Pergamon

Tetrahedron Letters 41 (2000) 229–233

TETRAHEDRON
LETTERS

Mechanistic duality of the side-chain substitution in electrophilic aromatic nitration. Unexpected large difference in deuterium isotope effect k_H/k_D between the side-chain nitration and nitrooxylation of deuterated *p*-xylenes

Nobuaki Nonoyama, Masao Iwaya and Hitomi Suzuki *

Department of Chemistry, School of Science, Kwansei Gakuin University, Uegahara 1-1-155, Nishinomiya 662-8501, Japan

Received 17 September 1999; revised 25 October 1999; accepted 29 October 1999

Abstract

A large difference in deuterium kinetic isotope effect observed between the side-chain nitration and nitrooxylation of deuterated *p*-xylenes, 1,4-$(CH_3)(CD_3)C_6H_4$ and 1,4-$(CD_3)_2C_6D_4$, suggests the operation of different mechanisms for these two types of side-chain substitution. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: nitration; mechanisms; isotope effects; nitrogen oxides; nitrous acid derivatives.

When treated with nitrating agent, polymethylated benzenes in which at least one pair of methyl groups exists in *para* relationship often undergo side-chain substitution in parallel with ring nitration, affording arylnitromethane and arylmethyl nitrate as important byproducts.[1] Mechanistic aspects of these non-conventional reactions have been subject to much discussion, and opinions among researchers are still far from consensus.[2] Some proposed the heterolytic process that assumes methylenecyclohexadiene **1** as the intermediate for benzylic compounds (Eq. 1), while the other advocated the electron transfer process that involves radical cation **2** and benzylic radical **3** as the precursors to side-chain substitution products (Eq. 2).

We have recently developed a new nitration methodology based on nitrogen dioxide (NO_2) and ozone (*kyodai*-nitration), which converts a wide variety of aromatic compounds to the corresponding mononitro to polynitro derivatives under mild conditions and in high yield.[3] Nitrogen trioxide (NO_3) is proposed as the initial electrophile, which is highly electron-deficient and oxidizes aromatic substrates by one-electron transfer process. However, the *kyodai*-nitration of some polymethylbenzenes is rather complicated; nitration, nitrooxylation and oxidation of alkyl side-chain take place in parallel with ordinary ring nitration. This complication may be attributed largely to the versatility of NO_3 as the reagent

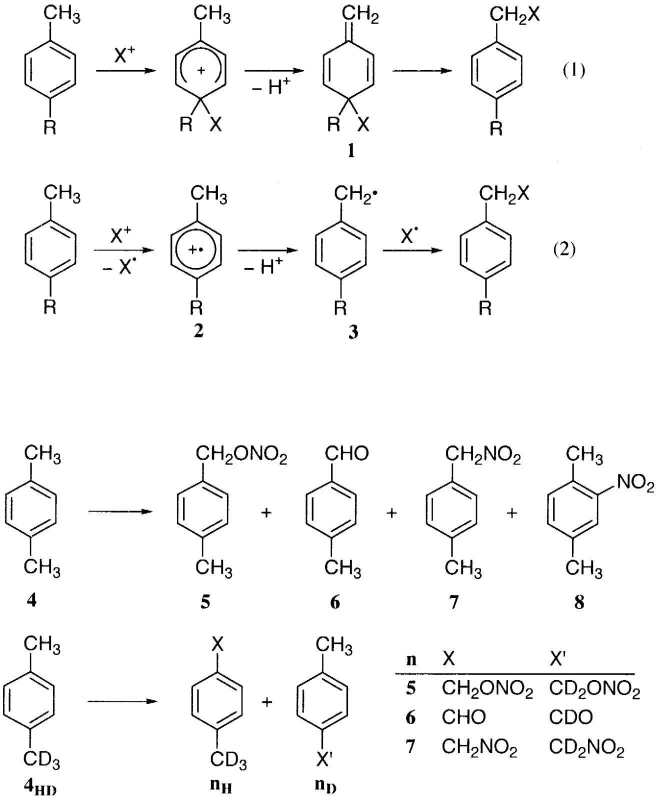
---

* Corresponding author. Fax: +81 798 51 0914; e-mail: hsuzuki@kwansei.ac.jp (H. Suzuki)

PII: S0040-4039(99)02053-5

to oxidize an aromatic substrate to a radical cation, to abstract a hydrogen from an alkyl side-chain to form a benzylic radical, or to add to an aromatic ring to form a cyclohexadienyl radical.

In order to look closer into the nature of these side-chain reactions, we have examined the inter- and intramolecular deuterium isotope effect of the *kyodai*-nitration of *p*-xylene at an early stage of the reaction. Thus, *p*-xylene **4** and its partially and fully deuterated derivatives 1,4-$(CH_3)(CD_3)C_6H_4$ $\mathbf{4_{HD}}$ and 1,4-$(CD_3)_2C_6D_6$ $\mathbf{4_{DD}}$ were nitrated under a variety of conditions and the product distributions were determined by HPLC, GC or ^{1}H NMR analysis. The reaction was quenched before complete disappearance of the substrates to avoid further transformation of the initial products. 2,6-Di-*tert*-butyl-4-methylpyridine was employed to examine the effect of a base catalyst. The major products were identified as 4-methylbenzyl nitrate **5**, *p*-tolualdehyde **6**, 4-methylphenylnitromethane **7**, and 2-nitro-*p*-xylene **8** (Scheme 1; Table 1). The minor products included 2,5-dinitro-*p*-xylene, 2-nitro-3,6-dimethylphenol, 2,6-dinitro-*p*-xylene, and unidentified highly polar substances in the decreasing order. Aldehyde **6** was probably a secondary product derived from the oxidative degradation of initially formed benzyl nitrite **12**.



n	X	X'
5	CH_2ONO_2	CD_2ONO_2
6	CHO	CDO
7	CH_2NO_2	CD_2NO_2

Scheme 1.

First, the intermolecular isotope effect v_H/v_D was examined for the consumption of substrates **4** and $\mathbf{4_{DD}}$ using the competition method and the results are summarized in Table 1. The observed value should reflect the relative contribution of the C–H/C–D bond rupture at substrate-determining stage, the large

Table 1
Isotope effect and yield in the nitration of *p*-xylene **4**

Entry	Reagents	Temp. /°C	Solvent	Intermolecular isotope effect[a,b] v_H/v_D	Intramolecular isotope effect k_H/k_D [b,c] (Conversion yield[d]/%) **$5_H/5_D$**	**$6_H/6_D$**	**$7_H/7_D$**	**8**	Conv.[d] /%
1	NO_2-O_3[e]	-70	CH_2Cl_2	1.37	4.4 (23)	4.6 (20)	1.3 (8)	– (3)	56
2	NO_2-O_3, Base[f]	-70	CH_2Cl_2	1.49	5.3 (39)	4.9 (43)	– (1)	– (<1)	41
3	NO_2-O_3	-10	CH_2Cl_2	1.11	3.5 (23)	2.9 (9)	1.6 (10)	– (19)	75
4	NO_2[g]	r.t.	CH_2Cl_2	1.34	3.0 (10)	2.5 (17)	3.0 (26)	– (12)	43
5	N_2O_5[h]	-70	CH_2Cl_2	1.05	1.0 (11)	– (<1)	1.3 (33)	– (19)	46
6	*fum*-HNO_3-Ac_2O[i]	-10	CH_2Cl_2	1.06	1.4 (22)	– (<1)	1.5 (14)	– (35)	79
7	*fum*-HNO_3-H_2SO_4[i]	-10	CH_2Cl_2	–	– (<1)	– (0)	– (0)	– (90)	61
8	CAN[j]	reflux	CH_3CN	1.78	2.7 (77)	– (<1)	– (<1)	– (11)	31

[a] All reactions were carried out using substrates **4** (1 mmol) and **4_{DD}** (1 mmol) in CH_2Cl_2 (20 cm^3). These values were calculated by comparing the relative consumption rates at initial stage of the reaction (conversion below 20%).
[b] Maximum errors were within 10% of the given values.
[c] The reactions were performed using a solution of substrate **4_{HD}** (1 mmol) in CH_2Cl_2 (10 cm^3).
[d] All products are known. Product distributions were determined by HPLC.
[e] Nitrogen dioxide (10 mmol) and ozone (10 mmol h^{-1}) were introduced over 5 min.
[f] 2,6-Di-*tert*-butyl-4-methylpyridine (0.5 mmol) was added.
[g] NO_2 (10 mmol) was used under oxygen.
[h] N_2O_5 (*ca.* 0.5 mmol) was generated from NO_2 and O_3 in CH_2Cl_2 at -20 °C.
[i] A mixture of two reagents and CH_2Cl_2 (3 cm^3) was added dropwise over 5 min.
[j] Substrate **4** (2 mmol) was reacted with CAN (4 mmol) in MeCN (30 cm^3).

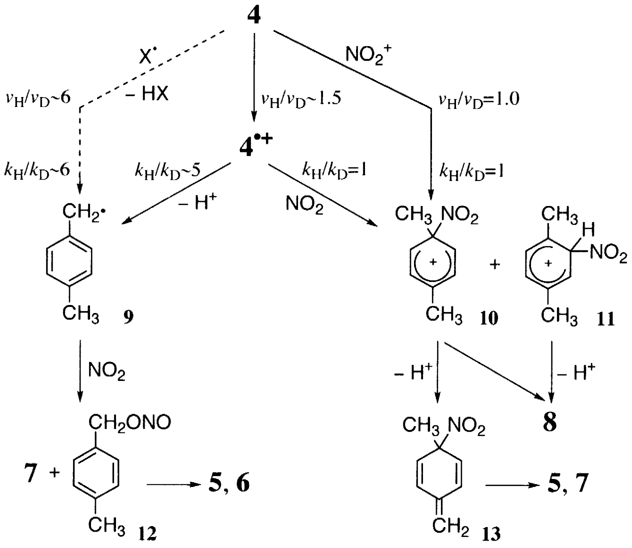
values supporting direct abstraction of hydrogen by an attacking species.[†] In the *kyodai*-nitration, the intermolecular isotope effect lies in the range 1.11–1.49, which rules out the possibility of direct hydrogen abstraction by a NO_3 radical as well as direct insertion of a NO_2 moiety into the C–H bond of alkyl side-chain. The back electron transfer may contribute somewhat to the apparent increase of the intermolecular isotope effect.[4]

The intramolecular isotope effect values k_H/k_D of the respective side-chain reactions, *i.e.* nitrooxylation **$5_H/5_D$**, oxidation **$6_H/6_D$** and nitration **$7_H/7_D$**, were obtained from the *kyodai*-nitration of partially deuterated *p*-xylene **1_{HD}**. A large isotope effect observed in the side-chain nitrooxylation **$5_H/5_D$**=3.5–5.3 and oxidation **$6_H/6_D$**=2.9–4.9 is highly indicative of the bond rupture at site-determining stage. These values are large enough to overshadow the temperature dependence of the isotope effect in our discussion.[5] A small intermolecular but a large intramolecular isotope effect is consistent with the one-electron transfer oxidation of substrate **4** by NO_3, followed by deprotonation of the resulting radical cation **$4^{\cdot+}$** to form the benzyl radical **9**, as shown in Scheme 2.

Noteworthy is the small isotope effect **$7_H/7_D$** observed in the side-chain nitration, which contrasts with the large **$5_H/5_D$** values for the side-chain nitrooxylation (entries 1 and 3). This also contrasts to the conventional aromatic nitration based on NO_2^+ ion, where all observed values were small and similar despite the different product distributions (entries 5–7). These observations are highly suggestive of the operation of different mechanisms for the formation of side-chain substitution products in the *kyodai*-nitration. A plausible explanation for the small **$7_H/7_D$** value is as follows; the radical cation **$4^{\cdot+}$** is trapped

---

[†] In the bromination of **4**, **4_{DD}** and **4_{HD}** with NBS-AIBN, the v_H/v_D and k_H/k_D values were as high as 6 in accordance with the direct hydrogen abstraction by bromine atom.



Scheme 2.

by NO_2 to form arenium ions **10** and **11**, the proton release from which would lead to a nitrotriene **13** and a ring nitration product **8**, the ratio of these varying considerably depending on the conditions employed. The triene intermediate **13** may collapse either heterolytically at the double allylic position to form a pair of benzyl cation and nitrite anion or homolytically to form an intimate pair of arylmethyl radical and NO_2, eventually leading to arylnitromethane **7** and benzylic nitrate **5**.

The arene radical cation $\mathbf{4}^{\cdot+}$ is highly likely to be a common intermediate for the *kyodai*-nitration as well as the non-conventional nitration based on NO_2,[6] cerium(IV) ammonium nitrate $Ce(NH_4)_2(NO_3)_6$ (CAN),[7] and tetranitromethane (TNM).[8] However, these reactions usually give rise to considerably different distributions of side-chain substitution products. However, this is not unexpected. In the *kyodai*-nitration at −70°C, where excess NO_2 exists mostly in the dimeric form,[9] benzyl radical **9** would be trapped by N_2O_4 preferentially through the oxygen to give nitrite **12** as the major initial product (entry 1). Added pyridine base would facilitate proton release from the intermediate radical cation $\mathbf{4}^{\cdot+}$, thus favoring the formation of the side-chain nitrooxylation and oxidation products **5** and **6** over the ring- and side-chain nitration products **8** and **7** (entry 2). Under these conditions, nitroxylene **8** accounts for only a minimal part of the products. A rise in temperature would increase the concentration of NO_2, which works favorably for the formation of ring substitution product **8** at the expense of side-chain substitution products **5** and **6** (entry 3). In contrast, the reaction of *p*-xylene and NO_2 at room temperature, where the radical cation $\mathbf{4}^{\cdot+}$ resulting from the one-electron oxidation[6,10] by in situ generated NO^+ would lose proton and couple with NO_2 at both nitrogen and oxygen, leading to nitromethane **7** as the major product together with products **5** and **6** (entry 4). This interpretation is in accord with the observed large values of $\mathbf{5_H}/\mathbf{5_D}$, $\mathbf{6_H}/\mathbf{6_D}$ and $\mathbf{7_H}/\mathbf{7_D}$ that are in the range 2.5–3.0. In the reaction with CAN (entry 8), the resulting radical **9** is rapidly oxidized by cerium(IV) to arylmethyl cation, which couples with the nitrate ligand to form the corresponding nitrate **5** as the main product. The nitration with acetyl nitrate afforded significant amounts of side-chain substitution products **5** and **7** (entry 6). Low deuterium isotope effect for both side-chain nitrooxylation and nitration rules out the intervention of radical species **9**. Noteworthy is that the reaction of **4** and N_2O_5 led to a considerable amount of benzyl nitrate **5** and arylnitromethane **7** (entry 5). The deuterium isotope effect was quite low again, which stands in marked contrast to the observations from the *kyodai*-nitration. In all these cases, little or no aldehyde **6** was detected. Although N_2O_5 can be prepared from NO_2 and ozone, an in situ mixture of these two compounds has proved to behave differently toward aromatic substrates in accordance with the involvement of NO_3 as the initial electrophile in the *kyodai*-nitration.

References

1. (a) Nightingale, D. V. *Chem. Rev.* **1947**, *40*, 117–140. (b) Hartshorn, S. R. *Chem. Soc. Rev.* **1974**, *3*, 167–192. (c) Suzuki, H. *Synthesis* **1977**, 217–238.
2. (a) Schofield, K. *Aromatic Nitration*; Cambridge University Press: Cambridge, 1980: pp. 215–221. (b) Olah, G. A.; Malhotra, R.; Narang, S. C. *Nitration, Methods and Mechanisms*; VCH: New York, 1989: pp. 164–169.
3. (a) Mori, T.; Suzuki, H. *Synlett* **1995**, 383–392. (b) Suzuki, T.; Noyori, R. *Chemtracts* **1997**, *10*, 813–817. (c) Ridd, J. H. *Acta Chem. Scand.* **1998**, *52*, 11–22. (d) Nonoyama, N.; Mori, T.; Suzuki, H. *Zh. Org. Khim.* **1998**, *34*, 1591–1601.
4. Baciocchi, E.; Rol, C.; Mandolini, L. *J. Am. Chem. Soc.* **1980**, *102*, 7597–7598.
5. Bell, R. P. *The Proton in Chemistry*; Chapman & Hall: London, 1973; Chapter 12.
6. Bosch, E.; Kochi, J. K. *J. Org. Chem.* **1994**, *59*, 3314–3325 and papers cited therein.
7. (a) Dinçtürk, S.; Ridd, J. H. *J. Chem. Soc. Perkin Trans. 2* **1982**, 965–970. (b) Baciocchi, E.; Rol, C.; Sebastiani, G. V.; Serena, B. *Tetrahedron Lett.* **1984**, *25*, 1945–1946. (c) Del Giacco, T.; Baciocchi, E.; Steenken, S. *J. Phys. Chem.* **1993**, *97*, 5451–5456. (d) Baciocchi, E.; Del Giacco, T.; Elisei, F. *J. Am. Chem. Soc.* **1993**, *115*, 12290–12295. (e) Freccero, M.; Pratt, A.; Albini, A.; Long, C. *J. Am. Chem. Soc.* **1998**, *120*, 284–297.
8. (a) Eberson, L.; Hartshorn, M. P.; Radner, F. *J. Chem. Soc. Perkin Trans. 2* **1992**, 1799–1806. (b) Eberson, L.; Calvert, J. L.; Hartshorn, M. P.; Robinson, W. T. *Acta Chem. Scand.* **1993**, *47*, 1025–1034. (c) Bockman, T. M.; Kim, E. K.; Kochi, J. K. *Bull. Soc. Chem. Fr.* **1993**, *130*, 323–335.
9. See references in Jones, K. *Comprehensive Inorganic Chemistry*; Bailar, J. C.; Emeléus, H. J.; Nyholm, R.; Trotman-Dickenson, A. F., Eds.; Pergamon: Oxford, 1973: Vol. 2, pp. 340–356.
10. Clemens, A. H.; Ridd, J. H.; Sandall, J. P. B. *J. Chem. Soc. Perkin Trans. 2* **1984**, 1659–1666.