Influence of Conformation and Proton-Transfer Dynamics in the Dibenzyl σ-Complex on Regioselectivity in Gattermann−Koch Formylation via Intracomplex Reaction

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The Gattermann−Koch formylations of diphenyl, diphenylmethane, dibenzyl, and 1,3-diphenylpropane were studied in HF−SbF_5, −TaF_5, −BF_3, −NbF_5, and CF_3SO_3H−SbF_5. While usual high *para* regioselectivity was obtained for diphenyl, diphenylmethane, and 1,3-diphenylpropane, unprecedented *ortho* regioselectivity was observed for dibenzyl which increased with decreasing the SbF_5/dibenzyl molar ratio and with strength of Lewis acids used in HF. A sandwich-like complex for monoprotonated dibenzyl resulting in *ortho* regioselectivity via the intracomplex reaction was suggested; therefore, the conformations of protonated diphenylmethane, dibenzyl, and 1,3-diphenylpropane and their proton-transfer dynamics were probed by semiempirical calculation (PM3). The calculation predicted that *ortho* monoprotonation was slightly preferable for dibenzyl, and remarkable preference of dibenzyl over other aromatic compounds was observed in *ortho*−*ortho* intramolecular inter-ring proton transfer via a fan-shaped complex rather than a sandwich-like complex. The experimental and theoretical data for dibenzyl are compatible with the intracomplex reaction, whereby CO is protonated by the *ortho* σ-complex undergoing rapid inter-ring proton transfer to generate formyl cation in the vicinity of the *ortho* position leading to *ortho* regioselectivity.

Introduction

Electrophilic aromatic substitution is a widely used classical method to prepare various aromatic compounds.[1] As shown in eq 1, the conventional aromatic substitution is known to consist of four steps, which are (1) formation of an electrophile (E^+) from a proelectrophile (P) through activation by a Brønsted or Lewis acid (A), (2) attack of the electrophile on an aromatic compound (ArH) forming a π-complex, (3) transition of the π-complex to a σ-complex, and (4) loss of proton from the σ-complex to give the product.

$$P + A \longrightarrow E^+ \overset{ArH}{\rightleftharpoons} \underset{\pi\text{-complex}}{[ArH{\bullet}E^+]} \longrightarrow \underset{\sigma\text{-complex}}{[ArHE^+]} \longrightarrow ArE + H^+ \quad (1)$$

In the conventional aromatic substitution, the formation and the attack of the electrophile are separate steps. The electrophile is formed and dispersed in the reaction medium before the attack on an aromatic compound. However, Cacace et al. recently suggested that an alternative route, the intracomplex reaction eq 2, is possible, whereby the electrophilic substitution occurs within the complex formed upon addition of a σ-complex to the proelectrophile.[2]

In eq 2, a protonated aromatic compound (ArH_2^+) acts as an acid to activate proelectrophile P to electrophile E^+. On the other hand, it has been reported that the

$$ArH_2^+ + P \longrightarrow [ArH_2^+{\bullet}P] \rightleftharpoons \underset{\pi\text{-complex}}{[ArH{\bullet}E^+]} \longrightarrow \underset{\sigma\text{-complex}}{[ArHE^+]} \longrightarrow ArE + H^+ \quad (2)$$

common factors such as electron density of the aromatic substrate,[3] reactivity of electrophiles,[4] stability of the reaction intermediates,[5] and steric factors[6] may influence the regioselectivity.[7]

The Gattermann−Koch formylation[8] has been considered as a typical electrophilic aromatic substitution with high *para* regioselectivity.[9] In previous work,[10] it was found, however, that the regioselectivity of 1-methylnaphthalene formylation in HF−SbF_5 drastically changes

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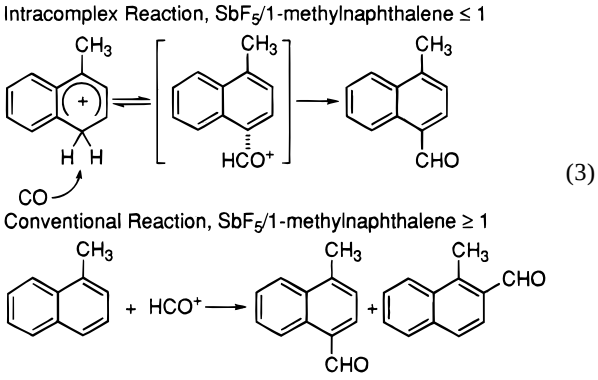
Table 1. Formylation of Dibenzyl in HF−SbF_5[a]

SbF_5/dibenzyl molar ratio	yields (%) for		regioselectivity (%) for		
	mono-aldehyde[c]	dialdehyde[d]	*ortho*	*meta*	*para*
0.25[b]	23 (72:2:26)	0	72	2	26
0.5[b]	38 (60:2:38)	6 (24:9:67)	52	2	46
0.75[b]	40 (50:2:48)	17 (14:9:77)	36	1	63
1.0[b]	38 (48:2:50)	26 (15:9:76)	32	1	67
1.25[b]	45 (37:3:60)	37 (10:9:81)	23	1	76
1.5[b]	45 (39:3:58)	51 (11:10:79)	23	1	76
1.75[b]	37 (39:3:58)	62 (11:11:78)	21	1	78
2.0[b]	2 (44:0:56)	96 (7:8:85)	11	0	89
2.5	0	97 (6:3:91)	7	0	93
3.0	0	95 (6:2:92)	7	0	93

[a] The formylation was carried out with HF (500 mmol) and dibenzyl (10 mmol) under 20 atm of CO pressure at 0 °C for 2 h. The regioselectivity (%) presents the total of mono- and dialdehyde regioselectivity. [b] Unreacted dibenzyl was recovered. [c] Isomer ratio of *o*-:*m*-:*p*-formyldibenzyl. [d] Isomer ratio of *o,o′*-:*o,p′*-:*p,p′*-diformyldibenzyl.

depending on the SbF_5/1-methylnaphthalene molar ratio. The kinetic study[10,11] showed that the change in regioselectivity is caused by the reaction path transfer depending on the SbF_5/1-methylnaphthalene molar ratio between the intracomplex and the conventional reactions, where the intracomplex reaction reflecting the structure of the σ-complex as a reaction precursor gives only 1-methyl-4-naphthaldehyde (eq 3).



(3)

This paper reports the regioselectivity of the intracomplex reaction in the Gattermann−Koch formylation reflecting not only the structure but also the proton-transfer dynamics of the σ-complex as a reaction precursor.

Results and Discussion

Formylation Studies. We previously reported that the formylation of diphenyl, diphenylmethane, and dibenzyl gives their corresponding dialdehydes with high *para* regioselectivity in HF−SbF_5.[9d,e] However, it was found that the regioselectivity of dibenzyl formylation changed from *ortho* to *para* with an increase in the SbF_5/dibenzyl molar ratio as shown in Table 1.[12] When the SbF_5/dibenzyl molar ratio was less than 2, the reaction mixture was heterogeneous. Therefore, to evaluate the influence of heterogeneous conditions on the regioselectivity, the formylation was conducted using various amounts of HF as listed in Table 2. When the SbF_5/dibenzyl molar ratio was less than 2, *ortho* regioselectivity increased with increasing the amount of HF, namely, with the dissolution of dibenzyl into HF−SbF_5. On the other hand, such tendency was not observed under the homogeneous conditions where the SbF_5/dibenzyl molar ratio was 2.5. These results indicate that the *ortho* regioselectivity is enhanced by the low SbF_5/dibenzyl molar ratio, but not by the heterogeneous conditions. When the SbF_5/dibenzyl molar ratio is less than 2, dibenzyl is mono- and diprotonated to be in an equilibrium condition between mono- and dications. As the ratio of monocation decreases with the SbF_5/dibenzyl molar ratio, the monocation seems to favor the *ortho* regioselectivity. The kinetic study[10] suggests that the intracomplex reaction can be predominant when the SbF_5/dibenzyl molar ratio is less than 2 because dibenzyl has two aromatic rings being almost chemically independent of each other.[9e] Taking into account the three-order equation containing two aromatic molecules for the intracomplex formylation,[10] two types of σ-complexes[13] as a reaction precursor are conceivable in the case of dibenzyl monocation, which are (1) the σ-complex comprised of two dibenzyls and one HF·SbF_5 and (2) the σ-complex comprised of one dibenzyl and one HF·SbF_5 to form a sandwich-like complex. The former σ-complex apparently will show high *para* regioselectivity, but the latter one seems to show *ortho* regioselectivity because the proton to produce formyl cation is located at the *ortho* position of dibenzyl (eq 4).

Table 2. Formylation of Dibenzyl in HF−SbF_5[a]

SbF_5/dibenzyl molar ratio	HF (mmol)	yields (%) for		regioselectivity (%) for		
		mono-aldehyde[c]	dialdehyde[d]	*ortho*	*meta*	*para*
1.0[b]	250	37 (36:2:62)	31 (12:9:79)	24	1	75
1.0[b]	500	38 (48:2:50)	26 (15:9:76)	32	1	67
1.0[b]	1000	46 (63:2:35)	23 (19:9:72)	43	1	56
1.25[b]	250	39 (30:2:68)	41 (10:9:81)	19	1	80
1.25[b]	500	45 (37:3:60)	37 (10:9:81)	23	1	76
1.25[b]	1000	45 (54:2:44)	37 (13:8:79)	31	1	68
2.5	250	0	97 (5:6:89)	8	0	92
2.5	500	0	97 (6:3:91)	7	0	93
2.5	1000	0	97 (5:3:92)	7	0	93

[a] The formylation was carried out with dibenzyl (10 mmol) under 20 atm of CO pressure at 0 °C for 2 h. The regioselectivity (%) presents the total of mono- and dialdehyde regioselectivity. [b] Unreacted dibenzyl was recovered. [c] Isomer ratio of *o*-:*m*-:*p*-formyldibenzyl. [d] Isomer ratio of *o,o′*-:*o,p′*-:*p,p′*-diformyldibenzyl.

The formation of such a sandwich-like complex has been suggested in several papers.[14] If the sandwich-like complex for the monocation is formed, the regioselectivity change in the dibenzyl formylation is explained by the change in ratio between mono- and dications depending on the SbF_5/dibenzyl molar ratio resulting in *ortho* and *para* regioselectivity, respectively (eq 4).[15] However, attempts to detect the sandwich-like complex by NMR failed.[16]

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(12) In control experiments, the elimination of the formyl group was not observed under the same conditions, and the regioselectivity for the formylation of monoformyldibenzyl was *para* about 90% in ratio.

(13) The σ-complex here is in equilibrium with the π-complex.

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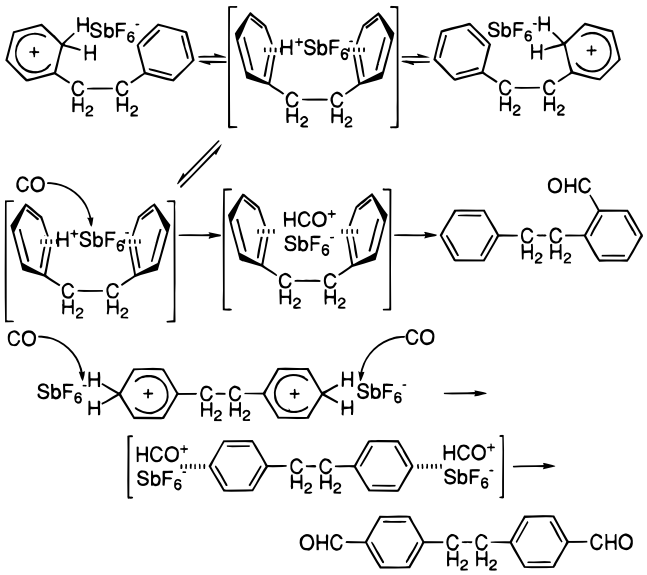
Table 3. Influence of Chain Length between Aromatic Rings on Formylation Regioselectivity[a]

substrate	yields (%) for mono-aldehyde[d]	yields (%) for dialdehyde[e]	regioselectivity (%) for *ortho*	*meta*	*para*
diphenyl	97 (0:0:100)	0	0	0	100
diphenyl[b]	15 (0:0:100)	77 (6:8:86)	9	0	91
diphenylmethane[c]	15 (2:0:98)	2 (0:0:100)	2	0	98
dibenzyl	38 (48:2:50)	26 (15:9:76)	32	1	67
1,3-diphenylpropane	50 (2:2:96)	24 (3:6:91)	4	1	95

[a] The formylation was carried out with HF (500 mmol), SbF_5 (10 mmol), and substrate (10 mmol) under 20 atm of CO pressure at 0 °C for 2 h. The regioselectivity (%) presents the total of mono- and dialdehyde regioselectivity. Unreacted substrate was recovered in all experiments. [b] The formylation was carried out with 25 mmol of SbF_5. [c] The cleavage of methylene chain occurred to give benzaldehyde.[9d,e] [d] Isomer ratio of *o*-:*m*-:*p*-formyldibenzyl. [e] Isomer ratio of *o*,*o*′-:*o*,*p*′-:*p*,*p*′-diformyldibenzyl.



(4)

To evaluate the existence of the sandwich-like complex, the formylation of various polynuclear aromatic compounds, in which the chain length between the aromatic rings differed, was conducted in HF−SbF_5. The results are summarized in Table 3. *Ortho* regioselectivity was observed only during dibenzyl formylation. This result clearly shows that only the distance between two aromatic rings of dibenzyl is appropriate for the formation of the sandwich-like complex leading to *ortho* regioselectivity. For diphenyl, the reaction mixtures were heterogeneous similar to dibenzyl when the SbF_5/diphenyl molar ratio was less than 2. As shown in Table 3, although only *para* formyldiphenyl was formed under heterogeneous conditions, both *ortho* and *para* formyldiphenyl were produced under homogeneous conditions. This result also supports that the heterogeneous conditions do not favor the *ortho* regioselectivity as mentioned before.

Table 4. Influence of Acidity of Formylation Regioselectivity[a]

Lewis acid	yields (%) for mono-aldehyde[b]	yields (%) for dialdehyde[c]	regioselectivity (%) for *ortho*	*meta*	*para*
SbF_5	38 (48:2:50)	26 (15:9:76)	32	1	67
TaF_5	45 (48:1:51)	26 (12:6:82)	30	1	69
BF_3	34 (41:1:58)	18 (9:6:85)	26	1	73
NbF_5	28 (23:2:75)	7 (6:6:88)	18	1	81

[a] The formylation was carried out with HF (500 mmol), Lewis acid (10 mmol), and dibenzyl (10 mmol) under 20 atm of CO pressure at 0 °C for 2 h. The regioselectivity (%) presents the total of mono- and dialdehyde regioselectivity. Unreacted dibenzyl was recovered in all experiments. [b] Isomer ratio of *o*-:*m*-:*p*-formyldibenzyl. [c] Isomer ratio of *o*,*o*′-:*o*,*p*′-:*p*,*p*′-diformyldibenzyl.

Table 5. Formylation of Dibenzyl in CF_3SO_3H−SbF_5[a]

SbF_5/dibenzyl molar ratio	yields (%) for mono-aldehyde[b]	yields (%) for dialdehyde[c]	regioselectivity (%) for *ortho*	*meta*	*para*
0.5	25 (14:1:85)	2 (0:0:100)	12	1	87
1.0	35 (12:1:87)	3 (4:5:91)	11	1	88
2.0	17 (20:1:79)	26 (5:4:91)	10	0	90
3.0	2 (34:0:66)	33 (10:4:86)	13	0	87

[a] The formylation was carried out with CF_3SO_3H (200 mmol) and dibenzyl (10 mmol) under 20 atm of CO pressure at 0 °C for 2 h. The regioselectivity (%) presents the total of mono- and dialdehyde regioselectivity. Unreacted substrate was recovered in all experiments. [b] Isomer ratio of *o*-:*m*-:*p*-formyldibenzyl. [c] Isomer ratio of *o*,*o*′-:*o*,*p*′-:*p*,*p*′-diformyldibenzyl.

To investigate the influence of acidity on the regioselectivity, dibenzyl formylation was carried out using various Lewis acids in HF. The results are tabulated in Table 4. The order of acidities are $SbF_5 > TaF_5 > BF_3 > NbF_5$.[17] *Ortho* regioselectivity decreased with a decrease in the acidity of the Lewis acids, namely, with a decrease in the coordination ability of superacids to form the sandwich-like complex. This tendency in regioselectivity depending on the stability of the sandwich-like complex is consistent with the notion that regioselectivity of the intracomplex reaction reflects the structure of the σ-complex as a reaction precursor.[10]

When dibenzyl formylation was carried out with CF_3SO_3H−SbF_5 instead of HF−SbF_5, a regioselectivity change was not observed as tabulated in Table 5. CF_3SO_3H−SbF_5 is well-known to be a far weaker acid than HF−SbF_5,[17a,b] but the acidity of CF_3SO_3H itself is strong enough to make the Gattermann−Koch formylation occur.[18] Therefore, the formylation in CF_3SO_3H−SbF_5 does not proceed via the sandwich-like complex regardless of the SbF_5/dibenzyl molar ratio.

Theoretical Studies. To evaluate the preference of dibenzyl over other aromatic compounds to form the sandwich-like complex in view of experimental results, the protonation energies and conformations were examined for diphenylmethane, dibenzyl, and 1,3-diphenylpropane by semiempirical calculations (PM3 in Hyperchem and GAMESS[19]). The calculation was performed not only for *ortho* and *para* σ-complexes but also for the *ipso* σ-complex because the *ipso* σ-complex can be another

(15) Protonation usually occurs at the *para* position of a substituent. (a) Olah, G. A.; Schlosberg, R. H.; Porter, R. D.; Mo, Y. K.; Kelly, D. P.; Mateescu, G. D. *J. Am. Chem. Soc.* **1972**, *94*, 2034. (b) Olah, G. A.; Mateescu, G. D.; Mo, Y. K. *J. Am. Chem. Soc.* **1973**, *95*, 1865. (c) Olah, G. A.; Staral, J. S.; Asencio, G.; Liang, G.; Forsyth, D. A.; Mateescu, G. D. *J. Am. Chem. Soc.* **1978**, *100*, 6299.

(16) Attempts to detect the sandwich-like complex in HF−SbF_5 and CF_3SO_3H−SbF_5 at various temperatures by NMR resulted in the observation of broad peaks which merged with baselines. This result indicates that the sandwich-like complex is in protonation equilibrium and has both π- and σ-complex natures.

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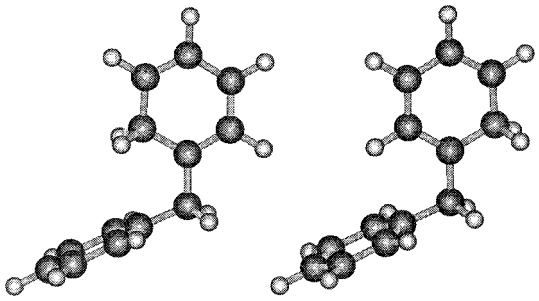


Figure 1. Conformations of *ortho* diphenylmethane σ-complexes (O^+, left; O^-, right).

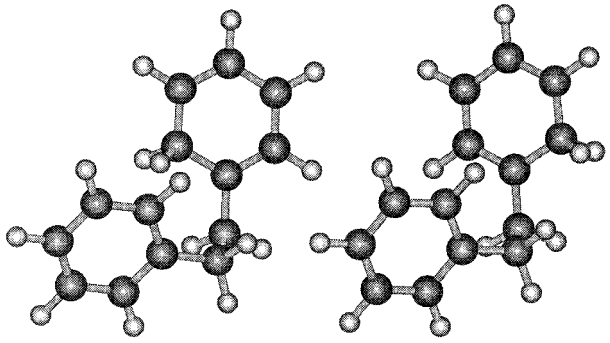
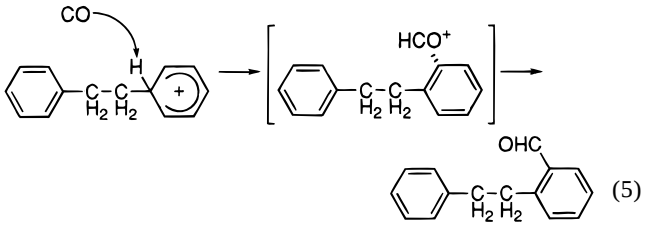


Figure 2. Conformations of *ortho* dibenzyl σ-complexes (O^+, left; O^-, right).

reaction precursor resulting in *ortho* regioselectivity in the intracomplex formylation (eq 5).



(5)

For diphenylmethane, the calculation predicted that *para* σ-complex was slightly favored over *ortho* σ-complex (0.2 kcal/mol) and that formation of *ipso* σ-complex was least favorable (10.1 kcal/mol). There were two minimum-energy conformations for the *ortho* σ-complex both having a 90° ring−ring torsional angle (perpendicular π-faces) with the protonated site pointing toward the opposite ring (O^+) and away from it (O^-), respectively (Figure 1), where O^+ was preferred by about 1.5 kcal/mol. For dibenzyl, *ortho* σ-complex was slightly favored over *para* σ-complex (1.0 kcal/mol) in contrast with diphenylmethane. *Ipso* σ-complex again was least favorable (9.5 kcal/mol). There were two minimum-energy conformations, O^+ and O^-, for the *ortho* σ-complex (Figure 2) similar to diphenylmethane. This was at ca. ±75° ring−ring dihedral angle, again with the protonated site pointing toward the opposite ring (O^+) being favored by about 1.4 kcal/mol. The cofacially constrained *para* σ-complex, a sandwich-like complex, was about 4.2 kcal/mol higher in energy compared to the unconstrained *para* σ-complex, a fan-shaped complex. For 1,3-diphenylpropane, *ortho* σ-complex was more favorable than *para* σ-complex with 0.8 kcal/mol difference in energy. The calculation results for diprotonation of dibenzyl showed that *para*−*para* diprotonation was favored over *para*−*ortho* (1.9 kcal/mol) and *ortho*−*ortho* (4.0 kcal/mol) diprotonation. The calculation results for protonation energies suggest that *ortho* monoprotonation is slightly preferable for dibenzyl and 1,3-diphenylpropane which is unusual in σ-complexes in superacids.[15] The interaction among proton and two aromatic rings, namely, a kind of cation−π interaction,[20] seems to favor the fan-shaped structure for coordination with *ortho* protonation.

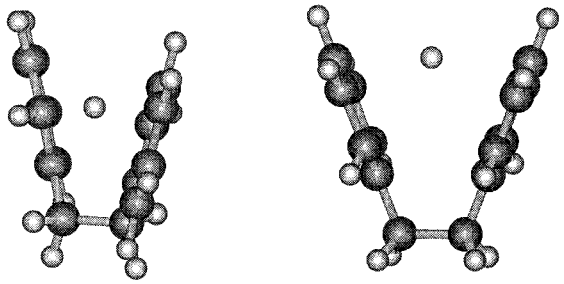


Figure 3. Transition conformations for $O^+ \rightarrow O'^+$ (left) and P → P′ (right) inter-ring proton transfer.

To evaluate the formation step of formyl cation, we scrutinized the transition-state energies for proton transfer at the PM3 level. *Ortho*−*ortho* and *para*−*para* inter-ring proton transfers were considered. As *ortho*−*para* inter- and intra-ring proton transfers were clearly unfavorable intuitively in view of a long-distance proton transfer, these processes were not considered. Transition-state modeling for diphenylmethane showed that the transition barriers for *ortho*−*ortho* ($O^+ \rightarrow O'^+$) and *para*−*para* (P → P′) inter-ring proton transfer were 12.6 and 31.3 kcal/mol, respectively. The result suggests that the proton transfer is unlikely to influence the formylation in view of the protonation energy for the *ipso* σ-complex, although *ortho*−*ortho* inter-ring proton transfer is significantly favorable over *para*−*para* inter-ring proton transfer. In the case of dibenzyl, the barriers for *ortho*−*ortho* and *para*−*para* inter-ring proton transfer were 3.3 and 26.2 kcal/mol, respectively, where the transition barrier for *ortho*−*ortho* inter-ring proton transfer was remarkably low. The transition conformations for $O^+ \rightarrow O'^+$ and P → P′ inter-ring proton transfer are shown in Figure 3, where the proton in *ortho*−*ortho* inter-ring transfer is closer to aromatic rings compared with that in *para*−*para* inter-ring transfer. The *ortho*−*ortho* inter-ring proton transfer occurred within a fan-shaped complex (ring−ring dihedral angle 75°) rather than a sandwich-like complex discussed before. To visually understand the proton-transfer dynamics in the dibenzyl σ-complex, a potential energy diagram is depicted in Figure 4 for intra-ring, inter-ring, and intra-ring/inter-ring proton-transfer pathways involving the *ortho* (O^+ and O^-) and *ipso* (I) σ-complexes. Proton transfers via the *ipso* σ-complex, which was higher in energy than the *ortho* σ-complex, were more energy demanding. On the other hand, 1,3-diphenylpropane showed that the barrier for *ortho*−*ortho* inter-ring proton transfer was 21.7 kcal/mol, and that for *para*−*para* inter-ring proton transfer was not available because of difficulty in convergence,

(19) Schmidt, M. W.; Baldridge, K. K.; Boatz, J. A.; Elbert, S. L.; Gordon, M. S.; Jensen, J. J.; Koseki, S.; Matsunaga, M.; Nguyen, K. A.; Su, S.; Windus, T. L.; Dupuis, M.; Montgomery, J. A. *J. Comput. Chem.* **1993**, *14*, 1347.

(20) Dougherty, D. A. *Science* **1996**, *271*, 163.

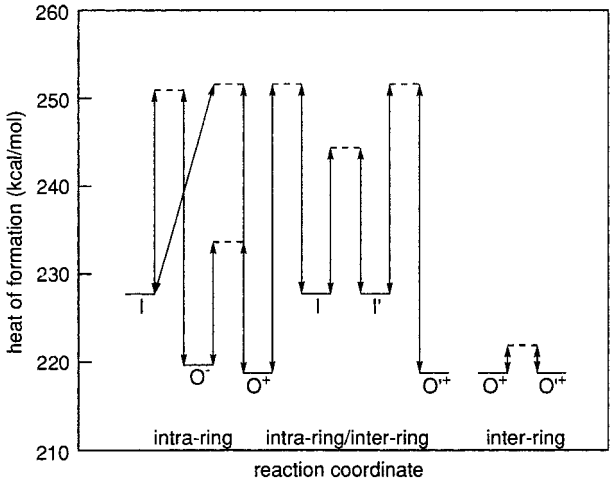


Figure 4. Potential energy profile for various proton-transfer processes in *ortho* and *ipso* dibenzyl σ-complexes.

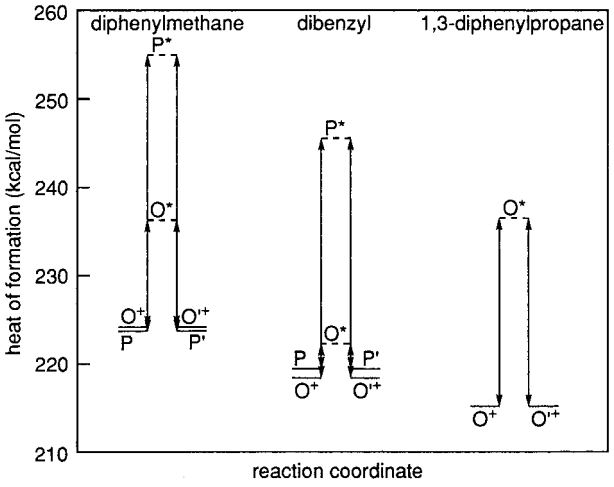


Figure 5. Potential energy profile for $O^+ \rightarrow O'^+$ and P → P′ inter-ring proton transfer. O* and P* represent transition states for $O^+ \rightarrow O'^+$ and P → P′ inter-ring proton transfer, respectively.

namely, a high barrier. The calculation results for the proton-transfer barriers summarized in Figure 5 show that only *ortho*−*ortho* inter-ring proton transfer for dibenzyl is a likely path. The mobility of the proton between two rings in the *ortho* dibenzyl σ-complex can make the *ortho* σ-complex more reactive to form formyl cation than the *para* σ-complex according to the intracomplex features.[2]

Conclusions

Taking together the experimental and theoretical results, it seems quite probable that in accord with eq 4, CO is protonated by the *ortho* dibenzyl σ-complex undergoing rapid inter-ring proton transfer to generate a formyl cation in the vicinity of the *ortho* position, leading to high *ortho* regioselectivity through the intracomplex mechanism. While the experimental study suggests influence of the conformation of the σ-complex as a reaction precursor on the regioselectivity, the theoretical study points that the crucial step to determine the regioselectivity is in the proton-transfer dynamics to produce the formyl cation. These results show that the specific features of the intracomplex reaction are in the proton-transfer dynamics itself being consistent with Cacace's concept.[2]

Experimental Section

All materials were of the highest available purity and used without further purification. HF and CF_3SO_3H contained 0.1 and 5 mol % H_2O, respectively. H_2O was considered to form $H_2O{\cdot}SbF_5$ quantitatively as an inert additive. The identification of products was performed by NMR (^1H and ^{13}C NMR, H−H COSY, C−H COSY, and COLOC) and MS after separation by distillation, recrystallization, and HPLC. The yields were determined by GC, and the isomer distributions were determined by GC and NMR.

Gattermann−Koch Formylation Procedures. Substrate (10 mmol) was added to a solution of Lewis acids with HF or CF_3SO_3H in a Hastelloy autoclave (100 mL) equipped with a Hastelloy magnetic stir bar under temperature control. The autoclave was sealed, and CO (20 atm) was introduced with vigorous stirring. After the reaction was over, the autoclave was depressurized and opened. The reaction was quenched with ice−water and extracted with benzene.

1,3-Diphenylpropane Preparation Procedures. 1,3-Dichloropropane (50 mmol, 5.65 g) was slowly added to a slurry of $AlCl_3$ (100 mmol, 13.3 g) in benzene (150 mL) at room temperature. After 2 h, the reaction mixture formed two liquid phases. The supernatant fraction was separated and washed with water. After evaporation of benzene, 1,3-diphenylpropane was separated by vacuum distillation.

NMR Study Procedures. Dibenzyl (10 mmol, 1.82 g) was added to a solution of various amounts of SbF_5 in HF (500 mmol, 10.0 g) or CF_3SO_3H (200 mmol, 30.0 g) in a Teflon round-bottom flask (300 mL) at 0 °C with stirring. A portion of the solution was transferred to a 5-mm Teflon NMR sample tube with a Teflon pipet, and then, the tube was sealed with a Teflon stopper. The NMR measurements were performed according to the procedures in ref 11a.

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