The influence of aromatic compound protonation on the regioselectivity of Gattermann–Koch formylation

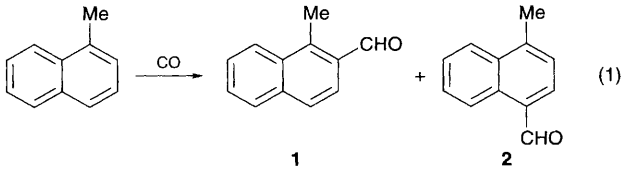
Mutsuo Tanaka,*[a] Masahiro Fujiwara,[a] Hisanori Ando[b] and Yoshie Souma[a]

[a] *Osaka National Research Institute, AIST, 1-8-31, Midorigaoka, Ikeda, Osaka, 563, Japan*
[b] *Research Institute of Innovative Technology for the Earth, 9-2, Kizugawadai, Kizucho, Soraku-gun, Kyoto, 619-02, Japan*

The regioselectivity of the Gattermann–Koch formylation is influenced by the protonation of aromatic compounds under a solvent-cage-like atmosphere.

Electrophilic substitution of aromatic compounds is a very common reaction. It has, however, a serious regioselectivity problem in that it produces a mixture of isomers which are difficult to separate. It has been reported that the regioselectivity of electrophilic aromatic substitution is controlled by the electron density of aromatic rings,[1] the nature of the electrophiles and substrates[2] and steric hindrance[2a] depending on the reaction type. On the other hand, Gattermann–Koch formylation[3] is known to show high regioselectivity[4] as observed in our previous studies.[5] Methylnaphthalenes are the only exception, showing a low regioselectivity in formylation using HF–SbF_5.[5c] This prompted us to study the regioselectivity of the Gattermann–Koch formylation and here we propose a new factor that influences the regioselectivity.

In order to investigate the reason why methylnaphthalenes showed such a low regioselectivity, the formylation of 1-methylnaphthalene using various compositions of HF–SbF_5 was carried out. The regioselectivity for the monoaldehyde only was examined because the dialdehyde is a secondary product. The formylation gave two monoaldehydes, 1-methyl-2-naphthaldehyde **1** and 4-methyl-1-naphthaldehyde **2** [eqn. (1)].



(1)

1 **2**

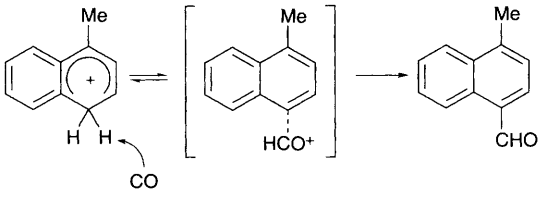
Surprisingly, the regioselectivity drastically changed at the point where the SbF_5/1-methylnaphthalene molar ratio was 1 and **1**:**2** was 0:1 or 3:7 as shown in Fig. 1. In control experiments, the formyl group did not migrate under these conditions.

To explain the regioselectivity change, we considered two factors: (i) the nature of formyl cation and (ii) the protonation of aromatic compounds. Recently, the existence of a dication as a real electrophile in electrophilic aromatic substitutions is proposed when strong acidity is needed to allow the reaction to occur.[6] Taking into account the protonation equilibrium of aromatic compounds in superacid,[7] the formyl cation in the HF–SbF_5 system seems to be a mono- or di-cation depending on the SbF_5/1-methylnaphthalene molar ratio which is less or greater than 1.

SbF_5/1-methylnaphthalene $\leqslant$ 1 SbF_5/1-methylnaphthalene $\geqslant$ 1

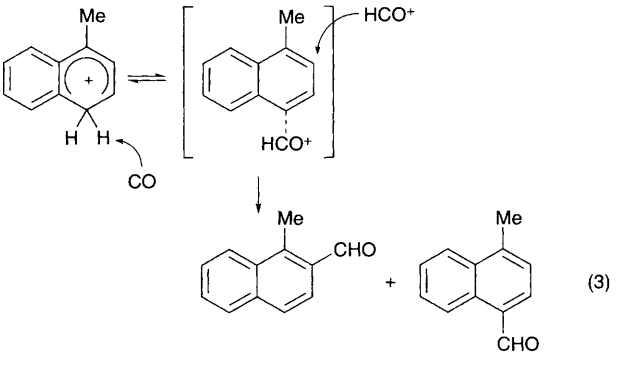
$$HCO^+ \underset{-H^+}{\overset{H^+}{\rightleftharpoons}} HCOH^{2+}$$

If the regioselectivity change is derived from the difference in the formyl cation nature, *i.e.* mono- or di-cation, the regioselectivity at the 4-position of 1-methylnaphthalene should be exclusively high for the monocation but low for the dication as shown in Fig. 1. On the other hand, taking into account the dual reactivity of the formyl cation as an electrophile and as a Brønsted acid,[8] the formation of the σ-complex, which has the ability to produce a formyl cation, seems to influence the regioselectivity when the formylation proceeds through the protonation equilibrium with the aromatic compound, CO and the superacid, namely, under a solvent-cage-like atmosphere.[9] It has been reported that the protonation of 1-methylnaphthalene occurs at the 4-position of 1-methylnaphthalene[10] and therefore the produced formyl cation with the protonated 1-methylnaphthalene probably exists close to the 4-position of 1-methylnaphthalene resulting in high regioselectivity at that position, [eqn. (2)]. On the other hand, when the formyl cation is formed



(2)

by both the σ-complex and the superacid, the formylation may show regioselectivity at both the 4- and 2-positions of 1-methylnaphthalene because the formyl cation produced by the superacid is free from the solvent-cage restriction, [eqn. (3)].



(3)

According to this hypothesis and the protonation equilibrium,[6,8] the regioselectivity change can be explained as follows. In the case of the HF–SbF_5 system, the formylation does not occur in the absence of SbF_5.[5b,c] Therefore, the formyl cation was formed by the σ-complex with HF·SbF_5 to give the high regioselectivity at the 4-position when the SbF_5/1-methylnaphthalene molar ratio was less than 1. On the other hand, the formyl cation was produced by both the σ-complex with HF·SbF_5 and HF·SbF_5 to form 1-methyl-2- and 4-methyl-1-naphthaldehyde when the SbF_5/1-methylnaphthalene molar ratio was greater than 1.

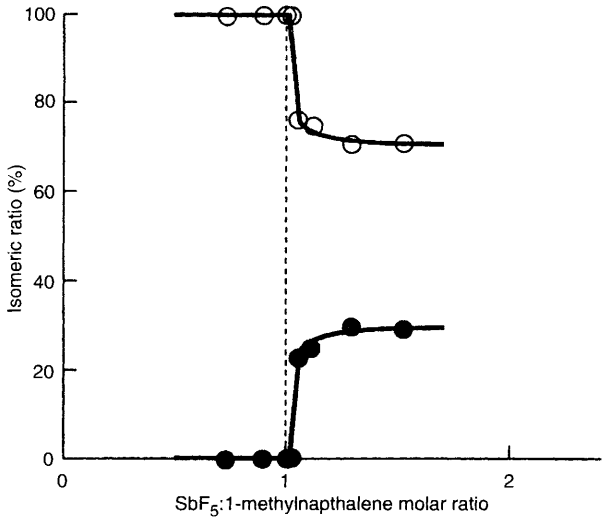
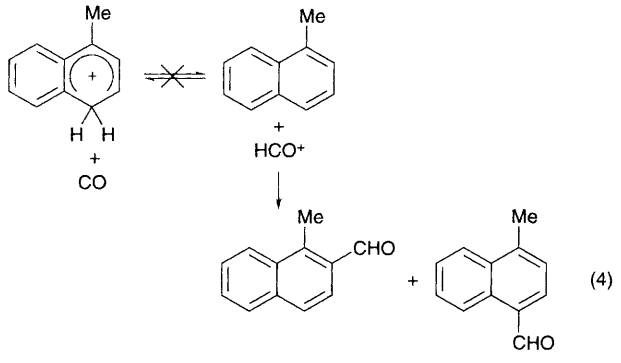


Fig. 1 Isomeric distribution of monoaldehyde. The formylation was carried out using HF (500 mmol) and 1-methylnaphthalene (10 mmol) with CO (20 atm) at 0 °C for 2 h. ● and ○ represent **1** and **2** respectively.

In order to clarify which factor causes the regioselectivity change of the Gattermann–Koch formylation, the formylation of 1-methylnaphthalene in HF–SbF_5 using HCOF[11] instead of CO was carried out and the regioselectivity of the HCOF formylation was compared with that of the Gattermann–Koch formylation. The HCOF formylation clearly poceeds without the formation of CO, namely, the formyl cation produced from HCOF immediately reacts with 1-methylnaphthalene without the protonation equilibrium among 1-methylnaphthalene, CO and superacid,[8,†] [eqn. (4)]. These experiments reveal the



(4)

significant difference in the regioselectivity as shown in Table 1, and in the case of the HCOF formylation, the regioselectivity was constant regardless of the SbF_5/1-methylnaphthalene molar ratio. When the SbF_5/1-methylnaphthalene molar ratio was 2, the formyl cation seems to be a dication because most of the 1-methylnaphthalene is protonated[7] and excess amounts of SbF_5 are found. Therefore, we concluded that the regioselectivity change was caused by the protonation of aromatic compounds.‡ When the SbF_5/1-methylnaphthalene molar ratio was 1, the HCOF formylation showed regioselectivity not only at the 4-position but also at the 2-position although the Gattermann–Koch formylation showed regioselectivity only at the 4-position of 1-methylnaphthalene. When the SbF_5/1-methylnaphthalene molar ratio was 1.25, the regioselectivity at the 4-position was lower in the Gattermann–Koch formylation than in the HCOF formylation. These results evidently suggest that the protonation of aromatic compounds in the Gattermann–Koch formylation directly influences the regioselectivity at the 4-position of 1-methylnaphthalene–an increase or decrease depending on the SbF_5/1-methylnaphthalene molar ratio.

Table 1 Formylation of 1-methylnaphthalene using HCOF or CO[a]

SbF_5 : substrate (molar ratio)	Reagent	T/°C	t	Yield of aldehyde (%)	**1**:**2**
1	HCOF	0	1 h	15	7:93
1.25	HCOF	0	1 h	45	6:94
1.25	HCOF	−40	1 h	33	6:94
2	HCOF	−40	1 h	50	6:94
1	CO	0	2 h	24	0:100
1.25	CO	0	10 min	12	32:68
1.25	CO	−40	2 h	13	36:64

[a] The formylation was carried out using HF (500 mmol) and 1-methylnaphthalene (10 mmol) with HCOF (80 mmol) or CO (20 atm). The formation of dialdehyde was not observed in these experiments.

Footnotes

† When HCOF was added to HF–SbF_5, a violent CO exhalation was observed. Only a trace amount of aldehyde was obtained when 1-methylnaphthalene was added to the solution. Furthermore, the Gattermann–Koch formylation produced only a trace amount of aldehyde under atmospheric CO pressure.

‡ We could not decide whether the nature of formyl cation was a monocation or a dication in this study.

References

1 S. Fukuzumi and J. K. Kochi, *J. Am. Chem. Soc.*, 1981, **103**, 7240.
2 (*a*) F. R. Jensen and H. C. Brown, *J. Am. Chem. Soc.*, 1958, **80**, 4046; (*b*) G. A. Olah and S. Kobayashi, *J. Am. Chem. Soc.*, 1971, **93**, 6964.
3 (*a*) L. Gattermann and J. A. Koch, *Chem. Ber.*, 1897, **30**, 1622; (*b*) G. A. Olah, *Friedel-Crafts and Related Reactions*, Wiley-Interscience, New York, vol. iii, 1964, 1153.
4 G. A. Olah, L. Ohannesian and M. Arvanaghi, *Chem. Rev.*, 1987, **87**, 671.
5 (*a*) M. Tanaka and Y. Souma, *J. Org. Chem.*, 1992, **57**, 2677; (*b*) M. Tanaka and Y. Souma, *J. Chem. Soc., Chem. Commun.*, 1991, 1551; (*c*) M. Tanaka, M. Fujiwara, H. Ando and Y. Souma, *J. Org. Chem.*, 1993, **58**, 3213.
6 (*a*) G. A. Olah, *Angew. Chem., Int. Ed. Engl.*, 1993, **32**, 767; (*b*) Y. Sato, M. Yato, T. Ohwada, S. Saito and K. Shudo, *J. Am. Chem. Soc.*, 1995, **117**, 3037.
7 M. Tanaka, M. Fujiwara and H. Ando, *J. Org. Chem.*, 1995, **60**, 2106.
8 M. Tanaka, M. Fujiwara and H. Ando, *J. Org. Chem.*, 1995, **60**, 3846.
9 G. A. Olah and R. J. Spear, *J. Am. Chem. Soc.*, 1975, **97**, 1845.
10 G. A. Olah, G. D. Mateescu and Y. K. Mo, *J. Am. Chem. Soc.*, 1973, **95**, 1865.
11 G. A. Olah and S. J. Kuhn, *J. Am. Chem. Soc.*, 1960, **82**, 2380.

Received, 1st August 1995; Com. 5/05131B