

Ozone-mediated nitration of adamantane and derivatives with nitrogen dioxide: selectivity in the hydrogen abstraction by nitrogen trioxide and subsequent coupling of the resulting carbon radicals with nitrogen dioxide¹

Hitomi Suzuki* and Nobuaki Nonoyama

Department of Chemistry, Graduate School of Science, Kyoto University, Kitashirakawa, Sakyo-ku, Kyoto, 606-01, Japan

In the presence of ozone at $-78\text{ }^{\circ}\text{C}$, nitrogen dioxide reacts rapidly and selectively with adamantane at a bridgehead position to give the corresponding nitro derivative as the sole major product. The relative reactivity has been determined for a series of 1-substituted adamantanes, which reveals that electron-withdrawing substituents exert a considerable influence on the ease of substitution at the γ -position as well as the distribution of the *N*- and *O*-functionalized products. The results may be rationalized in terms of the initial hydrogen abstraction by nitrogen trioxide, followed by rapid trapping of the resulting adamantyl radicals with nitrogen dioxide.

Introduction

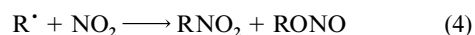
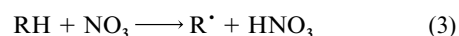
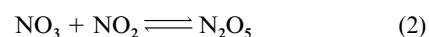
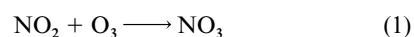
Direct nitration of aliphatic compounds is less common than aromatic nitration. Alkanes with a good leaving heteroatom group can be easily nitrated by nucleophilic substitution with a metal nitrite in a dipolar aprotic solvent such as dimethyl sulfoxide (DMSO) or dimethylformamide (DMF).² However, alkanes with no such advantage are quite difficult to nitrate with ordinary nitrating agents, attempts with forcing conditions usually resulting in the formation of a complex mixture of products. Recently, Olah *et al.* reported the electrophilic nitration of some cycloalkanes with nitronium tetrafluoroborate in nitromethane at room temperature; adamantane **1a** slowly underwent nitration to give 1-nitroadamantane **2a** in 66% yield after a week.³ A similar nitration was also carried out by Duddu and Damavarapu using nitronium trifluoromethanesulfonate, where the 1-nitro compound **2a** was obtained in 63% yield.⁴ Radical abstraction of a hydrogen atom from alkanes followed by coupling of the resulting radicals with lower oxides of nitrogen can be used to functionalize alkanes, which, however, often leads to an intractable mixture of oxidation, nitration, and oxidative cleavage products.

We have recently found that nitrogen dioxide, activated in the presence of ozone, enters easily into the aromatic nucleus as a nitro group at low temperatures (kyodai-nitration).⁵ This reaction is thought to proceed *via* electron transfer from an aromatic substrate to the nitrogen trioxide, a compound produced as the initial electrophile *in situ* from nitrogen dioxide and ozone. Nitrogen trioxide is a highly electron-deficient radical species of strong oxidizing ability (2.3–2.6 V *vs.* NHE in water),⁶ and readily abstracts a hydrogen atom from alkanes.⁷ It can be generated by the photodecomposition of dinitrogen pentaoxide^{7d} and cerium(IV) ammonium nitrate,⁸ anodic oxidation of nitrate anion,⁹ and reaction of nitrogen dioxide with ozone.¹⁰ The kyodai-nitration is based on the last method and provides the most convenient *in situ* produced nitrogen trioxide for the nitration of organic substrates.

In the present paper, we report the first example of the kyodai-nitration of aliphatic hydrocarbons, adamantane **1a** and its derivatives **1b–f**. The hydrocarbon **1a** is chosen as the model compound for examining the behaviour of alkanes toward the kyodai-nitration because of the high stability of its symmetrical carbon framework.

Results and discussion

Aliphatic kyodai-nitration is supposed to proceed *via* the homolytic process shown in Eqns. (1), (3) and (4). The initial step is



generation of the nitrogen trioxide from nitrogen dioxide and ozone [Eqn. (1)], which abstracts a hydrogen atom from an alkane RH to give an alkyl radical R[•] [Eqn. (3)]. The resulting carbon radical couples with nitrogen dioxide to yield a nitroalkane and an alkyl nitrite [Eqn. (4)]. In this work, we have examined the polar effect of a substituent group attached to the tertiary carbon of hydrocarbon **1** on the ease of hydrogen abstraction by nitrogen trioxide and observed a noticeable influence of the substituent on the overall reaction rate as well as the product distribution.

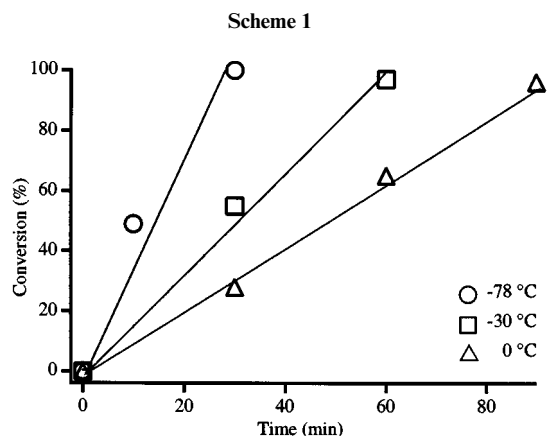
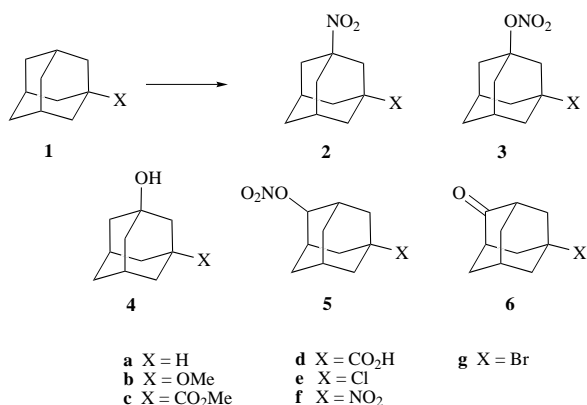
Kyodai-nitration of adamantane **1a**

Ozonized oxygen was bubbled through a stirred solution of hydrocarbon **1a** and an excess of nitrogen dioxide in dichloromethane at $-78\text{ }^{\circ}\text{C}$ to give 1-nitroadamantane **2a** as the major product. Accompanying minor products included 1-adamantyl nitrate **3a**, adamantan-1-ol **4a**, 2-adamantyl nitrate **5a** and adamantanone **6a** (Scheme 1). Firstly, we made some efforts to optimize the reaction and the representative results obtained are shown in Table 1. Since lower temperatures were generally found to give better results, we carried out most of the reactions at temperatures a little more than that of the melting point of the respective solvent employed. The use of dichloromethane realized the highest conversion and the best yield of 1-nitroadamantane **2a**. In other solvent systems, the progress of the reaction was a little slower. With hexane as the solvent, small amounts of hexan-2-yl and hexan-3-yl nitrates were also produced. This result indicates that the tertiary C–H bond of adamantane **1a** reacts preferentially even in the presence of a large excess of the secondary C–H bond of hexane; this con-

Table 1 Effect of solvents on the product distribution in the kyodai-nitration of adamantane **1a**^a

Solvent	T/°C	Conversion ^b (%)	Yield ^b (%)					
			2a	3a	4a	5a	6a	Others
CH ₂ Cl ₂	-78	100	82	10	1	1	1	—
C ₆ H ₁₄	-78	85	46	17	19	<1	1	— ^c
CCl ₄	-20	64	10	3	<1	2	<1	1e (49%)
MeCN	-30	31	23	5	1	1	<1	—
MeNO ₂	-20	28	22	5	<1	1	<1	—

^a All reactions were run for 1 h using hydrocarbon **1a** (5 mmol), nitrogen dioxide (30 mmol) and the given solvent (30 cm³). ^b Determined by GLC. ^c Hexan-2-yl nitrate (0.35 mmol) and hexan-3-yl nitrate (0.32 mmol) were produced as well.

**Fig. 1** Temperature dependence of the kyodai-nitration of adamantane **1a** in CH₂Cl₂ (2 mmol scale)

firmly the very good tertiary/secondary C–H selective nature of nitrogen trioxide. The lower yield of compound **2a** in the present case may be attributed to the poor solubility of nitrogen dioxide in hexane as well as the consequent oxidation of the adamantyl radical by dioxygen, thus leading to a noticeable increase in the relative proportion of the *O*-functionalized products **3a** and **4a**. Use of carbon tetrachloride as the solvent gave 1-chloroadamantane **1e** as the main product. Compound **1e** was no doubt formed *via* the abstraction of a chlorine atom from carbon tetrachloride by the 1-adamantyl radical; this strongly suggests that the kyodai-nitration of adamantane proceeds *via* an intermediate radical species. Reactions in acetonitrile and nitromethane both resulted in a low conversion, probably because of the poor solubility of the substrate in these solvents as well as the higher reaction temperatures necessary to effect the reaction.

As expected, the ease of the present reaction was largely dependent on the temperatures employed, but quite interestingly, the reaction became faster as the temperature was lowered (Fig. 1). The yield of 1-nitroadamantane **2a** also improved considerably at lower temperatures. Slowing down of the reaction at high temperature may be explained by increased trapping of nitrogen trioxide by nitrogen dioxide; the latter oxide exists in equilibrium with the dimeric form, dissociation of

which to the monomeric form increases as the temperature rises. This means that the life-time of nitrogen trioxide would become longer at lower temperatures, making it sufficiently reactive with the substrate even at -78 °C.

The effect of concentration of nitrogen dioxide on the overall reaction rates was also examined and found not to be so significant (Table 2). A lower concentration of nitrogen dioxide led to a higher proportion of the *O*-functionalized products **3a** and **4a** at the expense of **2a**; the most satisfactory yield of **2a** was achieved when the reaction was carried out in dichloromethane in the presence of an excess of nitrogen dioxide at -78 °C.

Reactions of adamantane **1a** with other nitrating agents

Adamantane can react with nitrogen dioxide smoothly in the presence of ozone at -78 °C (Fig. 1). Under similar conditions but without nitrogen dioxide, however, only a small amount of adamantane-1-ol **4a** was produced, which rules out the possibility that ozone itself may be an initial active species. It is noteworthy that the reaction failed to take place when substrate **1a** was introduced into the reaction system after ozone had been bubbled through it. These results may be taken to support our view that the active species in the kyodai-nitration of adamantane is a short-lived species generated *in situ* from nitrogen dioxide and ozone, *i.e.* nitrogen trioxide.

In order to probe further into the mechanism of the nitration path for the hydrocarbon **1a**, the dependence of product distribution on the reaction conditions was investigated using several different nitrating agents. Relative product ratios were found to vary over a wide range depending on the reagent and temperature employed (Table 2). At -78 °C all nitrating agents except the nitrogen dioxide–ozone system failed to react with the hydrocarbon **1a**, thus establishing the crucial role of the *in situ* generated nitrogen trioxide as the initial reactive species. A possible contribution of the nitronium ion may also be excluded in the kyodai-nitration at low temperatures, since the added methanesulfonic acid showed little effect. The composition of the kyodai-nitration product differs greatly from the products obtained under conventional ionic conditions.

Under typical ionic conditions based on the use of HNO₃–H₂SO₄ or N₂O₅–MeSO₃H, the reaction occurred exclusively at the tertiary position of the substrate **1a** *via* *O*-attack to give the nitrate **3a**. The active species involved here is presumably the nitronium ion, which by preferential electrophilic attack at the bridgehead C–H bond generates the 1-adamantyl cation, eventually leading to the nitrate **3a**. Thus, the classical nitration based on the nitronium ion provides a convenient means to introduce the oxygen function into the bridgehead position of the adamantane nucleus. The reactions with acetyl nitrate and dinitrogen pentoxide produced the nitro derivative **2a** and the nitrates **3a** and **5a** in ratios dependent on the conditions employed; this is presumably due to competition between the concurrent ionic and radical processes involving the nitronium ion and nitrogen trioxide as the respective attacking species.

Kyodai-nitration of the substituted adamantanes **1b–e**

The reaction of substituted adamantanes **1b–e** with nitrogen dioxide in the presence of ozone mainly produced the 1-

Table 2 Reactions of adamantane **1a** with various nitrating agents^a

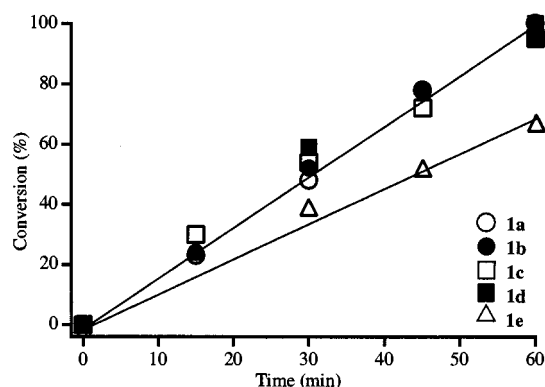
Reagent and conditions	Selectivity		Conv. ^b (%)	Product composition ^b (%)				
	3°/2°	2a/(3a + 4a)		2a	3a	4a	5a	6a
NO ₂ , ^c O ₃ , -78 °C, 0.5 h	>50	>10	>99	92	6	1	<1	<1
NO ₂ , ^c O ₃ , MeSO ₃ H (5 equiv.), -78 °C, 0.5 h	>50	>10	98	94	5	<1	1	—
NO ₂ (5 mol dm ⁻³), ^d O ₃ , -78 °C, 0.2 h	>50	>10	55	91	5	2	1	<1
NO ₂ (1 mol dm ⁻³), O ₃ , -78 °C, 0.2 h	>50	7.9	49	86	8	3	<1	<1
NO ₂ (0.2 mol dm ⁻³), O ₃ , -78 °C, 0.2 h	32	2.5	51	69	19	8	2	1
AcONO ₂ (8 equiv.), RT, 8 h	20	4.3	94	78	18	—	4	—
N ₂ O ₅ (3.5 equiv.), 0 °C, 1 h ^e	25	0.25	>99	19	76	1	4	—
N ₂ O ₅ (3.5 equiv.), MeSO ₃ H (5 equiv.), 0 °C, 1 h ^e	∞	0.01	>99	1	91	8	—	—
fuming HNO ₃ , H ₂ SO ₄ , RT, 20 h ^e	∞	0	71	—	99	1	—	—

^a All reactions were carried out using **1a** (2 mmol) and CH₂Cl₂ (30 cm³) under the given conditions. ^b Determined by GLC. ^c Concentration of nitrogen dioxide was 2 mol dm⁻³. ^d Part of the nitrogen dioxide was deposited as a white solid from the solution. ^e The reaction was carried out in CH₂Cl₂ (10 cm³).

Table 3 Reaction of the adamantanes **1a–f** with nitrogen dioxide and ozone^a

Substrate	Time (min.)	Conv. ^b (%)	Product yield ^b (%)		2/3
1a	20	99	2a (82)	3a (8)	10.3
1b	30	97	2b (66)	3b (10)	6.6
1c	30	96	2c (76)	3c (15)	5.1
1d	30	94 ^c	2d (69 ^c)	3d (20 ^c)	3.5
1e	45	94	2e (60)	3e (22)	2.7
1f	60	67	2f (<5)	3f (42 ^d)	<0.1

^a All reactions were carried out using hydrocarbon **1** (2 mmol), nitrogen dioxide (30 mmol) and CH₂Cl₂ (30 cm³) at -78 °C. ^b Determined by GLC. ^c Determined by HPLC. ^d Isolated yield.

**Fig. 2** Conversion profile of the kyodai-nitration of adamantanes **1a–e** in CH₂Cl₂ at -78 °C (5 mmol scale)

nitration products **2b–e** along with some 1-nitrates **3b–e** (Table 3). The alcohols **4b–e** and 2-substituted products **5b–e** and **6b–e** were also detected as by-products, but they were negligible in amount. The selectivity for the *N/O*-functionalization (**2/3**) is shown in Table 3. When a strongly electron-withdrawing group was present in adamantane, a higher proportion of *O*-functionalized product was observed and the **2/3** selectivity decreased.

All four adamantanes **1a–d** underwent kyodai-nitration almost at the same rate in dichloromethane at -78 °C (Fig. 2). In these reactions, therefore, the rate-determining step should presumably be the generation of nitrogen trioxide from nitrogen dioxide and ozone. 1-Chloroadamantane **1e** reacted more slowly than the others **1a–d**. Since it was difficult to obtain the absolute reaction rates, we determined the relative reactivity of these adamantane derivatives by a conventional competition method. In this the assumption was made that the reaction follows Eqn. (5) where the concentration of nitrogen trioxide

$$d[\mathbf{1x}]/dt = -k_x'[\text{NO}_3'][\mathbf{1x}] \quad (5)$$

Table 4 Relative reactivity of 1-substituted adamantanes Ad-X in the kyodai-nitration

X	Relative rate ^a	log k_x/k_H	σ_I
H (1a)	1.0	0	0
MeO (1b)	0.68	-0.17	0.27
CO ₂ Me (1c)	0.24	-0.62	0.20
CO ₂ H (1d)	0.25	-0.60	—
Cl (1e)	0.051 ^b	-1.30	0.46
NO ₂ (1f)	0.017 ^c	-1.76	0.65

^a Statistically corrected. ^b Determined by competition with **1c**. ^c Determined by competition with **1e**.

[NO₃'] is constant ($k_x'[\text{NO}_3'] = k_x$). The amount of substrate at a given time will then be expressed by Eqn. (6). Here, [1x], k_x'

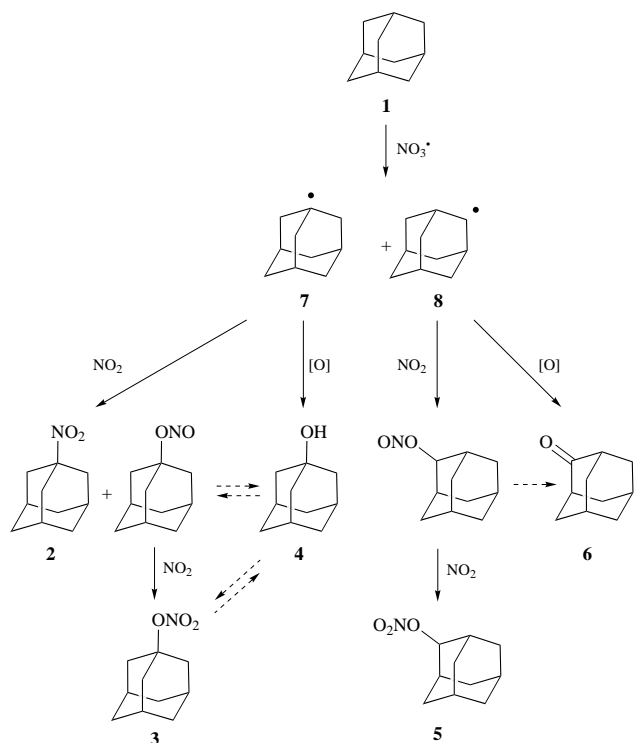
$$[\mathbf{1x}]/[\mathbf{1x}]_0 = \exp(-k_x t) \quad (6)$$

and k_x denote the concentration of substrate, second-order rate constant and pseudo-first-order rate constant, respectively, for a given adamantane derivative **1x**.

Equimolar proportions of two substrates were mixed and subjected to the reaction in dichloromethane at -78 °C. The progress of the reaction was monitored periodically by GLC with the kinetic data at an early stage of the reaction (conversion <50%) being employed for calculation of the rate constant k_x . The relative rate constants per tertiary C–H bond (k_x/k_H) in adamantanes **1a–f** are compared in Table 4.

Mechanism of the kyodai-nitration of adamantanes

The proposed mechanism for the kyodai-nitration of adamantanes is shown in Scheme 2. The reaction most likely proceeds *via* two consecutive stages, the first being hydrogen abstraction by nitrogen trioxide to produce the 1- and 2-adamantyl radicals **7** and **8**. Possible alternatives may involve ionic and electron-transfer mechanisms. The ionic mechanism, however, can be easily ruled out by the finding that the reaction of the hydrocarbon **1a** with nitric acid–sulfuric acid or nitronium salt^{3a} occurred very slowly even at room temperature, while both acetyl nitrate and nitrogen pentaoxide failed to react with the substrate at -78 °C. The second alternative may also be ruled out, since the electron transfer between adamantane (E_p , ca. 3 V vs. NHE) and nitrogen trioxide (E^0 , ca. 2.6 V) is apparently too endoergic to take place. We can readily distinguish the electron transfer mechanism from the hydrogen abstraction mechanism on the basis of the reaction products, since the positional selectivity is often different between the deprotonation of a cation radical and the hydrogen abstraction by a radical species. For example, no side-chain substitution products were obtained from the kyodai-nitration of compound **1b**, while the side-chain substituted compounds were the major product



Scheme 2

obtained from both the anodic oxidation and the photo-induced electron transfer reaction of the same substrate.^{7a} Since a possible role of dinitrogen pentoxide or ozone as the hydrogen-abstracting species was ruled out under our conditions, we may reasonably conclude that the nitrogen trioxide is involved as the initial reactive species in the aliphatic kyodai-nitration at low temperature.

In the second stage of the kyodai-nitration, the resulting adamantyl radicals **7** and **8** couple with nitrogen dioxide, leading to two different types of products, *N*-attached nitro compound and *O*-attached nitrite. In the case of the tertiary radical **7**, the *N*-attack was predominant, while from secondary radical **8** only the *O*-attached products **5** and **6** were produced. Under the conditions where the concentration of nitrogen dioxide was low, as was the case with the reaction in hexane (Table 1), the relative proportion of the *O*-attached products **3a** and **4a** becomes prominent (Table 2). This may reasonably be attributed to the increased coupling of the carbon radicals **7** and **8** with dioxygen or ozone.

Involvement of the electron-transfer oxidation process in the second stage may also be excluded by the observation that the reaction of 1-bromoadamantane **1g** with silver nitrite in DMSO or dichloromethane gave 1-nitroadamantane **2a** only in 1–6% yield, the main products being 1-adamantyl nitrite **9** and adamantane-1-ol **4a**. This reaction presumably proceeded *via* an S_N1 mechanism, involving coupling between the 1-adamantyl cation and nitrite anion. This is in marked contrast to the kyodai-nitration, where the *N*-attached products are mainly formed. Therefore, the second stage of the aliphatic kyodai-nitration is also considered to proceed *via* radical–radical coupling.

In the hydrogen abstraction by nitrogen trioxide from the C–H bond of substituted adamantanes **1a–f**, a considerable difference in the relative reaction rates was observed (Table 4). This result may be explained on the basis of the polar substituent effect,¹¹ the transition state of the hydrogen transfer being influenced by the electronic nature of a substituent at the γ -position. A similar polar effect has previously been reported for the hydrogen abstractions of 1-substituted adamantanes by bromine atom^{12a} and trichloromethyl radical.^{12b} In these reactions, a linear relationship has been observed between the

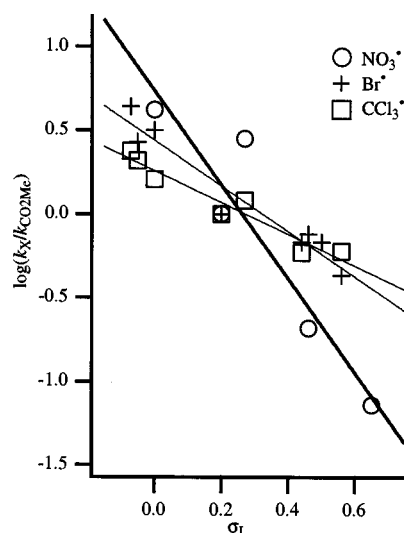
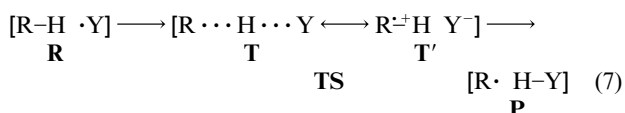


Fig. 3 Correlation between $\log(k_X/k_{\text{CO}_2\text{Me}})$ and σ_I for hydrogen abstraction by three radical species

reactivity and the electronic induction parameter σ_I (Fig. 3). In spite of the different radical species involved in these reactions, they all showed a negative slope [$\text{NO}_3^\cdot -2.81$ ($r = 0.934$), $\text{Br}^\cdot -1.36$ ($r = 0.968$) and $\text{CCl}_3^\cdot -0.95$ ($r = 0.965$)], which means that all these radical reactions are electrophilic in nature and the electron-withdrawing substituents destabilize the transition state. The transition state (TS) of hydrogen abstraction by these electrophilic radicals (Y^\cdot) may be represented as a resonance hybrid between the two extremes **T** and **T'** [Eqn. (7)]. In the



reaction with a strong electrophile (*e.g.* $\text{Y} = \text{NO}_3^\cdot$), there would be a large contribution from the polarized state **T'** which should be susceptible to the polar effect of a substituent present in the molecule. Hence it should show a larger negative slope as compared with those of less electrophilic radicals Br^\cdot and CCl_3^\cdot (Fig. 4).

1-Substituted adamantanes provide an ideal model to investigate the electronic effect of a substituent group present in saturated hydrocarbons, since there would be little direct interaction between an attacking species and a substituent, the latter being located at a position far from the reaction site because of the rigid adamantane framework. All three tertiary C–H bonds are equivalent in terms of the effect of a given substituent. 2-Substituted adamantanes are, however, devoid of such structural advantages; a substituent is present at the β - or δ -position to the reaction site, where the complexities arise from the interaction between the substituent and an attacking species as well as the competition between two pairs of non-equivalent tertiary C–H bonds.

The polar substituent effect may also be understood in a more straightforward way by a MOPAC calculation. For the hydrogen abstractions from the tertiary C–H bond of adamantane by NO_3^\cdot , Br^\cdot and CCl_3^\cdot radicals, AM1 calculation was made to estimate the respective heat of formation for the reactant **R**, product **P** and transition state **TS** (Table 5, Fig. 4). The **R** and **P** structures were not susceptible to the polar effect, thus little energy difference was observed between the **R** and **P** states of compounds **1a–f**. However, a significant difference appeared at the transition state **TS** and this became larger in the reaction of more electrophilic NO_3^\cdot as compared with less electrophilic Br^\cdot and CCl_3^\cdot .

The tertiary/secondary positional selectivity of adamantane **1a** has been reported for the reactions with several radical

Table 5 Comparison of calculated thermochemical parameters for the hydrogen abstraction of adamantanes **1a,b,d-f** by three different radical species^a

R-H	Y = NO ₃					Y = Br		Y = CCl ₃	
	H _f (R)	H _f (TS)	H _f (P)	E _a	ΔH _f	E _a	ΔH _f	E _a	ΔH _f
1a	-23.00	-19.76	-47.53	3.24	-24.54	4.07	0.68	20.97	12.11
1b	-58.66	-54.58	-82.82	4.08	-24.15	4.19	0.50	21.33	12.21
1d	-109.13	-104.67	-133.11	4.46	-23.98	4.38	0.63	21.63	12.76
1e	-28.40	-23.91	-52.35	4.49	-23.95	4.48	0.81	21.70	12.64
1f	-18.24	-12.55	-41.45	5.69	-23.21	4.92	0.61	22.68	13.42

^a Heat of formation [H_f(kcal mol⁻¹)] was calculated by AM1 method. Activation energy E_a and ΔH_f value were obtained from the equations E_a = [H_f(TS)] - [H_f(R)] and ΔH_f = [H_f(P)] - [H_f(R)]. As for the notation of R, P and TS, see Fig. 4.

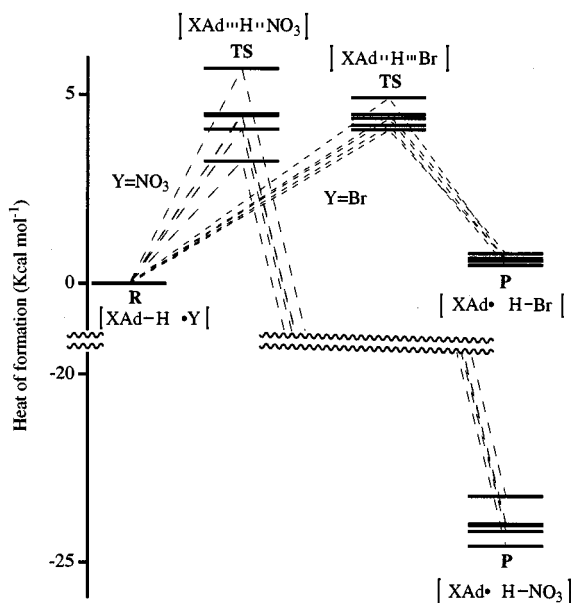


Fig. 4 Diagram comparison of the hydrogen abstraction of adamantanes **1a,b,d-f** by Br· and NO₃·, based on AM1 calculations

species; Bu'O· 0.9, Br· 0.9, Cl· 1–2, Bu'OO· 3.7 and CCl₃· 8–9, respectively.¹³ When compared with these previous values, a remarkably high selectivity (3°/2° >50) was observed in the aliphatic kyodai-nitration. A weak hydrogen-abstracting species of low Y–H bond dissociation energy (BDE) generally exhibits a high selectivity, because the transition state becomes more product-like on the reaction coordinate. In such a case, the tertiary/secondary selectivity does not seem to be explicable by BDE only; Bu'O· 103, Br· 88, Cl· 103, Bu'OO· 88 and CCl₃· 96 kcal mol⁻¹ respectively. In the reaction with a highly electrophilic radical such as NO₃·, the substrate has a radical cationic nature in the transition state as shown in Eqn. (7). Since the tertiary carbon predominates over the secondary one in the delocalization ability of positive charge, the tertiary/secondary selectivity should be enhanced as the attacking radical species becomes more electrophilic in nature.

The *N/O*-selectivity of substituted adamantanes **1a–f** is largely governed by the electronic nature of an intermediate carbon radical **7**, where the radical with a strongly electron-withdrawing group necessarily leads to an increase of *O*-attacked product **3**, since the polarized nitrogen dioxide molecule bears a negative charge on the oxygen atom (Table 3). The secondary carbon radical **8** is less electron-rich than the tertiary one **7**, hence the *O*-substituted compounds were the only 2-substituted adamantanes obtained.

Conclusion

The adamantanes **1a–e** react smoothly with nitrogen dioxide in the presence of ozone to give the corresponding nitration

product **2a–e** in good yield. The reaction proceeds *via* hydrogen abstraction by nitrogen trioxide, followed by trapping of the resulting adamantyl radicals with nitrogen dioxide. The relative reactivity of compounds **1a–f** as well as the *N/O*-selectivity of the reaction are found to be greatly dependent on the polar effect of a substituent group at the γ -position to the reaction site. Strongly electron-withdrawing substituents slow down the reaction and lead to the *O*-substituted products, while weakly electron-withdrawing substituents favour *N*-attack by nitrogen dioxide.

Experimental

General experimental details

¹H NMR spectra were obtained with a Varian Gemini-200 spectrometer for solutions in CDCl₃, with tetramethylsilane as an internal standard. *J* Values are given in Hz. Chemical ionization mass spectra were obtained on a Shimadzu GCMS QP-5000 instrument using isobutane as an ionizing gas. IR spectra were recorded for KBr pellets or liquid films on a Shimadzu FT-IR DR 8000/8100 IR spectrophotometer. GLC analyses were performed on a Shimadzu GC-17A gas chromatograph, using a J&W Scientific DB-5-30N-STD column (30 m × 0.25 mm i.d.). HPLC analyses were performed on a Shimadzu LC-10A liquid chromatograph using a GL Sciences Unisil Pack 5C18-250A column with methanol–water (6:4) as the eluent. For the isolation and purification of products by preparative liquid chromatography, a Yamazen ultra pack SI-40B silica gel column was employed with hexane–ethyl acetate (1–60:1) as the solvent.

The adamantanes **1a,d,e** and **g** were purchased from commercial sources. Compound **1b** was prepared from adamantan-1-ol and methyl iodide, and compound **1c** from **1d** and methanol. Dichloromethane was distilled from calcium hydride prior to use. Nitrogen dioxide (99% pure) was obtained in a cylinder from Sumitomo Seika Co. Ltd. and used after transfer distillation. An apparatus from Nippon Ozone Co. Ltd., type ON-1-2, was used for the generation of ozone and its efficiency was calibrated by iodometric titration. The machine produced ozone at a rate of 10 mmol h⁻¹ under the conditions of an oxygen flow rate 10 dm³ h⁻¹ and an applied voltage 80 V. Products were identified by IR, ¹H NMR, GC-MS analyses or by direct comparison with the authentic samples.

Kyodai-nitration of adamantane **1**: typical procedure

To a stirred mixture of adamantane **1a** (273 mg, 2.0 mmol) and dichloromethane (30 cm³) cooled to –78 °C was added liquid nitrogen dioxide (1.0 cm³, 30 mmol) after which ozonized oxygen was bubbled through the mixture at a low flow rate. After 20 min, the reaction was quenched by the addition of aq. NaHCO₃ to the mixture after which the organic phase was separated, washed, and dried (Na₂SO₄). GLC analysis with cyclododecane as an internal standard revealed the composition of the product mixture as follows: **2a** 82%, **3a** 8%, **4a** 0.6%, **5a** 1.3% and **6a** 0.5%. Removal of the solvent under reduced pressure left a white solid residue, which was chrom-

Table 6 Physical data of adamantane derivatives obtained

Compound Formula	Mp (°C) [lit. mp (°C)]	MS (CI, isobutane) <i>m/z</i> (%)	IR (KBr, ν_{\max} /cm ⁻¹)	¹ H NMR δ_{H} (200 MHz, CDCl ₃), <i>J</i> (Hz)	Elemental analysis C, H, N (%) [calc. C, H, N (%)]
2a C ₁₀ H ₁₅ NO ₂	160–162 (159) ^a	182 (M ⁺ + 1, 0.4%), 166 (5), 152 (3), 135 (100)	2919, 2857, 1534, 1370, 1105, 1055, 881	1.72 (6 H, br s), 2.22 (9 H, br s)	
2b C ₁₁ H ₁₇ NO ₃	40.0–40.2	212 (M ⁺ + 1, 11%), 180 (35), 165 (100)	2923, 2857, 1518, 1368, 1117, 1100, 1053, 870	1.61 (2 H, br s), 1.75 (4 H, br s), 2.15 (4 H, d, <i>J</i> 2.6), 2.21 (2 H, s), 2.46 (2 H, br s), 3.27 (3 H, s)	62.32, 8.07, 6.73 [62.54, 8.11, 6.63]
2c C ₁₂ H ₁₇ NO ₄	49.8–50.0	240 (M ⁺ + 1, 68%), 224 (12), 210 (16), 193 (100)	2932, 2863, 1717, 1523, 1262, 1088, 714	1.70 (2 H, br s), 1.88 (4 H, br s), 2.20 (4 H, br s), 2.37 (4 H, br s), 3.70 (3 H, s)	60.18, 7.22, 5.87 [60.24, 7.16, 5.85]
2d C ₁₁ H ₁₅ NO ₄	149–152	226 (M ⁺ + 1, 44%), 210 (14), 197 (33), 181 (39), 179 (100)	2934, 2869, 1680, 1534, 1368, 1283, 868, 704	1.72 (2 H, br s), 1.91 (4 H, br s), 2.21 (4 H, br s), 2.39 (4 H, br s)	58.45, 6.80, 6.20 [58.66, 6.71, 6.22]
2e C ₁₀ H ₁₄ ClNO ₂	156–159	200 (M ⁺ – 16, 16%), 180 (56), 171 (78), 169 (100), 151 (56), 135 (98)	2938, 2865, 1536, 1366, 1049, 841, 731	1.66 (2 H, br s), 2.11 (4 H, d, <i>J</i> 2.8), 2.19 (4 H, d, <i>J</i> 3.2), 2.45 (2 H, br s), 2.58 (2 H, s)	55.41, 6.57, 6.51 [55.69, 6.54, 6.49]
3a C ₁₀ H ₁₅ NO ₃	104–105 (103–104) ^b	152 (M ⁺ – 45, 26%), 135 (100)	2917, 2859, 1609, 1458, 1279, 1041, 868	1.70 (6 H, t, <i>J</i> 3.0), 2.13 (6 H, d, <i>J</i> 3.2), 2.27 (3 H, br s)	
3b C ₁₁ H ₁₇ NO ₄	Oil (Oil) ^c	228 (M ⁺ + 1, 2%), 183 (13), 165 (100), 151 (32)	2930, 2861, 1620, 1456, 1277, 1051, 860 (neat)	1.59 (2 H, s), 1.74 (4 H, br s), 2.07 (4 H, br s), 2.12 (2 H, s), 2.44 (2 H, br s), 3.26 (3 H, s)	
3c C ₁₂ H ₁₇ NO ₅	<30	256 (M ⁺ + 1, 34%), 211 (100), 193 (90)	2921, 2863, 1732, 1620, 1456, 1300, 1285, 1256, 1232, 1084, 862 (neat)	1.68 (2 H, t, <i>J</i> 3.0), 1.87 (4 H, d, <i>J</i> 2.8), 2.10 (4 H, d, <i>J</i> 3.0), 2.28 (2 H, s), 2.38 (2 H, m), 3.69 (3 H, s)	56.04, 6.67, 5.49 [56.46, 6.71, 5.49]
3d C ₁₁ H ₁₅ NO ₅	148–150 (130–132) ^c	242 (M ⁺ + 1, 43%), 197 (29), 179 (100), 151 (35), 135 (49)	2948, 1698, 1630, 1454, 1416, 1358, 1282, 866	1.69 (2 H, t, <i>J</i> 2.7), 1.90 (4 H, d, <i>J</i> 2.5), 2.12 (4 H, d, <i>J</i> 3.0), 2.31 (2 H, s), 2.41 (2 H, m)	54.96, 6.30, 5.71 [54.77, 6.27, 5.81]
3e C ₁₀ H ₁₄ ClNO ₃	42.4–42.6	197 (M ⁺ – 35, 44%), 181 (38), 179 (100), 151 (18), 135 (21)	2928, 2865, 1622, 1458, 1277, 1042, 862	1.63 (2 H, t, <i>J</i> 3.0), 2.10 (8 H, d, <i>J</i> 2.9), 2.43 (2 H, m), 2.56 (2 H, s)	51.72, 6.06, 6.13 [51.84, 6.09, 6.05]
3f C ₁₀ H ₁₄ N ₂ O ₅	78.5–79.0	180 (M ⁺ – 62, 31%), 151 (100), 135 (2)	2870, 1626, 1522, 1456, 1365, 1281, 1061, 907, 855	1.69 (2 H, t, <i>J</i> 3.0), 2.14 (4 H, br s), 2.22 (4 H, br s), 2.57 (2 H, t, <i>J</i> 2.8), 2.64 (2 H, s)	49.71, 5.87, 11.62 [49.59, 5.83, 11.56]
5a C ₁₀ H ₁₅ NO ₃	30.0–30.3	151 (M ⁺ – 46, 17%), 135 (100)	2923, 2857, 1620, 1452, 1283, 924, 878	1.5–2.0 (12 H, m), 2.19 (2 H, br s), 5.09 (1 H, br s)	60.66, 7.71, 7.12 [60.90, 7.67, 7.12]

^a R. W. Murray, R. Jeyaraman and L. Mohan, *Tetrahedron Lett.*, 1986, **27**, 2335. ^b Ref. 4. ^c Ref. 6a.

atographed on silica gel using hexane–ethyl acetate (50:1) as an eluent to give **2a** (276 mg, 76%), **3a** (30 mg, 7.7%) and **5a** (4.5 mg, 1.2%). Spectral data for the products are summarized in Table 6.

Determination of relative reaction rates: typical procedure

To a stirred mixture of 1-chloroadamantane **1c** (389 mg, 2.0 mmol), methyl adamantane-1-carboxylate **1d** (364 mg, 2.0 mmol), cyclododecane (45.1 mg; internal standard) and dichloromethane (30 cm³) was added liquid nitrogen dioxide (1.0 cm³, 30 mmol) at –78 °C, after which ozonized oxygen was bubbled through the mixture at a low flow rate. After the start of the reaction, the progress was monitored by GLC for 10 min at intervals of 2 min. The reaction rate was calculated by Eqn. (6). The plot of conversion *versus* time fitted sufficiently well to an exponential curve for rate constants to be estimated.

Reaction of adamantane **1a** with dinitrogen pentaoxide

Dinitrogen pentaoxide was distilled from a mixture of fuming nitric acid and phosphorus pentaoxide at 38 °C and dissolved in dry dichloromethane at –78 °C. The concentration of dinitrogen pentaoxide in a prepared solution was determined by titration. A solution of adamantane **1a** (273 mg, 2.0 mmol) in dichloromethane (5 cm³) was added in one portion to a stirred solution of dinitrogen pentaoxide (5 cm³ containing 7 mmol of N₂O₅) at 0 °C. The progress of the reaction was monitored by GLC at appropriate intervals of time. Product compositions were determined by GLC analysis with cyclododecane as an internal standard.

Reaction of 1-bromoadamantane **1a** with silver nitrite

A mixture of 1-bromoadamantane (0.21 g, 1 mmol), silver

nitrite (0.30 g, 2 mmol), cyclododecane (73 mg, internal standard) and dichloromethane (15 cm³) was stirred at room temperature in the dark under argon. After 18 h, the reaction mixture was analysed by GLC to show that the product composition was as follows: **2a** 6%, **3a** 8% and **4a** 23%; 1-adamantyl nitrite **9** was not determined. The mixture was then filtered and evaporated to afford a residue, which was chromatographed on silica gel to give **4a** (0.07 g, 48%) and **9** (0.03 g, 18%) as the major isolable products. On storage in the air, compound **9** gradually decomposed to form the alcohol **4a** with release of nitrogen dioxide.

1-Adamantyl nitrite 9. White crystals which readily decomposed when heated; δ_{H} 1.76 (6 H, t, *J* 3.0), 2.13 (6 H, d, *J* 3.1) and 2.29 (3 H, m); *m/z* 180 (M⁺ – 1, 4%), 151 (21) and 135 (100); ν_{\max} (KBr)/cm⁻¹ 2912, 2857, 1608, 1454, 1070, 831, 808, 781 and 743.

Reaction of adamantane **1a** with acetyl nitrate

Acetyl nitrate was prepared *in situ* from acetic anhydride (1.9 cm³), fuming nitric acid (0.66 cm³) and dichloromethane (20 cm³) at –78 °C under argon. A solution of adamantane **1a** (0.27 g, 2 mmol) in dichloromethane (10 cm³) was added with stirring to the above mixture which was then allowed to warm gradually to room temperature. After 8 h, the reaction was quenched by the addition of iced water to the mixture which was then extracted with dichloromethane. The product composition was analysed by GLC.

Reaction of adamantane **1a** with fuming nitric acid–sulfuric acid

A mixture of fuming nitric acid (0.46 cm³) and 98% sulfuric acid (1.0 cm³) in dichloromethane (3 cm³) was added dropwise to a stirred solution of adamantane **1a** (0.27 g, 2 mmol) in

dichloromethane (7 cm³) at 0 °C. The reaction mixture was allowed to warm gradually to room temperature and, after 20 h, it was treated with iced water, to quench the reaction, and extracted with dichloromethane. The product composition was analysed by GLC.

Calculations

All semi-empirical calculations were carried out with the MOPAC (ver. 6.10) program using AM1 Hamiltonian¹⁴ implemented on a Sony Tektronix CAChe system (ver. 3.8). Unrestricted Hartree–Fock wave functions were employed for all calculations. Transition state structures were calculated by SADDLE and optimized using the extra keywords TS and PRECISE. IRC calculations based on the transition state structures thus obtained led to the original reactant and product structures.

Acknowledgements

Financial support of this work by a Grant-in-Aid for Specially Promoted Scientific Research (No. 08101003) of the Ministry of Education, Science, Sports and Culture of Japan and also by a grant from Japan Science and Technology Corporation (DX 96120) is gratefully acknowledged.

References

- 1 The present work was published in a preliminary form: H. Suzuki and N. Nonoyama, *J. Chem. Soc., Chem. Commun.*, 1996, 1783.
- 2 (a) N. Kornblum, H. O. Larson, R. K. Blackwood, D. D. Mooberry, E. P. Oliveto and G. E. Graham, *J. Am. Chem. Soc.*, 1956, **78**, 1497; (b) N. Kornblum, R. A. Smiley, R. K. Blackwood and D. C. Iffland, *J. Am. Chem. Soc.*, 1955, **77**, 6269.
- 3 (a) G. A. Olah, P. Ramaiah, C. B. Rao, G. Sanford, R. Golam, N. J. Trivedi and J. A. Olah, *J. Am. Chem. Soc.*, 1993, **115**, 7246; (b) G. A. Olah and C. H. Lin, *J. Am. Chem. Soc.*, 1971, **93**, 1259.

- 4 R. Duddu and R. Damavarapu, *Synth. Commun.*, 1996, **26**, 3495.
- 5 For a survey, see: T. Mori and H. Suzuki, *Synlett*, 1995, 383.
- 6 P. Neta and R. E. Huie, *J. Phys. Chem.*, 1986, **90**, 4644.
- 7 (a) M. Mella, M. Freccero, T. Soldi, E. Fasani and A. Albini, *J. Org. Chem.*, 1996, **61**, 1413; (b) E. Baciocchi, T. Del Giacco and G. V. Sebastiani, *Tetrahedron Lett.*, 1987, **28**, 1941; (c) T. Shono, Y. Yamamoto, K. Takigawa, H. Maekawa, M. Ishifune and S. Kashimura, *Chem. Lett.*, 1994, 1045; (d) I. Tabushi, S. Kojo and Z. Yoshida, *Chem. Lett.*, 1974, 1431. There are a few reports about the reaction of alkyl aromatics with nitrogen trioxide at benzylic position. However, these reactions are highly likely to proceed not *via* direct hydrogen abstraction but *via* deprotonation of a cation radical generated by one-electron transfer oxidation. See (e) E. Baciocchi, F. D'Acunzo, C. Galli and O. Lanzalunga, *J. Chem. Soc., Perkin Trans. 2*, 1996, 133; (f) T. Del Giacco, E. Baciocchi and S. Steenken, *J. Phys. Chem.*, 1993, **97**, 5451.
- 8 T. W. Martin, R. E. Rummel and R. C. Gross, *J. Am. Chem. Soc.*, 1964, **86**, 2595. Also see refs. 7a and 7b.
- 9 A. Boughriet and M. Wartel, *Electrochim. Acta*, 1991, **36**, 889; also see ref. 7c.
- 10 R. P. Wayne, I. Barnes, P. Biggs, J. P. Burrows, C. E. Canosa-Mas, J. Hjorth, G. LeBras, G. K. Moortgat, D. Perner, G. Poulet, G. Restelli and H. Sidebottom, *Atm. Environ.*, 1991, **25a**, 1.
- 11 J. M. Tedder, *Tetrahedron*, 1982, **38**, 313.
- 12 (a) G. J. Gleicher, J. L. Jackson, P. H. Owens and J. D. Unruh, *Tetrahedron Lett.*, 1969, 833; (b) P. H. Owens, G. J. Gleicher and L. M. Smith, Jr., *J. Am. Chem. Soc.*, 1968, **90**, 4122.
- 13 (a) I. Tabushi, Y. Aoyama, S. Kojo, J. Hamuro and Z. Yoshida, *J. Am. Chem. Soc.*, 1972, **94**, 1177; (b) F. Minisci, F. Fontana, S. Araneo, F. Recupero, S. Banfi and S. Quici, *J. Am. Chem. Soc.*, 1995, **117**, 226.
- 14 M. J. S. Dewar, G. G. Zoebisch, E. F. Healy and J. J. P. Stewart, *J. Am. Chem. Soc.*, 1985, **107**, 3902.

Paper 7/04419D

Received 23rd June 1997

Accepted 21st July 1997