distillation under reduced pressure, and stored in glass ampules under Ar. Triphenylmethane (**2**) and diphenylmethanol (**6**) were recrystallized from hexanes. Diphenylmethane (**3**) was purified by distillation. Triphenylmethanol (**4**) was recrystallized from MeOH.

Acid-Catalyzed Reactions of Benzaldehyde with Benzene. (A) Analysis by Column Chromatography. To a solution of **1** (106 mg, 1.0 mmol) in dry benzene (specified equivalents) was added TFSA (8.8 mL, 100 mmol) slowly at room temperature. The heterogeneous red suspension was heated to 50 °C and stirred vigorously for the specified period under Ar. The suspension was added slowly to 200 mL of ice–water and extracted with 200 mL of CH_2Cl_2. The organic layer was separated, washed with brine, dried over Na_2SO_4, and evaporated to give an oil. The residue was purified by column

(11) Keumi, T.; Morita, T.; Shimada, T.; Teshima, N.; Kitajima, H.; Prakash, G. K. S. *J. Chem. Soc., Perkin Trans. 2* **1986**, 847–852.

(12) Hartz, N.; Golam, R.; Olah, G. A. *J. Am. Chem. Soc.* **1993**, *115*, 1277–1285.

chromatography (hexanes to hexanes:AcOEt = 10:1) to give a mixture of **3** and **5** as a colorless oil, and **4** as a powder. The quantitative separation of **3** and **5** was difficult, and the yield of **3** and **5** was estimated from NMR integration. The reaction of **3** (84 mg, 0.5 mmol) + **4** (130 mg, 0.5 mmol) in benzene in the presence of TFSA was carried out similarly.

Data for 2: colorless powder; ^{1}H NMR δ 7.28 (t, 6 H, J = 7.3 Hz), 7.22 (t, 3 H, J = 7.8 Hz), 7.11 (d, 6 H, J = 7.8 Hz), 5.55 (s, 1 H); identical with the authentic sample (TLC, NMR, GC).

Data for 3: colorless oil; ^{1}H NMR δ 7.27 (t, 4 H, J = 7.7 Hz), 7.2 (m, 6 H), 3.98 (s, 2 H). MS (EI) *m/e* 168 (M^+); identical with the authentic sample (TLC, NMR, GC).

Data for 4: mp 163−163.5 °C (lit.[13] mp 160−162 °C) (recrystallized from MeOH, colorless cubes); ^{1}H NMR δ 7.2−7.3 (m, 15 H), 2.80 (s, 1 H, disappeared after treatment with D_2O); identical with the authentic sample (TLC, NMR). Anal. Calcd for $C_{19}H_{16}O$: C, 87.66; H, 6.19. Found: C, 87.46; H, 5.94.

Data for 5: colorless powder; ^{1}H NMR δ 8.44 (s, 2 H), 8.01 (dd, 4 H, 6.6, 3.2 Hz), 7.47(dd, 4 H, 6.6, 3.2 Hz); identical with the authentic sample (TLC, NMR).

(B) Analysis by GC. To a solution of **1** (21 mg, 0.2 mmol) in dry benzene (7.8 g, 100 mmol) was added a mixture of acids (1.8 mL, ca. 100 equiv) slowly at room temperature. The solution was heated to 50 °C and stirred vigorously for the specified period under Ar. The solution (suspension) was added slowly to 50 mL of ice−water, and the organic layer was separated. The aqueous layer was extracted with 1 mL of hexanes, and the combined organic layer was washed with brine, dried over Na_2SO_4, and diluted to 10 mL to give a solution for quantitative analysis. The yield of **1**−**4** was estimated by GC in the presence of internal standards (*p*-bromochlorobenzene for **1**, bibenzyl for **3**, and 1-(diphenylmethyl)-4-nitrobenzene for **2** and **4**).

(13) Ungnade, H. E.; Crandall, E. W. *J. Am. Chem. Soc.* **1949**, *71*, 2209−2210.

Acid-Catalyzed Reaction of Diphenylmethanol (6) with Benzene. To a solution of **6** (184 mg, 1.0 mmol) in dry benzene (39 g, 500 mmol) was added TFSA (8.8 mL, 100 mmol) dropwise for 1 min at 5 °C. The heterogeneous suspension was stirred vigorously for 10 min at 5 °C. The suspension was added slowly to 200 mL of ice−water and extracted with 200 mL of CH_2Cl_2. The organic layer was separated, washed with brine, dried over Na_2SO_4, and evaporated to give a pale yellow solid. The residue was purified by column chromatography (hexanes to hexanes:AcOEt = 10:1) to give 190 mg (0.78 mmol, 78%) of **2** as a colorless solid and 2 mg (0.02 mmol, 2%) of **3** as a colorless oil.

Acid-Catalyzed Reaction of Triphenylmethane (2) with Benzene. To a solution of **2** (244 mg, 1 mmol) in dry benzene (39 g, 500 mmol) was added TFSA (8.8 mL, 100 mmol) at room temperature. The heterogeneous red solution was stirred vigorously at 50 °C for 19 h under Ar. The solution was added slowly to 200 mL of ice water and extracted with 200 mL of CH_2Cl_2. The organic layer was separated, washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by column chromatography (hexanes to hexanes:AcOEt = 10:1) to give 86 mg (0.51 mmol, 51%) of **3** as a colorless oil and 119 mg (0.46 mmol, 46%) of **4** as a colorless powder.

NMR Observations. The aldehydes (10−15 mg, 0.1 mmol) were dissolved in 0.9 mL (10 mmol, 100 equiv) of TFSA or TFSA-*d*, and the solutions were heated to 50 °C in NMR tubes. External CH_2Cl_2 in TFSA was used as the external standard (5.33 ppm). Data for **1:** ^{1}H NMR (TFSA-*d*, 30 °C) δ 9.71 (s, 1 H), 8.58 (br s, 2 H), 8.42 (t, 1 H, J = 7.6 Hz), 7.97 (t, 2 H, J = 7.8 Hz). Data for 4-fluorobenzaldehyde: ^{1}H NMR (TFSA, 30 °C) δ 9.61 (s, 1 H), 8.6−8.7 (br d, 2 H), 7.61 (t, 2 H, J = 8.5 Hz). Data for 2-fluorobenzaldehyde: ^{1}H NMR (TFSA, 30 °C) δ 9.92 (s, 1 H), 8.4−8.5 (m, 2 H), 7.71 (t, 1 H, J = 7.8 Hz), 7.56 (t, 1 H, J = 9.3 Hz).

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