

SHORT COMMUNICATION

RADICAL MECHANISM OF NUCLEOPHILIC SUBSTITUTION ON HALOCYCLOHEXANE SYSTEMS

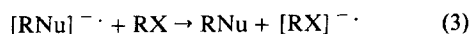
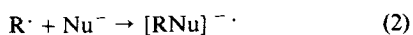
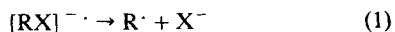
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Chlorocyclohexane does not react in the dark with diphenylphosphide ions in liquid ammonia, but it reacts under irradiation to give the substitution product. Bromocyclohexane reacts slowly in the dark, but this reaction is strongly accelerated by light, and inhibited by *p*-dinitrobenzene. 3-Bromo-2-tetrahydropyranyl allyl ether (used as a radical probe) reacts with diphenylphosphide ions under irradiation to give both the straightforward and the cyclized substitution products. This photostimulated reaction is also inhibited by *p*-dinitrobenzene. It is suggested that the chloro- and bromocyclohexanes and related compounds react under irradiation by the $S_{RN}1$ mechanism of nucleophilic substitution.

Nucleophilic substitution reactions of cycloalkyl halides have been studied and interesting results were obtained. For example, cyclopropyl and cyclobutyl halides react with nucleophiles with ring opening whereas compounds with five-, six and seven-membered rings react with nucleophiles by an S_N2 mechanism without rearrangement.¹ On the other hand, five-membered-ring compounds are about 14 times more reactive than cyclohexyl derivatives and cyclobutyl derivatives are 11 times more reactive than cyclohexyl derivatives.² Radical processes also show the same tendency.³

In addition to the classical reaction mechanisms for aliphatic nucleophilic substitution, such as the S_N1 and S_N2 mechanisms,¹ it has been found that several alkyl halides react by the radical mechanism of nucleophilic substitution, or $S_{RN}1$.⁴ This radical nucleophilic substitution is a chain process which involves radical and radical anions as intermediates. The main steps of this mechanism are shown in Scheme 1.⁵



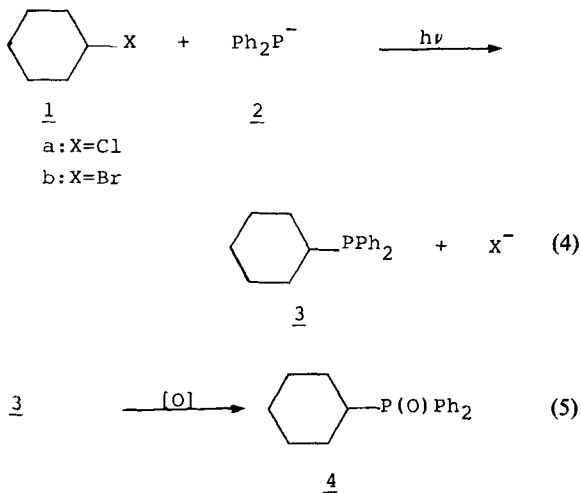
Scheme 1

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Cyclopropyl chlorides and bromides react by the $S_{RN}1$ mechanism,^{4,6} and we were interested in establishing whether cyclohexyl halides, which have a relatively low reactivity toward polar nucleophilic substitution,¹ could react through the radical mechanism of nucleophilic substitution. (It has been reported⁷ that chlorocyclohexane reacts with trimethylstannyl sodium in tetrahydrofuran, and 37% S_N2 substitution and 31% electron transfer was proposed, whereas bromocyclohexane reacts with 94% electron transfer and 4% halogen metal exchange.)

Cyclohexyl chloride (**1a**) did not react with diphenylphosphide ions (**2**) in liquid ammonia in the dark during 180 min, but under irradiation, in a reactor equipped with four 250-W UV lamps emitting maximally at 350 nm (Philips Model HPT, water refrigerated), it gave 33% yield of the substitution product **3**, isolated as cyclohexyldiphenylphosphine oxide (**4**) [equations (4) and (5)] (experiments 1 and 2, Table 1). Compound **4**: solid, m.p. 166–168 °C (recrystallized from hexane–dichloromethane, 8:2) (lit.: 168–169 °C;⁸ 165 °C⁹); ¹H NMR (δ), 1.26–2.43 (11 H broad peaks), 7.28–7.80 (10 H, m); ¹³C NMR (δ), 37.14 (¹ J_{CP} = 72.94, C₁), 24.70 (² J_{CP} = 2.82, C₂), 26.00 (³ J_{CP} = 24.18, C₃), 25.66 (C₄), 131.89 (¹ J_{CP} = 94.70, C_i), 131.00 (² J_{CP} = 9.27, C_o), 128.42 (³ J_{CP} = 11.28, C_m), 131.30 (⁴ J_{CP} = 2.80, C_p); mass spectrum, m/z (relative intensity) 284 (M⁺, 25), 283

(30), 229 (28), 202 (100), 183 (8), 155 (17), 135 (12), 125 (11), 77 (60). Cyclohexane and/or cyclohexene are completely lost when liquid ammonia is allowed to evaporate. We quantified only the substitution product.



p-Dinitrobenzene (*p*-DNB) has been used as an inhibitor of $S_{RN}1$ reactions.⁵ When 20 mol-% of *p*-DNB were added to the photostimulated reaction, it was completely inhibited (experiment 3, Table 1). The facts that **1a** does not react in the dark, but does so under irradiation, and that this photostimulated reaction is inhibited by *p*-DNB, suggest that **1a** reacts with **2** by the $S_{RN}1$ mechanism of nucleophilic substitution.

Cyclohexyl bromide (**1b**) reacts in the dark with **2** (4% and 21% yield of **4** in 10 and 30 min, respectively; experiments 4 and 6, Table 1). However, under irradiation it gives higher yields of **4** (30% and 93% in 10 and 30 min, respectively; experiments 5 and 7). The

photostimulated reaction was partially inhibited by *p*-DNB (experiment 8), but it has no effect in the dark reaction (experiment 9).

We synthesized the cyclizable radical probe **5** in order to demonstrate the cyclohexyl radicals are formed under these conditions (for reviews, see Refs. 10 and 11. Compound **5** was prepared according to Torii *et al.*¹²). The photostimulated reaction of **5** (5 min) gave, after oxidation with hydrogen peroxide, 13 20% of the substitution product **6** and a 69% yield of the cyclized substitution product **7** [equation (6)] (experiment 3, Table 2). Compound **6**: viscous liquid, isolated by preparative radial thin-layer chromatography (TLC) on silica gel, eluted with diethyl ether; ¹H NMR (δ), 1.45–2.74 (5 H, m), 3.32–4.22 (4 H, m), 4.58–4.81 (2 H, m), 4.94 (1 H, d, $J = 1.2$ Hz), 5.21–5.68 (1 H, m), 7.48–7.90 (10 H, m) ¹³C NMR (δ), 21.71 (² $J_{CP} = 3$, C₄), 24.4 (³ $J_{CP} = 9$, C₅), 40.3 (² $J_{CP} = 70$, C₃), 64.4 (C₆), 69.2 (C₈), 99.5 (C₂), 116.28 (C₁₀), 133.44 (C₉), 133.28 (¹ $J_{CP} = 68.5$, C_i), 130.52 (² $J_{CP} = 3$, C_o), 127.75 (³ $J_{CP} = 8.6$, C_m and C_{m'}), 131.1 (⁴ $J_{CP} = 3.4$, C_p and C_{p'}), 133.86

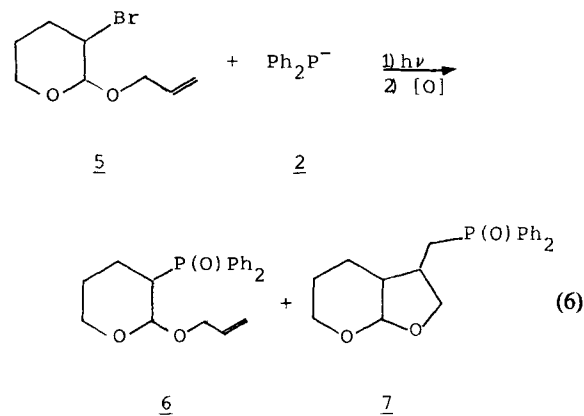


Table 1. Reactions of halocyclohexanes with diphenylphosphide ions (**2**) in liquid ammonia^a

Experiment No.	X in <i>c</i> -C ₆ H ₁₁ X	Conditions	Yield of <i>c</i> -C ₆ H ₁₁ P(O)Ph ₂ (%) ^b
1	Cl	Dark, 180 min	2
2	Cl	$h\nu$, 180 min	33
3 ^c	Cl	$h\nu$, 180 min	≤ 0.1
4	Br	Dark, 10 min	4
5	Br	$h\nu$, 10 min	30
6	Br	Dark, 30 min	21
7	Br	$h\nu$, 30 min	93
8 ^c	Br	$h\nu$, 30 min	25
9 ^c	Br	Dark, 30 min	20

^a Concentration of substrates and nucleophile 3×10^{-3} M.

^b Quantified by gas-liquid chromatography using the internal standard method, compared with an authentic sample.

^c *p*-DNB (20 mol-%) was added.

Table 2. Reactions of substrate **5** with diphenylphosphide ions (**2**) in liquid ammonia

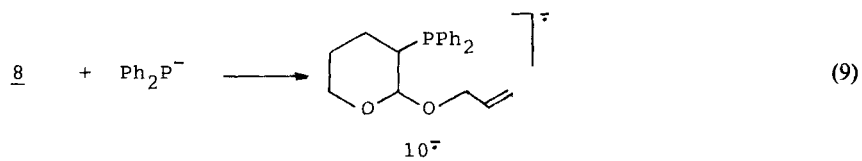
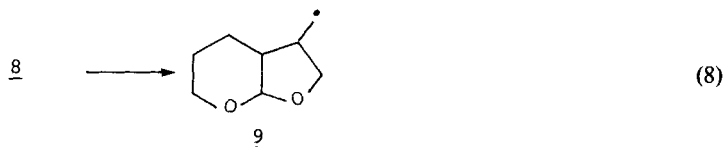
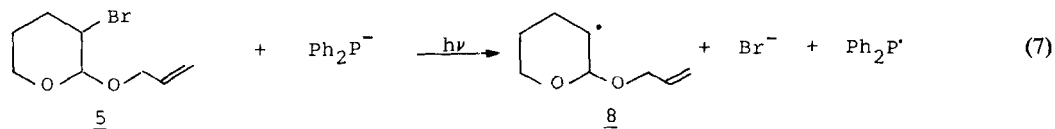
Experiment No.	5 mM	2 mM	Conditions ^a	Substitution products (%) ^b	
				6	7
1	3.3	3.3	Dark	6	6
2	0.6	0.6	$h\nu$	5	93
3	2.4	2.3	$h\nu$	20	69
4	19.9	18.8	$h\nu$	61	39
5 ^c	2.0	1.9	$h\nu$	12	24

^a Reaction time 5 min.^b Quantified by gas-liquid chromatography using the internal standard method, compared with authentic samples.^c *p*-DNB (20 mol-%) was added.

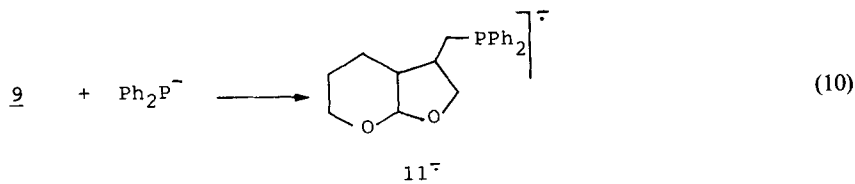
(¹*J*_{CP} = 72, *C*_i), 128.34 (³*J*_{CP} = 8.5, *C*_m); mass spectrum, *m/z* (relative intensity) 342 (*M*⁺, 2), 301 (29), 256 (47), 201 (100), 141 (33), 77 (26); high-resolution mass spectrum, *m/z* 343.1469 ([*M* + *H*]⁺ calculated 343.1463). Compound **7**: solid, isolated by preparative radial TLC on silica gel, eluted with diethyl ether; m.p. 94–95 °C (recrystallized from light petroleum-dichloromethane, 8:2); ¹H NMR (δ) 1.47–3.0 (8 H, m), 3.52–3.97 (4 H, m), 5.19 (1 H, d, *J* = 3.5), 7.48–7.9 (10 H, m); ¹³C NMR (δ), 19.1 (*C*₄), 22.5 (*C*₅), 27.5 (¹*J*_{CP} = 70.5, *C*₁₀), 34.3 (²*J*_{CP} = 3, *C*₉), 36.8 (³*J*_{CP} = 9, *C*₃), 60.2 (*C*₆), 69.6 (³*J*_{CP} = 9, *C*₈), 100.9 (*C*₂), 132.4 (¹*J*_{CP} = 95, *C*_i), 130.15 (²*J*_{CP} = 10, *C*_o), 128.25 (³*J*_{CP} = 10, *C*_m), 131.4 (*C*_p); mass spectrum, *m/z* (relative intensity) 342 (2), 258 (11), 215 (41), 202 (100), 183 (13), 155 (12), 77 (18); high-resolution mass spectrum, *m/z* 343.1461 ([*M* + *H*]⁺ calculated 343.1463). The high-resolution mass spectra were measured in the Chemical Instrumentation Center at Yale University.

In the dark (5 min) 6% of **6** and 6% of **7** were obtained (experiment 1, Table 2) and the photostimulated reaction was inhibited by *p*-DNB (experiment 5). These results can be explained by an *S*_{RN1} reaction according to Scheme 2.

The photostimulated reaction between **5** and Ph₂P⁻ ions gives the radical **8** and Br⁻ ions [equation (7)]. Radical **8** either is trapped by the double bond to give the rearranged radical **9** [equation (8)], or reacts with Ph₂P⁻ ions to give the radical anion **10**^{-•} [equation (9)]. Radical **9** also reacts with the nucleophile to give the radical anion of the rearranged substitution product **11**^{-•} [equation (10)]. There is evidence to indicate the radicals will react intramolecularly with a suitably situated C=C bond in competition with reaction with a nucleophile.^{14,15} Both radical anions **10**^{-•} and **11**^{-•} transfer their extra electron to substrate **5** to give radical **8** and products **10** and **11**, respectively [equations (11) and (12)], which are oxidized to products **6** and **7** after work-up [equations (13) and (14)].



Scheme 2. (Continued)



Scheme 2

Scheme 2 shows that radical **8** has two competitive reactions, the intramolecular reaction with the double bond [equation (8)] and the intermolecular reaction with the nucleophile **2** [equation (9)], but only the latter depends on the concentration of nucleophile **2**. We studied the same reaction in more dilute solution in order to decrease the rate of equation (9) and found that there was a considerable increase in the cyclized product **7** (93% yield) and a decrease in the straightforward substitution product **6** (5% yield) (experiment 2, Table 2). On the other hand, in more concentrated solution there was an increase in the amount of product **6** (experiment 4, Table 2).

On the basis of these results, we suggest that **1a** reacts with **2** under irradiation by the $S_{\text{RN}}1$ mechanism, and **1b** and **5** also react with **2** by this mechanism to the extent of more than 90%. The reaction of these substrates in the dark suggests that some ionic mechanism is also taking place.

On the other hand, the competition between the reaction of the secondary radical **8** with the nucleophile and the reaction with the double bond suggests that the secondary radical **8** is more reactive than the tertiary radicals, where this type of competition did not occur.¹⁴

The scope and limitation of these reactions, together with the reactions of other halocycloalkanes, are under investigation and will be reported with mechanistic details in a subsequent paper.

ACKNOWLEDGEMENTS

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