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Photochemistry of Alkyl Halides. 12. Bromides vs Iodides[1]

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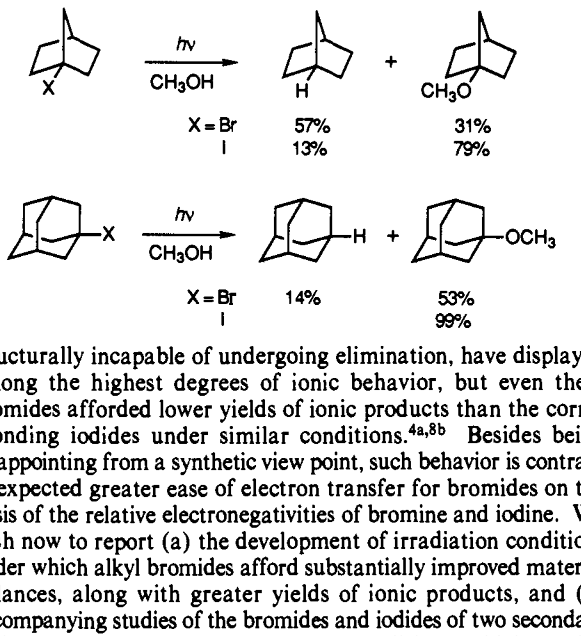
Abstract: Conditions have been developed for optimizing ionic photobehavior and good material balances from alkyl bromides. Hydroxide ion serves as an efficient scavenger for the byproduct HBr while giving minimal competing photoreduction via electron transfer to the alkyl bromide. The photobehavior of bromides **1**, **11**, **25**, and **40** has been examined and compared with that of the corresponding iodides **2**, **12**, **26**, and **41** under these conditions. In each case, the bromide gave higher yields of products derived from out of cage radical intermediates than the corresponding iodide. However, labeling studies with the 2-norbornyl bromides **11** and iodides **12** showed that, of products not formed from the out of cage 2-norbornyl radical **13**, the bromides **11** gave a higher percentage of products from the ionic intermediates **15** and **16** than did the iodides. Thus, electron transfer within the radical pair cage **14** is apparently more rapid for bromides than iodides, as expected on the basis of the relative electronegativities of bromine and iodine. It is suggested that the substantially higher yields of out of cage radical products from alkyl bromides may be due in part to formation of the radical pair with greater excess energy, which results in more rapid escape from the cage. The epimeric 2-norbornyl bromides **11x** and **11n** underwent no detectable interconversion and afforded somewhat different product ratios. The more hindered epimer **11n** underwent conversion to products at a slower rate than **11x**. By contrast, iodides **12x** and **12n** underwent substantial interconversion via out of cage transfer of an iodine atom from iodide **12** to radical **13**. Epimerization was significantly attenuated in the more viscous solvent *tert*-butyl alcohol.

Studies from these laboratories[2] and those of others[3] have shown that irradiation of alkyl iodides in solution affords mixtures of radical and ionic products, with the latter usually greatly predominating. This has proven to be a convenient and powerful method for the generation of carbocations, including many that are not readily available by classical, ground-state procedures such as bridgehead cations,[4] the 7-norbornyl cation,[5] and small-ring cyclic and α-unsubstituted vinyl cations.[6] The cationic intermediates apparently arise via a previously unrecognized electron transfer within an initially formed radical pair cage (Scheme I).[2,7]

Since the ionic products are usually obtained in high yields, the reaction is of synthetic, as well as mechanistic, interest. Unfortunately, the corresponding alkyl bromides, which are less expensive and more readily available, have displayed disappointing photobehavior in solution, usually affording lower material balances and substantially higher yields of radical-derived products.[4a,6,8] The two bridgehead bromides shown, which are structurally incapable of undergoing elimination, have displayed among the highest degrees of ionic behavior, but even these bromides afforded lower yields of ionic products than the corresponding iodides under similar conditions.[4a,8b] Besides being disappointing from a synthetic view point, such behavior is contrary to expected greater ease of electron transfer for bromides on the basis of the relative electronegativities of bromine and iodine. We wish now to report (a) the development of irradiation conditions under which alkyl bromides afford substantially improved material balances, along with greater yields of ionic products, and (b) accompanying studies of the bromides and iodides of two secondary and two primary systems under these conditions, which provide additional insights into the relative involvement of ionic and radical pathways in the photobehavior of alkyl bromides and iodides.



Results

2-Bromo- (1) and 2-Iodoadamantane (2). In our original studies, irradiation of bromide **1** in methanol afforded a mixture of the reduction product **7** (19% yield) and the nucleophilic substitution product **10** (47% yield), with only a modest material balance.[4a] Addition of 1 mol equiv of triethylamine as a scavenger for the byproduct HBr afforded a slightly higher material balance and gave, in addition to **7** and **10**, the 1,3-elimination product **8** (Table I).[7c] However, there was an accompanying increase in the yield of the reduction product **7**, presumably because of competing reaction via an amine–halide exciplex (eq 1) followed

$$\begin{tikzcd} (RX\cdot NEt_3)^* \arrow[r] & RX^{\overline{\cdot}} + \overset{+}{\cdot}NEt_3 \arrow[d] \\ & R\cdot + X^- \end{tikzcd} \qquad (1)$$

by rapid hydrogen atom transfer from the resulting amine radical cation to the alkyl radical.[4a] We have now found that photoreduction of alkyl bromides can be minimized by using the poorer electron donor hydroxide ion as the HBr scavenger in methanol

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[1] Part 11: Kropp, P. J.; Sawyer, J. A.; Snyder, J. J. *J. Org. Chem.* **1984**, *49*, 1583-1589.

[2] Kropp, P. J. *Acc. Chem. Res.* **1984**, *17*, 131-137.

[3] For a review of the photobehavior of alkyl halides in solution, see: Lodder, G. In *The Chemistry of Functional Groups, Supplement D*; Patai, S., Rappoport, Z., Eds.; Wiley: London, 1983; Chapter 29.

[4] (a) Kropp, P. J.; Poindexter, G. S.; Pienta, N. J.; Hamilton, D. C. *J. Am. Chem. Soc.* **1976**, *98*, 8135-8144. (b) Kropp, P. J.; Worsham, P. R.; Davidson, R. I.; Jones, T. H. *J. Am. Chem. Soc.* **1982**, *104*, 3972-3980. (c) Reddy, D. S.; Sollott, G. P.; Eaton, P. E. *J. Org. Chem.* **1989**, *54*, 722-723.

[5] Kropp, P. J.; Davidson, R. I.; Tise, F. P. McCraw, G. L.; Underwood, G. A. Manuscript in preparation.

[6] Kropp, P. J.; McNeeley, S. A.; Davis, R. D. *J. Am. Chem. Soc.* **1983**, *105*, 6907-6915.

[7] (a) Poindexter, G. S.; Kropp, P. J. *J. Am. Chem. Soc.* **1974**, *96*, 7142-7143. For subsequent demonstrations of electron transfer within radical pairs, see: (b) Pokhodenko, V. D.; Khizhnyi, V. A.; Koshechko, V. G.; Samarskii, V. A. *Theor. Exp. Chem.* (*Engl. Transl.*) **1975**, *11*, 489-493; *Teor. Eksp. Khim.* **1975**, *11*, 579-584. (c) Pokhodenko, V. D.; Khizhnyi, V. A.; Samarskii, V. A. *Theor. Exp. Chem.* (*Engl. Transl.*) **1975**, *11*, 564-567; *Teor. Eksp. Khim.* **1975**, *11*, 674-678. (d) Lawler, R. G.; Barbara, P. F.; Jacobs, D. *J. Am. Chem. Soc.* **1978**, *100*, 4912-4914. (e) Arnett, E. M.; Molter, K. E.; Marchot, E. C.; Donovan, W. H.; Smith, P. *J. Am. Chem. Soc.* **1987**, *109*, 3788-3789. (f) Lee, S.-G. *J. Chem. Soc., Chem. Commun.* **1987**, 1115-1117. (g) DeCosta, D. P.; Pincock, J. A. *J. Am. Chem. Soc.* **1989**, *111*, 8948-8950.

[8] (a) Dannenberg, J. J.; Dill, K.; Waits, H. P. *J. Chem. Soc., Chem. Commun.* **1971**, 1348-1349. Dannenberg, J. J.; Dill, K. *Tetrahedron Lett.* **1972**, 1571-1574. (b) Kropp, P. J.; Jones, T. H.; Poindexter, G. S. *J. Am. Chem. Soc.* **1973**, *95*, 5420-5421. (c) Perkins, R. R.; Pincock, R. E. *Tetrahedron Lett.* **1975**, 943-946. (d) Kropp, P. J.; Gibson, J. R.; Snyder, J. J.; Poindexter, G. S. *Tetrahedron Lett.* **1978**, 207-210. (e) Binkley, R. W.; Bankaitis, D. *J. Carbohydr. Chem.* **1982**, *1*, 1-8. (f) Kropp, P. J.; Pienta, N. J. *J. Org. Chem.* **1983**, *48*, 2084-2090. (g) Bhalerao, V. K.; Nanjundiah, B. S.; Sonawane, H. R.; Nair, P. M. *Tetrahedron* **1986**, *42*, 1487-1496. (h) Subbharao, K. V.; Damodaran, N. P.; Dev, S. *Tetrahedron* **1987**, *43*, 2543-2548.

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Scheme I

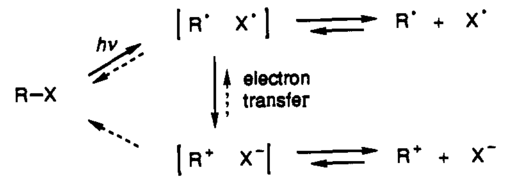


Table I. Irradiation of 2-Bromo- (1) and 2-Iodoadamantane (2)[a]

			yield, %[b]					
halide	solvent	time, h	halide	7	8	9	10	(8 + 9)/10
1	CH$_3$OH[c]	8	d	38	10		25	
	CH$_3$OH[e]	5	19	18	19	5	32	0.75
2	CH$_3$OH[e]	1	3	1	19	4	73	0.32

[a] Conducted as described in the Experimental Section. [b] Determined by gas chromatographic analysis relative to an internal hydrocarbon standard on aliquots removed from the reaction mixture. [c] Contained 1 mol equiv of triethylamine. [d] Trace. [e] Contained ammonium hydroxide.

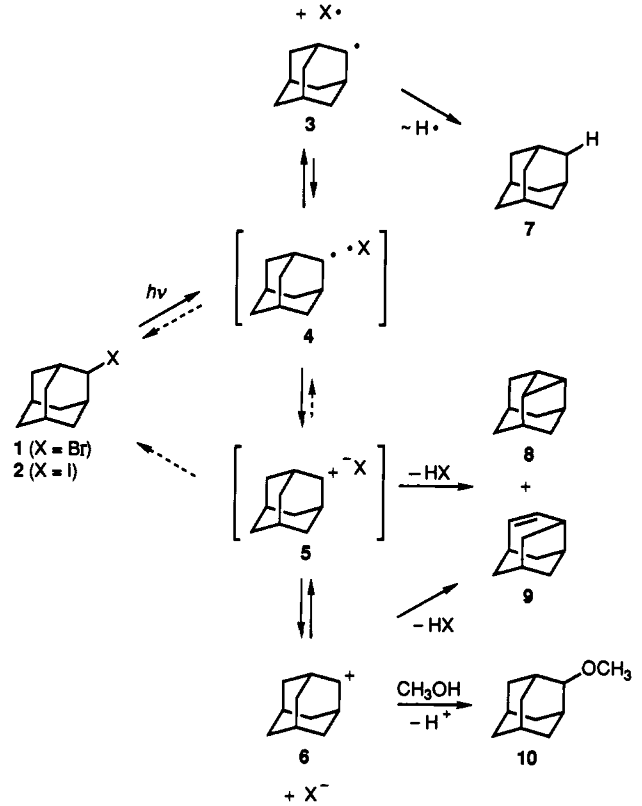
as solvent and have adopted these as standard conditions for the irradiation of bromides.[9,10] Under these conditions, bromide **1** afforded products **7**, **8**, and **10**—along with the rearranged product **9**, which had not previously been observed—with an excellent material balance. The corresponding iodide **2** afforded the same four products, but with even less of the reduction product **7** and substantially more of the nucleophilic substitution product **10**, under these conditions.

Products **7–10** apparently arise as shown in Scheme II. There is precedent for formation of the elimination products **8** and **9** from cationic intermediates[11] but apparently none from radical precursors. In principle, **8** and **9** might arise from either the ion pair **5** or the free cation **6**. The larger ratio of the elimination products **8** and **9** to the nucleophilic trapping product **10** from bromide **1** than from iodide **2** indicates that the free cation **6** is at least not the sole precursor to both types of products and is consistent with the greater basicity of Br$^-$ leading to more effective proton transfer within the ion pair **5** when X = Br.

2-Bromo- (11) and 2-Iodonorbornanes (12). The other secondary system studied, the 2-norbornyl system, was selected both because C-2 is a stereocenter and because the radical and carbocationic properties of the system have been well characterized and are easily distinguished. Irradiation of the exo bromide **11x** in methanol had previously been found to afford the reduction product norbornane (**18**) in 92% yield.[8a] By contrast, the use of ammonium hydroxide as an HBr scavanger afforded a mixture of products **17–21**, with equal amounts of the elimination products **19** and **20** predominating (Table II). The endo epimer **11n** gave the same four products **17–21**, but with the 1,3-elimination product **20** predominating. Surprisingly, the endo epimer **11n** underwent conversion to products with a quantum yield about one-fourth that of its exo counterpart **11x** under identical conditions. There was no detectable interconversion between **11x** and **11n**. Both isomers underwent somewhat more rapid conversion in *tert*-butyl alcohol, with a small increase in the ratio of the 1,3-elimination product **20** to the 1,2-elimination product **19** compared with that obtained in methanol. The difference in efficiencies of conversion of the epimers was somewhat less in *tert*-butyl alcohol, with the quantum yield for conversion of **11n** about half that of **11x**.

The corresponding iodides **12x** and **12n** also afforded principally the elimination products **19** and **20**. However, in contrast with the bromides **11**, there was no detectable formation of the radical products **17** and **18** and substantially more of the nucleophilic substitution product **21** (R = CH$_3$). Moreover, only minor differences in product ratios from the two epimers were observed, and **12x** and **12n** were found to undergo interconversion.[12,13] Iodide recovered after 50% conversion of **12n** to products was found by NMR analysis to be a 1:3 epimeric mixture of **12x** and **12n** when the irradiation was conducted in methanol but only a 1:12 mixture when *tert*-butyl alcohol was used as the solvent.[14]

Scheme II



The principal routes to photoproducts **17–21** are depicted in Scheme III. Dimer **17** and the reduction product **18** clearly arise via competitive coupling of the free radical **13** and hydrogen atom transfer from the solvent.[15,16] Nortricyclene (**20**) and the ether **21** are the expected products from competing deprotonation and nucleophilic trapping of the 2-norbornyl cation (**16**).[17,18] Nortricyclene (**20**) might also arise via proton transfer within the ion pair **15**. Since the ratio of nortricyclene (**20**) to ether **21** varied with the starting halide, both pathways to **20** appear to be involved.[19,20]

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[9] There is, of course, an equilibrium between hydroxide and methoxide ions under these conditions: $HO^- + CH_3OH \rightleftharpoons HOH + CH_3O^-$.

[10] By contrast, however, the presence of sodium methoxide afforded enhanced photoreduction of an aryl-substituted vinyl bromide, which is a much better electron acceptor than a saturated alkyl bromide: Verbeek, J. M.; Cornelisse, J.; Lodder, G. *Tetrahedron* **1986**, *42*, 5679–5684.

[11] Sinnott, M. L.; Soresund, H. J.; Whiting, M. C. *J. Chem. Soc., Chem. Commun.* **1969**, 1000–1001. See also: Alford, J. R.; McKervey, M. A. *Ibid.* **1970**, 615–616.

[12] Light-induced epimerization of iodide **12n** was previously observed during its preparation.[13]

[13] Brown, H. C.; De Lue, N. R.; Kabalka, G. W.; Hedgecock, H. C., Jr. *J. Am. Chem. Soc.* **1976**, *98*, 1290–1291.

[14] For other examples of light-induced epimerization of alkyl iodides, see: (a) Reference 4b. (b) Roth, R. C.; Binkley, R. W. *J. Org. Chem.* **1985**, *50*, 690–693. (c) Reference 5.

[15] Some disproportionation to norborane (**18**) and 2-norbornene (**19**) likely accompanies coupling of radical **13**. However, the ratio of disproportionation to coupling (k_d/k_c) is probably small for **13** because of the strain involved in introducing two trigonal centers in the norbornyl framework. For example, k_d/k_c for the cyclobutyl radical is 0.5.[16]

[16] Sheldon, R. A.; Kochi, J. K. *J. Am. Chem. Soc.* **1970**, *92*, 4395–4404.

[17] Quenching of the 2-norbornyl cation **16** in methanolic sodium methoxide is reported to give a mixture of nortricyclene (**20**) and ether **21** (R = CH$_3$).[18]

[18] Olah, G. A.; White, A. M.; DeMember, J. R.; Commeyras, A.; Lui, C. Y. *J. Am. Chem. Soc.* **1970**, *92*, 4627–4640.

[19] Hydrogen atom transfer from the 2-norbornyl radical (**13**) or within the radical pair **14** to afford nortricyclene (**20**) should be minor compared with formation of 2-norbornene (**19**). For example, 1,2-elimination predominated over 1,3-elimination in the thermal decomposition of 2-methyl-2-norbornyl peroxyesters in cumene by ratios of 15–19:1.[20]

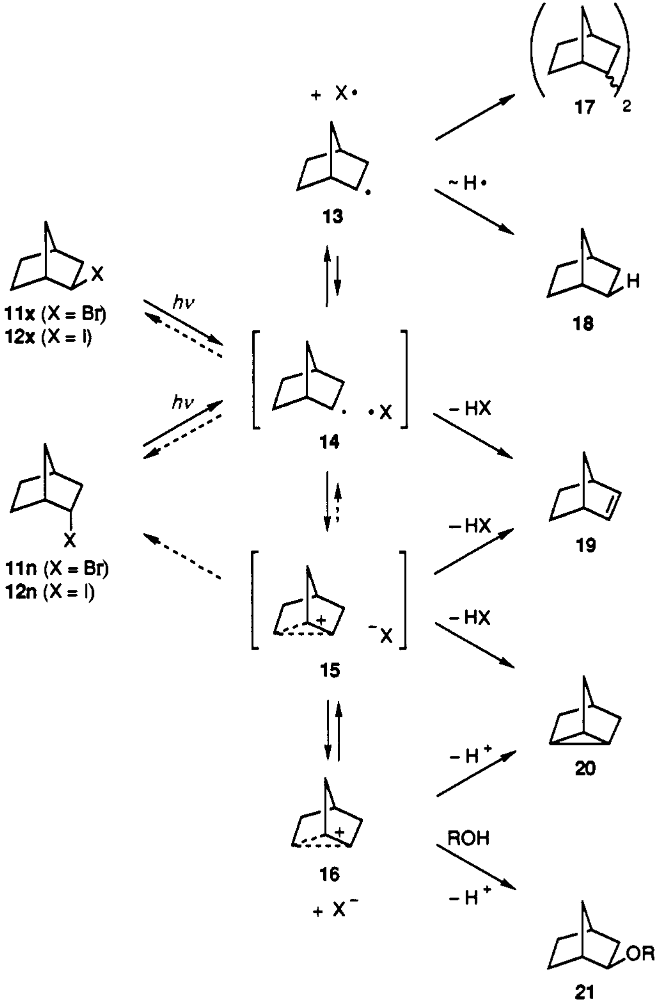
[20] Bartlett, P. D.; Fickes, G. N.; Haupt, F. C.; Helgeson, R. *Acc. Chem. Res.* **1970**, *3*, 177–185.

Table II. Irradiation of 2-Bromo- (**11**) and 2-Iodonorbornanes (**12**)[a]

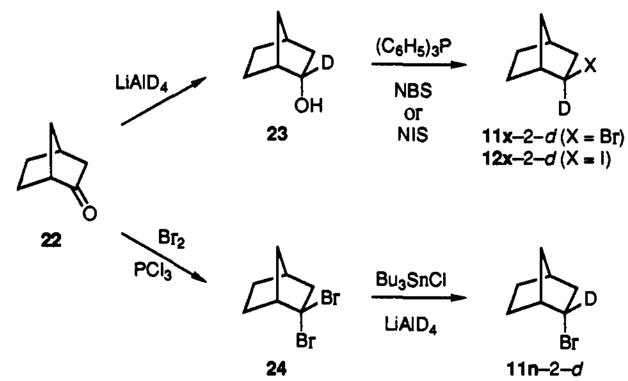
halide	solvent	time, h	yield, %[b] halide	**17**	**18**	**19**	**20**	**21**	**20/21**	R
11x	CH_3OH	3	35	5	9	20	20	11	1.8	CH_3
		6	11	8	13	27	27	14	1.9	CH_3
	$(CH_3)_3COH$	1.5	47	2	2	25	27	1		$(CH_3)_3C$
		3	21	3	3	31	37	1		$(CH_3)_3C$
11n	CH_3OH	3	62	2	5	10	13	5	2.6	CH_3
		6	42	2	7	13	19	8	2.4	CH_3
		12	21	2	9	18	26	10	2.6	CH_3
	$(CH_3)_3COH$	1.5	59	2	3	13	21	1		$(CH_3)_3C$
		3	39	3	3	16	32	2		$(CH_3)_3C$
		6	18	4	5	18	43	2		$(CH_3)_3C$
12x	CH_3OH	1.5	10			36	26	20	1.3	CH_3
	$(CH_3)_3COH$	4	16			41	43			
12n	CH_3OH	1.5	7			36	31	21	1.5	CH_3
	CH_3OH	0.5[c]	62[d]			15	13	10	1.3	CH_3
	$(CH_3)_3COH$	0.75[c]	50[e]							

[a] Conducted in the presence of ammonium hydroxide as described in the Experimental Section. [b] Determined by gas chromatographic analysis relative to an internal hydrocarbon standard on aliquots removed from the reaction mixture. [c] Conducted with twice the standard amount of **12n**. [d] ^1H NMR analysis of recovered material showed it to be 25% **12x** and 75% **12n**. [e] ^1H NMR analysis of recovered material showed it to be 10% **12x** and 90% **12n**.

Scheme III



Scheme IV



The origin of 2-norbornene (**19**) is less clear since it could arise from either hydrogen atom transfer within the radical pair **14** or proton transfer within the ion pair **15**.[15] To obtain further insight into the formation of **19**, derivatives of bromides **11x** and **11n** and iodide **12x** labeled with deuterium at C-2 were prepared as shown in Scheme IV and their photobehavior studied. As seen in Table III, treatment of labeled alcohol **23** with triphenylphosphine and the appropriate *N*-halosuccinimide afforded derivatives of **11x** and **12x** that were exclusively exo, but in which the label was partially scrambled between C-1 and C-2. Stepwise substitution via a carbocationic intermediate apparently competes to some extent with concerted displacement in this reaction. On the other hand, treatment of dibromide **24** with Bu_3SnD afforded bromide **11n** that was only 92% endo but was deuterated exclusively at C-2.

The results from irradiation of the labeled derivatives are summarized in Table III. Ether **21** (R = CH_3) obtained from irradiation of all three labeled halides had complete equilibration of deuterium between C-1 and C-2, along with partial equilibration at C-6, as expected for formation from a 2-norbornyl cationic intermediate **16** having a moderate lifetime.[21] By contrast, norbornane (**18**) was formed from the labeled bromides **11x**-*2-d* and **11n**-*2-d* with little loss of deuterium from C-2. Moreover, the deuterium was 85–87% in the endo position, regardless of the initial stereochemistry, as expected for preferential transfer of a hydrogen atom to the exo side of the 2-norbornyl radical (**13**).[22,23]

Because of the equivalence of C-1, -2, and -6 in nortricyclene (**20**), no conclusions with regard to equilibration at these positions can be drawn.[24] However, the 2-norbornene (**19**) isolated from

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(21) The 2-norbornyl cation **16** undergoes a 6,1,2 hydride shift with a rate of 1 × 10^6 s^{-1} at 25 °C.[18]

(22) In contrast with the 2-norbornyl cation (**16**), which undergoes almost exclusive reaction from the exo face, the 2-norbornyl radical (**13**) has only a moderate preference for reacting in atom-transfer reactions from the exo face, with the degree of selectivity dependent on the atom donor involved.[20]

(23) The small amount of scrambling of deuterium to C-1 in norbornane (**18**) may arise from some recombination within the ion pair **15** to afford a mixture of **11x**-*1-d* and **11x**-*2-d*, followed by secondary photolysis of this material.

(24) The lack of any significant loss of deuterium in the formation of nortricyclene (**20**) indicates that α-elimination to a carbene intermediate does not occur in the 2-norbornyl system. 2-Norbornylidene undergoes exclusive 1,3-insertion to nortricyclene (**20**): Friedman, L.; Schechter, H. *J. Am. Chem. Soc.* **1961**, *83*, 3159–3160. Freeman, P. K.; George, D. E.; Rao, V. N. M. *J. Org. Chem.* **1964**, *29*, 1682–1684.

Table III. Deuterium Distributions in Halides **11x**-*2-d*, **11n**-*2-d*, and **12x**-*2-d* and Their Photoproducts[a]

	halide				**18**			**19**			**20**		**21** (R = CH_3)			
	1	2x	2n	(%)[b]	1	2x	2n	1	2	(%)[b]	1	3	1	2n	6x	6n
11x-*2-d*	18		82	(36)	22	10	68	40	60	(80)	99	1	42	40	10	8
11n-*2-d*		92	8	(0)	7	14	79[c]	32	68	(64)[d]	97	3[d]	42	41	9	8[c]
		92	8	(0)				20	80	(40)[e]						
12x-*2-d*	14		86	(28)				27	73	(54)	99	1[c]	44	43	7	6
	19	4	77	(38)[f]												

[a] Irradiations were conducted according to the preparative procedure outlined in the Experimental Section and deuterium distributions determined by ^1H and ^2H NMR analysis. [b] Percent scrambling between C-1 and -2. [c] 100% D_1 by mass spectral analysis. [d] 96% D_1 by mass spectral analysis. [e] Irradiation conducted in the presence of a 1.5-kG external magnetic field. [f] Recovered from irradiation of a sample of the preceding iodide until 47% conversion to photoproducts had occurred.

Table IV. Irradiation of Bromide **11x** and Iodide **12x** in an External Magnetic Field[a]

			yield, %[b]						
halide	field, kJ	time, h	halide	**17**	**18**	**19**	**20**	**21**[c]	**19**/(**20** + **21**)
11x	0	3	18	5	10	26	27	14	0.63
	0.75	3	25	5	9	24	23	13	0.66
	1.1	3	34	5	9	21	20	11	0.68
	1.5	3	39	5	8	20	18	10	0.71
12x	0	2.5	4			42	30	24	0.78
	1.5	2.5	14			39	27	20	0.83

[a] Conducted in methanol containing ammonium hydroxide as described in the Experimental Section. [b] Determined by gas chromatographic analysis relative to an internal hydrocarbon standard on aliquots removed from the reaction mixture. [c] R = CH_3.

11n-*2-d* was found to have partial scrambling of the label between C-1 and C-2, as expected from competing formation via cationic and radical pathways.[25] Similarly, the exo derivatives **11x**-*2-d* and **12x**-*2-d*, which had undergone partial scrambling between C-1 and -2 during their preparation, afforded 2-norbornene (**19**) with increased scrambling at these positions. The data in Table III indicate that the percent ionic pathway to 2-norbornene (**19**), as reflected by the percent increase in scrambling, is 64–69% for bromides **11x** and **11n** but only 36% for iodide **12x**. Finally, iodide isolated from 47% photoconversion of **12x**-*2-d* had 10% scrambling of the label between C-1 and C-2 and contained 4% of the epimer **12n**-*2-d*.

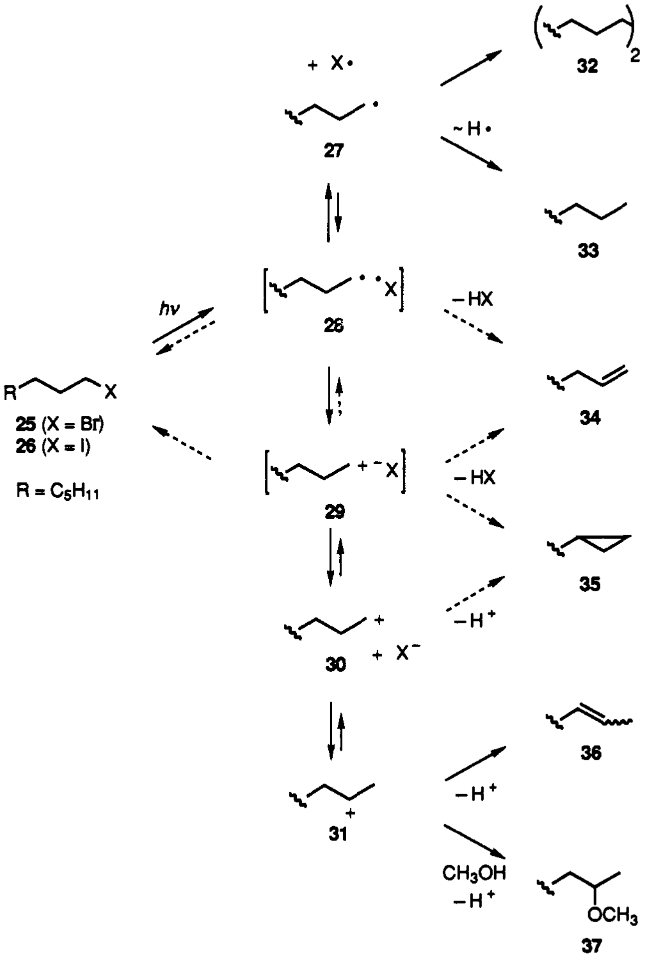
Since product ratios from caged radical pairs are often subject to magnetic field effects, bromide **11x** and iodide **12x** were irradiated in the presence of an external magnetic field (Table IV). Radical pair **14** should experience decreased S → T intersystem crossing efficiency as a function of field strength, with the maximum effect observed when the external field exceeds the magnitude of the hyperfine couplings.[26] Indeed, the rate of disappearance of bromide **11x** decreased with increasing field strength, as expected if decreased S → T intersystem crossing permitted increased recombination of singlet radicals to starting halide **11x**. Iodide **12x** displayed a similar, though smaller, effect. Moreover, irradiation of the labeled bromide **11n**-*2-d* in the presence of an external magnetic field afforded 2-norbornene (**19**) with reduced deuterium scrambling (Table III) consistent with decreased intersystem crossing permitting increased hydrogen atom transfer within the singlet radical pair **14** to give unscrambled 2-norbornene (**19**). And there was the expected accompanying increase in the yield of **19** relative to the ionic products **20** and **21**.[27]

Table V. Irradiation of 1-Bromo- (**25**) and 1-Iodooctane (**26**)[a]

		yield, %[b]							
halide	time, h	halide	**32**	**33**	**34**	**35**	**36**	**37**
25	8	11	16	18	30	2	4[c]	2
26	3	6		3	67	2	6[c]	1

[a] Conducted in methanol solution containing ammonium hydroxide as described in the Experimental Section. [b] Determined by gas chromatographic analysis relative to an internal hydrocarbon standard on aliquots removed from the reaction mixture. [c] An approximately 1:1 mixture of the *E* and *Z* isomers.

Scheme V



1-Bromo- (25) and 1-Iodooctane (26). Previous irradiation of the primary bromide **25** in methanol gave exclusively the reduction product octane (**33**).[4a] By contrast, irradiation in the presence of ammonium hydroxide has now afforded a mixture of six products **32**–**37**, with the 1,2-elimination product 1-octene (**34**) predominating (Table V). Under the same conditions, the analogous iodide **26** afforded substantially more 1-octene (**34**)—with none of the radical-coupling product **32** and much less of the reduction product octane (**33**).

These products apparently arise as shown in Scheme V. The major difference between bromide **25** and iodide **26** is the formation by the former of substantially greater quantities of hex-

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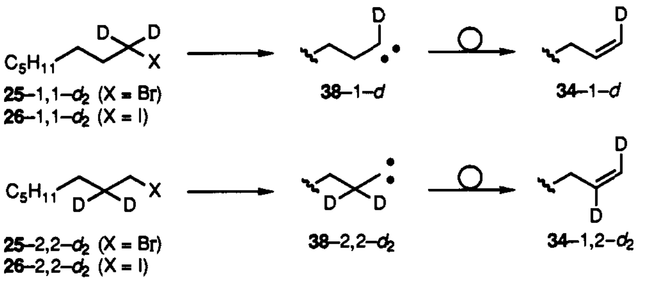
[25] The lack of any detectable deuterium at C-6 confirms the conclusion that the ionic pathway to 2-norbornene (**19**) involves the ion pair **15** rather than the free cation **16**, which, as seen in ether **21** (R = CH_3), has suficient lifetime for partial C-2, -6 equilibration.

[26] Gould, I. R.; Turro, N. J.; Zimmt, M. B. *Adv. Phys. Org. Chem.* **1984**, *20*, 1–53.

[27] However, the observed effects were small, and there was not a significant decrease in the yields of the out of cage products **17** and **18**, which would be expected to accompany decreased intersystem crossing efficiency. Thus, it is not clear what conclusions can be safely drawn without further study of magnetic field effects in this system, which are currently underway.

Scheme VI



Scheme VII

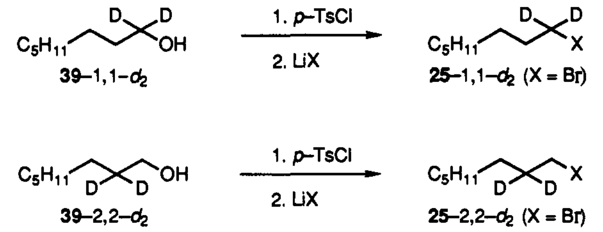


Table VI. Deuterium Distributions in Bromides 25-*1,1*-d_2 and 25-*2,2*-d_2 and Their Photoproducts 33 and 34[a]

	25		33		34	
	1	2	1	2	1	2
25-*1,1*-d_2	100		100[b]		99[c]	
25-*2,2*-d_2	2	98	2	98	9	91

[a] Irradiations were conducted according to the preparative procedure outlined in the Experimental Section and deuterium distributions determined by ^1H and ^2H NMR analysis. [b] 99% D_2, 1% D_1 by mass spectral analysis. [c] 92% D_2, 8% D_1 by mass spectral analysis.

adecane (32) and octane (33), which arise via competing coupling and hydrogen atom abstraction of the out of cage radical 27.[28] Unfortunately, the relative involvement of the radical pair 28 and the ion pair 29 in the formation of the major product, 1-octene (34), from each halide cannot be assessed. However, the 1,3-elimination product 35 most likely arises from either the ion pair 29 or the free ion 30 in each case.[29] The 2-octenes 36 and the ether 37 clearly arise from the rearranged cation 31.

A previous study showed that a number of primary and secondary alkyl iodides undergo partial α-elimination on irradiation.[1] Thus, the labeled iodide 26-*1,1*-d_2 gave 1-octene (34) containing 19% of 34-*1*-*d* formed by loss of an α-deuterium atom (Scheme VI). Similarly, iodide 26-*2,2*-d_2 gave 22% of 34-*1,2*-d_2 in which one of the deuterium atoms had migrated to C-1. These observations imply that 19–22% of 1-octene (34) was formed via net α-elimination of DI or HI to afford the carbene intermediate 38-*1*-*d* or 38-*2,2*-d_2, respectively. Since there was no significant isotope effect on the quantum yield for α-elimination, it apparently occurs in a stepwise, rather than concerted, fashion involving either the radical pair 28 or ion pair 29.

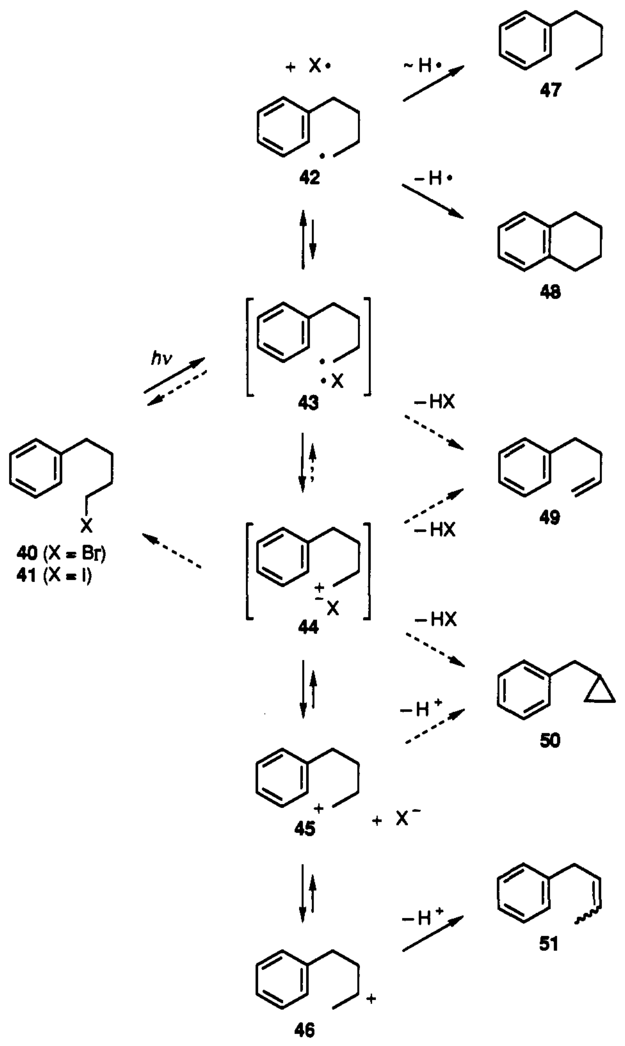
It was thus of interest to determine the relative involvement of α-elimination in the photobehavior of bromide 25. The analogous labeled derivatives of 25 were prepared as shown in Scheme VII. As seen in Table VI, the reduction product 33 was obtained from each of the derivatives with no change in location or amount of the label, as expected. However, 1-octene (34) was obtained from bromide 25-*1,1*-d_2 with loss of 7% of deuterium and from bromide 25-*2,2*-d_2 with 7% migration of deuterium from C-2 to C-1. Thus, bromide 25 undergoes partial α-elimination but to a lesser extent than iodide 26.[30]

Table VII. Irradiation of 1-Bromo- (40) and 1-Iodo-4-phenylbutane (41)[a]

		yield, %[b]					
halide	time, h	halide	47	48	49	50	51
40	6	30	15	14	32	2	2[c]
41	2.5	7	4	10	67	2	10[c]

[a] Conducted in methanol solution containing ammonium hydroxide as described in the Experimental Section. [b] Determined by gas chromatographic analysis relative to an internal hydrocarbon standard on aliquots removed from the reaction mixture. [c] An approximately 1:1 mixture of the *E* and *Z* isomers.

Scheme VIII



1-Bromo- (40) and 1-Iodo-4-phenylbutane (41). Previous irradiation of the primary bromide 40 in the presence of triethylamine afforded principally the reduction product 47, accompanied by small amounts of the cyclization product 48 and the 1,2-elimination product 49.[8h] As noted previously, reduction under these conditions involves photoinitiated electron transfer from the amine (eq 1) followed by transfer of a hydrogen atom from the resulting amine radical cation. When zinc wool was employed as the HBr scavenger, the cyclization and elimination products 48 and 49 were obtained as the principal products in approximately equal yields, accompanied by a small amount of the reduction product 47.[8g] The use of ammonium hydroxide as scavenger has now afforded a substantially higher ratio of the

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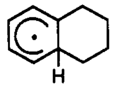
(28) Although disproportionation usually accompanies coupling of radicals, it is only a minor process for a linear 1-alkyl radical such as 27. For example, k_d/k_c for the 1-butyl radical is 0.1.[16]

(29) Although carbocations generated solvolytically usually do not give cyclopropanes, those generated by reactions involving less solvent participation frequently do: Keating, J. T.; Skell, P. S. In *Carbonium Ions*; Olah, G. A., Schleyer, P. v. R., Eds.; Wiley-Interscience: New York, 1970; Vol. 2, Chapter, 15.

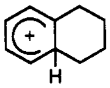
(30) The carbene route is also not a major pathway to the 1,3-elimination product 35 from bromide 25 since 1,2-insertion predominates over 1,3-rearrangement in linear 1-alkyl carbenes. For example, the ratio of 1,2- to 1,3-insertion for 1-pentylidene is 10:1: Mansoor, A. M.; Stevens, I. D. R. *Tetrahedron Lett.* **1966**, 1733–1737.

elimination (**49**) to the cyclization product (**48**) accompanied by some of the reduction product **47** and the ionic products **50** and **51** (Table VII).[31] The lower yield of the 1,2-elimination product **49** in the presence of the less efficient heterogeneous scavenger zinc wool is probably due to radical addition of HBr to **49** to regenerate bromide **40**.

The corresponding iodide **41** gave the same five products **47–51**, but with substantially higher yields of the elimination products **49** and **51** (Table VII).[32] The products from bromide **40** and iodide **41** apparently arise as shown in Scheme VIII. Disproportionation of the 4-phenylbutyl radical (**42**) affords, in addition to 4-phenylbutane (**47**), principally tetralin (**48**), via the cyclized radical **42a**, rather than 4-phenyl-1-butene (**49**).[33] However, since the yield of tetralin (**48**) from iodide **41** exceeds that of the reduction product **47**, some tetralin (**48**) apparently also arises via deprotonation of the cyclized cation **45a**.[32b] The principal product **49** apparently arises from the radical pair **43**, the ion pair **44**, or some combination of the two.[34] Cyclopropane **50** and the rearranged elimination products **51** clearly arise from the ionic intermediates **45** and **46**, respectively.[27]



42a



45a

Discussion

Removal of the byproduct HBr, which is both a strong acid and a source of radicals, affords greatly improved material balances from alkyl bromides, especially those that give unsaturated products. This can be readily accomplished with hydroxide ion in methanol without suffering any significant competing photoreduction resulting from electron transfer to the alkyl bromide. Under these conditions, bromides **1**, **11**, **25**, and **40** underwent efficient photoconversion with good material balances.

Bromides vs Iodides. Although the photobehavior of bromides **1**, **11**, **25**, and **40** qualitatively resembled that of iodides **2**, **12**, **25**, and **41**, in each case the bromide gave out of cage radical products in substantially higher yield than the corresponding iodide. Thus, escape from the initially formed radical pair **4**, **14**, **28**, or **43**, relative to competing hydrogen atom or electron transfer, occurs more readily for bromides, despite the fact that the more electronegative bromine atom would be expected to undergo both hydrogen atom and electron transfer more readily than iodine.

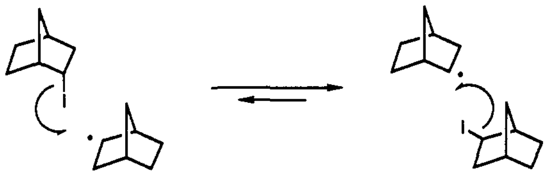
We previously suggested that electron transfer might occur to iodine more readily than expected on the basis of electronegativity because of either its greater polarizability or the lesser charge point density that would result compared with bromine.[4a] However, the present results suggest that the difference in behavior is due not to unexpectedly high rates of electron transfer for iodides but, rather, more rapid rates of separation from the radical pair for bromides. This is best seen by focusing on the in-cage products from the 2-norbornyl halides **11** and **12**. The labeling studies summarized in Table III show that 2-norbornene (**19**) arises predominantly (64–69%) from ion pair **15** for the bromides **11** but principally (63%) from the radical pair **14** for the iodides **12**. These distributions, combined with the yields of the ionic products nortricyclene (**20**) and the ether **21** (R = CH_3), afford a ratio of in-cage radical to total ionic products of only 1:8 for bromides **11** but 1:3 for iodides **12**. Thus, of the material that is not lost by diffusion from the radical pair **14**, a higher percentage is converted to products via the ion pair **15** (or cation **16**) when X = Br, as expected on the basis of the relative electronegativities of bromine and iodine.

Table VIII. Excess Energy after Bond Cleavage[a]

	bromides		iodides	
	1	**25**	**2**	**26**
$\lambda_{0,0}$[b]	471	484	379	390
D_0(R–X)[c]	285	285	222	224
Δ	186	199	157	166

[a] In kilojoules per mole. [b] Estimated from the onset of absorption. [c] Values used are those for 1- and 2-bromo- and 1- and 2-iodopropane: Streitwieser, Jr., A.; Heathcock, C. H. *Introduction to Organic Chemistry*, 3rd ed.; Macmillan: New York; 1985.

Scheme IX



The more efficient diffusion from the cage for bromides may arise, at least in part, from greater excess energy remaining after cleavage of the carbon–halogen bond of the excited state. As shown in Table VIII for bromides **1** and **25** and iodides **2** and **26**, the difference between the energy of the 0,0 level of the n,σ^* excited state and the bond dissociation energy is substantially greater for bromides than iodides. This excess energy is transmitted to the two fragments as a combination of vibrational and translational energy. Combined with the lower mass of bromine, the greater translational energy results in more rapid diffusion from the cage.

It is interesting to note that a lower percentage of the total ionic product arises from nucleophilic trapping of the 2-norbornyl cation **16** to afford ether **21** (R = CH_3) for the bromides **11** (21–23%) than iodides **12** (34%). A similar trend is evident in Table I for bromide **1** and iodide **2**. This difference probably arises from the greater basicity of bromide, which permits proton transfer to compete more effectively with escape from the ion pair **5** or **15** for bromides than iodides. On the other hand, the 1-octyl halides **25** and **26** and the 4-phenyl halides **40** and **41** afford comparable amounts of the out of cage ionic products **35–37** and **50** and **51**, respectively. Separation of the ion pairs **29** and **44** probably occurs less readily due to the lesser stability of primary carbocations **30** and **45**.

Epimerization. Once out of the cage, the alkyl radical can abstract a hydrogen atom from the solvent or undergo combination/disproportionation with a second alkyl radical. Another available pathway in the case of iodides is transfer of an iodine atom from a molecule of unreacted starting material. Halogen atom transfer occurs readily for alkyl iodides ($k \approx 2 \times 10^5$ M^{-1} s^{-1})[35] and accounts for the observed interconversion of iodides **12x** and **12n** (Scheme IX).[22,36] In the more viscous solvent *tert*-butyl alcohol, in which escape from the radical cage **14** occurs more slowly, there was substantially less epimerization. In contrast with iodides, halogen atom transfer is much slower for alkyl bromides ($k \approx 6 \times 10^2$ M^{-1} s^{-1}),[35] allowing abstraction of a hydrogen atom from methanol ($k \approx 1 \times 10^4$ s^{-1})[37] to compete. Hence, bromides **11x** and **11n** underwent no detectable epimerization during the course of irradiation.

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[31] In contrast with the preceding bromides, which were excited by direct absorption, it is likely that the photobehavior observed for bromide **40** is initiated, at least in part, by transfer of energy from the phenyl group to the C-Br chromophore since similar results were obtained on irradiation of bromide **40** at 254 nm. Moreover, 2-bromobutane quenches the fluorescence of propylbenzene.[8a]

[32] Photoproducts **47–49**, but not **50** and **51**, were previously observed from iodide **41**: (a) Charlton, J. L.; Williams, G. J.; Lypka, G. N. *Can. J. Chem.* **1980**, *58*, 1271–1274. (b) References 8g and 8h.

[33] (a) DeTar, D. F.; Weis, C. *J. Am. Chem. Soc.* **1956**, *78*, 4296–4301. (b) Winstein, S.; Heck, R.; Lapporte, S.; Baird, R. *Experientia* **1956**, *12*, 138–141. (c) Kochi, J. K.; Gilliom, R. D. *J. Am. Chem. Soc.* **1964**, *86*, 5251–5256.

[34] Radical pair **43** cannot be a source of tetralin (**48**), which is formed only out of cage,[30b] presumably because the rate of cyclization to intermediate **42a** is slower than the rate of diffusion from the cage. A similar argument can be applied to the formation of tetralin (**48**) from ion pair **44**.

[35] Newcomb, M.; Sanchez, R. M.; Kaplan, J. *J. Am. Chem. Soc.* **1987**, *109*, 1195–1199.

[36] For extensive evidence that photoepimerization of another alkyl iodide involves, at least principally, an out of cage radical chain process, see ref 14b.

[37] Estimated from the rate constant for abstraction of a hydrogen atom from tetrahydrofuran: Newcomb, M.; Kaplan, J. *Tetrahedron Lett.* **1988**, *29*, 3449–3450.

In principle, epimerization might also occur via recombination of the radical or ion pair.[38] The observed magnetic field effects for bromide **11x** and iodide **12x** and the partial scrambling of **12x**-*2-d* recovered after partial conversion (Table III) show that some recombination occurs within both the radical pair cage **14** and the ion pair cage **15**.[39] However, the lack of any detectable epimerization of bromides **11x** and **11n** indicates that recombination, at least for bromides, occurs without accompanying loss of stereochemical integrity.

Differences between Bromides 11x and 11n. Bromide **11n** undergoes less efficient conversion to products in methanol than the epimer **11x** under identical irradiation conditions, despite the similarity of their UV absorption spectra. This is probably not due to enhanced recombination within the radical pair **14n** since the endo side of the 2-norbornyl radical is more hindered than the exo face. The difference is most likely due to steric interaction of the endo bromine substituent with the adjacent endo hydrogen atoms at C-5 and C-6 retarding bond cleavage. If so, this is apparently the first photochemical example of steric departure control.[40] The smaller difference in the efficiencies of conversion of the epimeric bromides **11** to products in *tert*-butyl alcohol is probably due to less separation in the radical pair in the more viscous solvent. The failure of the epimeric iodides **12x** and **12n** to display a significant difference in efficiency of conversion to products is likely due to the longer length of the C–I bond, which reduces steric interaction of the halogen atom with the C-5 and C-6 endo hydrogen substituents.[41]

Finally, it is interesting to note that the endo epimer **11n** affords a larger ratio of nortricyclene (**20**) to both 2-norbornene (**19**) (1.4) and the ether **21** (R = CH_3) (2.5) in methanol than does the exo epimer **11x** (ratios of 1.0 and 1.9, respectively). This is probably due to the bromine atom in the ion pair **15** arising from bromide **11n** being initially on the endo side, where it can more readily abstract a proton from C-6 to afford nortricyclene (**20**) than if it were on the exo side. The preference of the endo epimer to give nortricyclene (**20**) relative to 2-norbornene (**19**) is even greater in the more viscous solvent *tert*-butyl alcohol (ratio of 2.0 vs 1.4).

The balance of radical vs ionic photobehavior in alkyl halides is clearly related to the properties of radical pairs and depends on the identity of the component radicals and the environment in which they are created. Studies continue on the generation of radical pairs from other precursors, as well as on the effects of environmental changes on their behavior.

Experimental Section

General Procedures. Infrared spectra were obtained on neat samples with a Beckman 4250 spectrophotometer and are reported to the nearest 5 cm^{-1}. Ultraviolet absorption spectra were obtained on a Hewlett-Packard 8451A diode array spectrophotometer in the solvent specified. Proton NMR spectra were determined in $CDCl_3$ solution on a Bruker AC-200 spectrometer, and deuterium spectra were obtained on a Varian XL-400 spectrometer in CCl_4 solution. Mass spectra were obtained on a Micromass 7070F instrument. Gas chromatographic analyses were performed on a Hewlett-Packard 5750 instrument equipped with a 10 ft × 0.125 in. stainless steel column containing either 20% SF-96, 20% Carbowax 20M, or 20% β,β-oxydipropionitrile on 60–80 mesh Chromosorb W. Preparative gas chromatography was performed on a Varian Aerograph 90-P instrument equipped with 10 ft × 0.25 in. stainless steel columns packed as described above.

Irradiations. Irradiations were conducted in 200 × 14 mm quartz tubes made of 1-mm wall thickness General Electric type 204 clear fused quartz tubing and placed in a water-cooled quartz immersion well that was either suspended in a Rayonet RPR-100 photochemical reactor equipped with a circular array of 16 G8T5 lamps (iodides) or postioned 6 cm from a 450-W Hanovia medium-pressure mercury arc lamp and reflector (bromides). For magnetic field studies, the immersion well was placed between the poles of a Variflux VFM-2 magnet. All solvents employed in distillations were used as received except for those treated as follows: *tert*-butyl alcohol, distillation from CaH_2; methanol, distillation from Mg and storage over 3-Å molecular sieves; pentane, distillation from Br_2.

In a typical small-scale irradiation, either 50 μL or 50 mg of the substrate and 50 μL of tetradecane (internal standard) were added to an oven-dried tube along with 5 mL of purified solvent. The tube was then fitted with a rubber stopper pierced with two hypodermic needles, one of which was attached to a section of polyethylene capillary tubing for the introduction of N_2 into the solution and for the withdrawal of aliquots. The solution was deaerated by bubbling for at least 5 min, an aliquot was removed for gas chromatographic analysis, and irradiation was commenced. The temperature of the solution was maintained at 10 °C with water cooling. Aliquots were removed periodically during the course of the irradiation and analyzed by gas chromatography. No reaction occurred in the absence of light.

Preparative-scale irradiations were conducted with 0.05 M solutions containing 0.2–2.0 g of substrate. The resulting mixture was poured into an equal volume of water and extracted with three portions of 2-methylbutane. The combined organic layers were washed with water and saturated NaCl solution and then dried over anhydrous Na_2SO_4. The solvent was removed by a rotary evaporation, and the products were isolated by preparative gas chromatography.

Irradiation of **2-Bromo-** (**1**) **and 2-Iodotricyclo[3.3.1.1^{3,7}]decane** (**2**). Bromide I was obtained commercially, and iodide **2** was prepared as previously described.[44] Preparative irradiations conducted as outlined above afforded the following products.

Tricyclo[3.3.1.1^{3,7}]decane (**7**) was isolated as a colorless, amorphous solid that was identified by comparison with a commercial specimen.

Octahydro-2,4-methano-1*H*-cycloprop[*cd*]indene (**8**) was isolated as a colorless, amorphous solid: ^{1}H NMR δ 2.21 (s, 2 H, 2 × CH), 2.10 (m, 1 H, CH), 1.80 (s, 3 H, CH_2 and CH), 1.35 (m, 7 H, 2 × CH_2 and 3 × CH), 1.15 (t, 1 H, J = 8 Hz, CH); lit.[42] mp 202.5–203.5 °C; ^{1}H NMR (CCl_4) δ 2.4–1.0 (m, 14).

2,3,3a,4,5,7a-Hexahydro-2,5-methano-1*H*-indene (**9**) was isolated as a colorless, amorphous solid: ^{1}H NMR δ 6.20 (m, 2 H, CH-4 and -5), 2.65 (m, 2 H, CH-3, -6), 2.30 (m, 2 H, CH-1, -8), 2.59 (m, 8 H, 4 × CH_2); lit.[43] mp 183–185 °C; ^{1}H NMR (CCl_4) δ 6.11 (m, 2 H, CH-4 and -5), 2.62 (m, 2 H, CH-3, -6), 1.34–2.50 (m, 10 H).

2-Methoxytricyclo[3.3.1.1^{3,7}]decane (**10**) was isolated as a colorless liquid: ^{1}H NMR δ 3.35 (s, 4, CH_3O- and CH-2), 1.95 (s, 4, 4 × CH), 1.68 (m, 10, 5 × CH_2); lit.[44] bp 47 °C (12 mmHg); ^{1}H NMR (CCl_4) δ 3.30 (1 H, CH-2), 2.3–1.2 (14 H).

Preparation of *exo*-2-Bromobicyclo[2.2.1]heptane (11x). The procedure used was a modification of that employed by Roberts et al.[45] To a 100-mL round-bottomed flask containing 10.1 g (0.107 mol) of bicyclo[2.2.1]hept-2-ene (**19**) was added 41.4 g of 48% hydrobromic acid. A condenser was placed in the neck of the flask, and the solution was heated at 59 °C for 9 h. After dilution with 100 mL of water, the organic phase was separated from the aqueous phase. To the organic phase was added 150 mL of 2-methylbutane. The aqueous phase was back-extracted with 50 mL of 2-methylbutane. The combined organic phases were washed with two 50-mL portions of saturated $NaHCO_3$ solution and 100 mL of water and dried over 50 mL of saturated NaCl solution followed by anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the resulting mixture distilled to give 15.9 g (85% yield) of bromide **11x** as a colorless liquid (100% exo by ^{1}H NMR): bp 67–69 °C (6.3 mmHg) (lit.[45] bp 82 °C (29 mmHg)); UV λ_{max} (2-methylbutane) 218 nm (ϵ 188); λ_{max} (methanol) 220 nm (ϵ 164); IR 2950, 2865, 1450, 1310, 1300, 1240, 1225, 1185, 940, 886, 756 cm^{-1}; ^{1}H NMR δ 3.96 (m, 1 H, CH-2), 2.49 (d, 1 H, J = 4 Hz, CH-1), 2.29 (s, 1 H, CH-4), 2.02 (m, 2 H, CH_2-3), 1.83 (d of t, 1 H, J_{HCH} = 10 Hz, J_{HCCH} = 2 Hz, CH-7_{syn}),

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(38) It has traditionally been assumed that extensive recombination occurs on irradiation of iodides in solution since quantum yields for product formation are approximately 0.1–0.3, whereas photocleavage of the carbon–iodine bond has been assumed to occur with nearly unit quantum efficiency: Calvert, J. G.; Pitts, J. N., Jr. *Photochemistry*; Wiley: New York, 1966; p 525. However, the quantum yield of product formation from ethyl iodide in the gas phase, in which recombination is unlikely, has recently been shown to be only 0.31: Shepson, P. B.; Heicklen, J. *J. Phys. Chem.* **1981**, *85*, 2691–2694.

(39) Similarly, the presence of some scrambling between C-1 and C-2 in norbornane (**18**) obtained from irradiation of the labeled bromides **11x**-*2-d* and **11x**-*2-d* (Table III) is probably due to some recombination of ion pair **15** (X = Br) leading to partially scrambled bromide **11**, which on further irradiation led to partially scrambled norbornane (**18**).

(40) The concept of steric hindrance to departure of the leaving group in rigid bicyclic systems was originally applied to solvolytic processes: Brown, H. C.; Muzzio, J. *J. Am. Chem. Soc.* **1966**, *88*, 2811–2822.

(41) The reduced interaction is reflected in the MM2 strain energy for iodide **12n**, which is 7 kJ/mol lower than that of bromide **11n**.

(42) Udding, A. C.; Strating, J.; Wynberg, H.; Schlatmann, J. L. M. A. *Tetrahedron Lett.* **1966**, 657–658.

(43) Black, R. M.; Gill, G. B. *J. Chem. Soc., Chem. Commun.* **1970**, 972–973.

(44) Udding, A. C.; Strating, J.; Wynberg, H. *Tetrahedron Lett.* **1968**, 1345–1350.

(45) Roberts, J. D.; Trumbull, E. R., Jr.; Bennett, W.; Armstrong, R. *J. Am. Chem. Soc.* **1950**, *72*, 3116–3124.

1.54 (m, 2 H, CH-5x and -6x), 1.26 (d of t, 1 H, J_{HCH} = 10 Hz, J_{HCCH} = 2 Hz, CH-7_{anti}), 1.10 (m, 2 H, CH-5n and -6n). The infrared spectrum was consistent with that published.[45]

Preparation of *endo*-2-Bromobicyclo[2.2.1]heptane (11n). The procedure used for large quantities was a modification of that of Bach et al.[46] To a 100-mL three-necked flask fitted with a condenser was added 7.1 g (0.028 mol) of crude 2,2-dibromobicyclo[2.2.1]heptane (**24**).[47] The flask was placed in an ice bath, and 8.7 g (30 mmol) of tributylstannane was slowly added over a 1-h period. The flask was then heated to 35 °C and stirred overnight. Distillation gave 3.7 g (67% yield) of bromide **11n** as a colorless liquid, bp 39–40 °C (1.8 mmHg). Gas chromatographic and ^{1}H NMR analysis showed exclusively endo stereochemistry, along with the presence of 5% of *endo*-2-chlorobicyclo[2.2.1]heptane.

For material of higher purity, the method of Brown[48] was used. To a 500-mL four-necked round-bottomed flask equipped with a N_2 inlet, thermometer, and two addition funnels was added 28.2 g (0.30 mol) of bicyclo[2.2.1]hept-2-ene (**19**) in 100 mL of dry tetrahydrofuran. The flask was cooled to 0 °C, and 105 mL of 1 M borane in tetrahydrofuran was slowly added. The solution was stirred for 30 min at 0 °C, warmed to 25 °C, and stirred for an additional 30 min. Excess hydride was slowly quenched with 2 mL of methanol. Dibromine (16 mL) and 86 mL of 3.84 M methanolic $NaOCH_3$ were placed in separate addition funnels and added simultaneously at such a rate that the reaction mixture was always slightly yellow and the temperature was maintained at 20–25 °C. After addition was complete, 50 mL of pentane, 20 mL of water, and 20 mL of saturated K_2CO_3 were added to the flask. The organic layer was separated, and the aqueous layer was extracted with three 50-mL portions of 2-methylbutane. The combined organic layers were washed with water and saturated NaCl and dried over anhydrous Na_2SO_4. Removal of solvent and distillation of the resulting oil gave 6.6 g of crude bromide **11** (82% endo by ^{1}H NMR), which was heated under reflux for 4 h in 80% aqueous ethanol. Workup and column chromatography (silica gel and 2-methylbutane) gave 3.37 g (6% yield) of the endo isomer **11n** as a colorless liquid (100% endo by ^{1}H NMR): UV λ_{max} (2-methylbutane) 220 nm (ϵ 150); λ_{max} (methanol) 219 nm (ϵ 163); IR 2960, 2870, 1450, 1315, 1300, 1255, 1245, 1225, 1185, 1165, 955, 945, 890, 850, 755, 745 cm^{-1}; ^{1}H NMR δ 4.26 (m, 1 H, CH-2), 2.41 (s, 1 H, CH-1), 2.16 (m, 1 H, CH-4), 1.97 (m, 1 H, CH-3), 1.54 (m, 3 H, CH-3, -5x, -6x), 1.42 (m, 4 H, CH_2-7, CH-5n and -6n). The infrared spectrum was consistent with that published.[49]

Preparation of *exo*-2-Iodobicyclo[2.2.1]heptane (12x). The general method of Stone and Schechter[50] was employed by adding 47.0 g (0.5 mol) of bicyclo[2.2.1]hept-2-ene (**19**) to a cooled mixture of 250 g (1.5 mol) of KI and 221 g (2.14 mol) of 95% orthophosphoric acid. The solution was heated to 150 °C overnight, cooled, and extracted with three 200-mL portions of diethyl ether. The organic layer was washed with three 100-mL portions of saturated $NaHCO_3$ solution and two 100-mL portions of water and dried over 100 mL of saturated NaCl solution followed by anhydrous Na_2SO_4. Distillation from KOH pellets afforded 99.7 g (90% yield) of iodide **12x** as a colorless liquid (100% exo by ^{1}H NMR): bp 87 °C (15 mmHg); UV λ_{max} 263 nm (ϵ 680); IR 1452, 1314, 1222, 1178, 946 cm^{-1} (lit.[51] IR 2920, 1440, 1300, 1210, 1170, 940, 750); ^{1}H NMR δ 3.96 (m, 1 H, CH-2), 2.60 (s, 1 H, CH-1), 2.18 (m, 3 H, CH-4, CH_2-3), 1.38 (m, 6 H, 3 × CH_2).

Preparation of *endo*-2-Iodobicyclo[2.2.1]heptane (12n). The procedure of Brown and Kabalka[13] gave 1.86 g (28% yield) of iodide **12n** as a colorless liquid (99% endo by ^{1}H NMR): ^{1}H NMR δ 4.23 (m, 1 H, CH-2), 2.38 (s, 1 H, CH-1), 2.25 (m, 1 H, CH-3n), 2.07 (s, 1 H, CH-4), 1.82 (m, 1 H, CH-3x), 1.56 (m, 6 H, 3 × CH_2) (lit.[13] ^{1}H NMR (CCl_4) δ 4.20 (m, 1 H, CH-2)).

Irradiation of Bromides 11x and 11n and Iodides 12x and 12n. From preparative irradiations conducted as described above, the following products were isolated and characterized.

2,2′-Bicyclo[2.2.1]heptane (17) was isolated as a colorless liquid that was identified by comparison with a sample prepared as previously described:[52] ^{1}H NMR δ 2.13 (m, 4 H, CH-1, -1′, 4, -4′), 1.58 (s, 2 H, CH-2, -2′), 1.43 (m, 4 H), 1.25 (m, 6 H), 1.08 (m, 6 H).

Bicyclo[2.2.1]heptane (18) and bicyclo[2.2.1]hept-2-ene (19) were identified by comparison with commercial specimens.

Tricyclo[2.2.1.0^{2,6}]heptane (20) was isolated as a colorless, amorphous solid: ^{1}H NMR δ 1.97 (s, 1 H, CH-4), 1.20 (s, 6 H, CH_2-3, -5, -7), 0.97 (s, 3 H, CH-1, -2, -6) (lit.[53] ^{1}H NMR (CCl_4) δ 1.88 (s, 1 H, CH-4), 1.19 (s, 6 H, 3 × CH_2), 0.98 (s, 3 H, CH-1, -2, -6)).

***exo*-2-Methoxybicyclo[2.2.1]heptane (21, R = CH_3)** was isolated as a colorless liquid: ^{1}H NMR δ 3.15 (s, 3 H, CH_3O–), 3.11 (s, 1 H, CH-2), 2.28 (s, 1 H, CH-1), 2.13 (s, 1 H, CH-4), 1.39 (m, 5 H, CH_2-3, CH-5x, -6x, -7_{syn}), 0.94 (m, 3 H, CH-5n, -6n, CH-7_{anti}) (lit.[54] ^{1}H NMR (CCl_4) δ 3.20, 3.15, (m, s, 4 H), 2.25 (m, 2 H), 0.90–1.77 (m, 8 H)).

***exo*-2-*tert*-Butoxybicyclo[2.2.1]heptane (21, R = $C(CH_3)_3$)** was isolated as a colorless, amorphous solid and identified by comparison with a sample prepared as previously described:[54] ^{1}H NMR δ 3.35 (m, 1 H, CH-2n), 2.08 (m, 2 H, CH-1, -4) (lit.[54] ^{1}H NMR (CCl_4) δ 3.35 (m, 1 H), 2.08 (m, 2 H), 1.08–1.78, 1.12 (m, s, ~17 H)).

Labeling Studies. A. Preparation of *exo*-2-Bromobicyclo[2.2.1]heptane-*2-d* (11x-*2-d*). A modification of Bose's general procedure was used.[55] *endo*-Bicyclo[2.2.1]heptan-2-ol-*2-d* (**23**) was first prepared by the addition of 40 mL of diethyl ether to 0.71 g (16.9 mmol) of $LiAlD_4$ contained in an oven-dried three-necked round-bottomed flask followed by the slow addition of a solution of 6.05 g (54.9 mmol) of bicyclo-[2.2.1]heptan-2-one (**22**) in 30 mL of diethyl ether. The resulting mixture was stirred for 15 min and then heated under reflux for 1 h. The mixture was cooled in an ice bath, and 4 mL of water was added dropwise. The resulting precipitate was removed by filtration, and the ether solution was dried over saturated NaCl solution followed by anhydrous Na_2SO_4 and concentrated by rotary evaporation.

To a 500-mL flask containing 150 mL of CH_2Cl_2 was added 3.10 g (17.4 mmol) of *N*-bromosuccinimide. The flask was cooled to 0 °C while a solution of 4.51 g (17.2 mmol) of triphenylphosphine in 75 mL of CH_2Cl_2 was slowly added. A solution of 2.00 g (17.7 mmol) of the labeled alcohol in 75 mL of CH_2Cl_2 was then added and the resulting mixture stirred overnight. Diethyl ether (150 mL) was added to the solution, and the organic phase was washed with water and dried over saturated NaCl solution followed by anhydrous Na_2SO_4. Removal of solvent and chromatography on silica gel gave on elution with 2-methylbutane 0.62 g (20% yield) of bromide **11x**-*2-d* as a colorless liquid, which was found to have the isotopic composition shown in Table III.

B. Preparation of *endo*-2-Bromobicyclo[2.2.1]heptane-*2-d* (11n-*2-d*). The labeled bromide was prepared by the general procedure of Giering.[56] To a 1-L two-necked round-bottomed flask were added 3.2 g (10 mmol) of tributylchlorostannane, 7.5 g (30 mmol) of 2,2-dibromobicyclo-[2.21]heptane (**24**),[47] and 150 mL of dry tetrahydrofuran (under N_2). Lithium aluminum deuteride (0.46 g, 11 mmol) was added in small portions over a 3-h period while a gentle reflux was maintained. The mixture was allowed to cool to room temperature, and excess deuteride was quenched with water. The resulting suspension was filtered, and 200 mL of water was added to the solvent. The aqueous layer was extracted with three 150-mL portions of 2-methylbutane. The combined organic layers were washed with 200 mL of water and dried over 100 mL of saturated NaCl solution followed by anhydrous Na_2SO_4. Distillation afforded 3.7 g (70% yield) of bromide **11n**-*2-d* as a colorless liquid, bp 45 °C (3 mmHg), which was found to have the isotopic composition shown in Table II.

C. Preparation of *exo*-2-Iodobicyclo[2.2.1]heptane-*2-d* (12x-*2-d*). A modification of Bose's general procedure was used.[55] To a 500-mL round-bottomed flask containing 150 mL of CH_2Cl_2 was added 4.00 g (17.8 mmol) of *N*-iodosuccinimide. The flask was cooled to 0 °C while a solution of 4.68 g (17.8 mmol) of triphenylphosphine in 75 mL of CH_2Cl_2 was slowly added. A solution of 2.00 g (17.7 mmol) of *endo*-bicyclo[2.2.1]heptan-2-ol-*2-d* (**23**), prepared as described previously, in 75 mL of CH_2Cl_2 was then added and the resulting mixture stirred overnight. The solution was washed with two 50-mL portions of 10% sodium thiosulfate and 50 mL of water and dried over 50 mL of saturated NaCl solution followed by anhydrous Na_2SO_4. Removal of solvent by rotary evaporation and chromatography on silica gel gave, on elution with 2-methylbutane, 1.32 g (33% yield) of iodide **12x**-*2-d* as a colorless liquid, which was found to have the isotopic composition shown in Table III.

D. Irradiation. Isotopic analyses of products obtained from irradiation of these halides by the preparative procedure outlined above are summarized in Table III.

Irradiation of 1-Bromo- (25) and 1-Iodooctane (26). From preparative irradiations conducted according to the general procedure described

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above the following products were isolated and characterized. Hexadecane (**32**), octane (**33**), 1-octene (**34**), and (*E*)- and (*Z*)-2-octene (**36**) were obtained as colorless liquids and identified by comparison of their gas chromatographic retention times and ^{1}H NMR spectra with those of commercial samples.

Pentylcyclopropane (**35**) was isolated as a colorless liquid: ^{1}H NMR δ 1.30 (m, 8 H, 4 × CH_2), 0.87 (t, 3 H, $J = 6$ Hz, CH_3–), 0.62 (m, 1 H, CH-1), 0.50 (m, 2 H, CH-2α, -3α), 0.00 (m, 2 H, CH-2β, -3β); lit.[57] bp 128 °C; ^{1}H NMR δ 1.3 (m, 8 H, CH_2), 0.9 (t, 3 H, $J = 6$ Hz, CH_3), 0.45 (m, 3 H); IR 3100 cm^{-1}.

2-Methoxyoctane (**37**) was isolated as a colorless liquid: ^{1}H NMR δ 3.47 (s, 4 H, CH-2 and -OCH_3), 1.31 (m, 10 H, 5 × CH_2), 1.14 (d, 3 H, $J = 6$ Hz, CH_3-1), 0.93 (t, 3 H, $J = 10$ Hz, CH_3-8); lit.[4a] ^{1}H NMR (CCl_4) δ 3.47 (br s, 4 H), 1.31 (m, 10 H), 1.14 (d, 3 H, $J = 6.5$ Hz), 0.93 (m, 3 H).

Labeling Studies. A. Preparation of 1-Bromooctane-*1,1*-d_2 (25-*1,1*-d_2). In accordance with the general procedure of Kabalka,[58] 1.3 g (0.01 mol) of 1-octanol-*1,1*-d_2 (**38**-*1,1*-d_2)[1] was dissolved in 10 mL of $CHCl_3$ and cooled to 0 °C. To this solution, 1.6 g (0.02 mol) of pyridine was added. After 5 min of stirring, 2.9 g (0.02 mol) of 4-methylbenzenesulfonyl chloride was added in small portions. The solution was kept at 0 °C for 3 h and then extracted with 60 mL of diethyl ether. The ether layer was washed with three 30-mL portions of 1 N HCl, two 30-mL portions of 30% $NaHCO_3$ solution, and 50 mL of water and dried over saturated NaCl solution followed by anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation gave 3.5 g of the tosylate as a colorless oil.

The tosylate was converted to bromide via a modification of the procedure of Wiberg.[59] To a 25-mL flask fitted with a condenser were added 3.50 g (0.012 mol) of the tosylate and 10 mL of dry acetone. Lithium bromide (3.0 g, 0.04 mol) was added and the acetone brought to reflux for 18 h. The flask was cooled, and 100 mL of water was added. The aqueous layer was extracted with three 50-mL portions of diethyl ether, 100 mL of 2-methylbutane, and 50 mL of diethyl ether. The combined organic fractions were washed with two 100-mL portions of water and dried over 50 mL of saturated NaCl solution followed by anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and chromatography of the resulting liquid on alumina gave 1.32 g (68% yield) of bromide **25**-*1,1*-d_2 as a colorless liquid: IR 2950, 2910, 2840, 2140, 1460, 1000, 980 cm^{-1}; ^{1}H NMR δ 1.82 (t, 2 H, $J = 7$ Hz, CH_2-2), 1.26 (m, 10 H, 5 × CH_2), 0.86 (t, 3 H, $J = 6$ Hz, CH_3-); ^{2}H NMR (CCl_4) δ 3.37 (s, CD_2-1). Analysis by ^{1}H and ^{2}H NMR showed 100% d_2 at C-1.

B. Preparation of 1-Bromooctane-*2,2*-d_2 (25-*2,2*-d_2). A 1.9-g sample of 1-octanol-*2,2*-d_2 (**38**-*2,2*-d_2)[1] was treated in a manner identical with that described for alcohol **38**-*1,1*-d_2. Chromatography on alumina and removal of the solvent by rotary evaporation gave 1.83 g (67% yield) of bromide **25**-*2,2*-d_2 as a colorless liquid: IR 2950, 2920, 2850, 2190, 2080, 1460, 1370, 1230, 840 cm^{-1}; ^{1}H NMR δ 3.36 (s, 2 H, CH_2-1), 1.25 (m, 10 H, 5 × CH_2), 0.86 (t, 3 H, $J = 6$ Hz, CH_3–); ^{2}H NMR (CCl_4) δ 1.81 (s, CD_2-2).

C. Irradiation. The results from irradiation of **25**-*1,1*-d_2 and **25**-*2,2*-d_2 are summarized in Table VI.

(4-Bromobutyl)- (40) and (4-Iodobutyl)benzene (41). The results from irradiation of bromide **39** and iodide **40**, prepared as described previously,[8h] are summarized in Table I. From preparative-scale irradiations conducted as outlined above, the following products were obtained as colorless liquids and identified by comparison of their gas chromatographic retention times, IR and ^{1}H NMR spectra with those of commercial samples: butylbenzene (**47**), 1,2,3,4-tetrahydronaphthalene (**48**), 3-butenylbenzene (**49**), (cyclopropylmethyl)benzene (**50**), and (*E*)- and (*Z*)-2-butenylbenzene (**51**).

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Investigation of Domain Structure in Proteins via Molecular Dynamics Simulation: Application to HIV-1 Protease Dimer

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Abstract: A general method for the investigation of domain structure in proteins based on the analysis of molecular dynamics simulations is described. The method is based on the idea that residues of a domain move in concert with one another, as determined by the analysis of the cross-correlation coefficients for atomic displacements computed from the simulation history. The correlation coefficients are displayed in the form of a two-dimensional "dynamical cross-correlation map" (DCCM) on which each type of protein domain has a signature appearance. Domain–domain correlations appear as off-diagonal elements in the DCCM and indicate novel aspects of action-at-a-distance and through-space communication in the structure which originate uniquely in the dynamical motions. The method is illustrated here with an analysis of a molecular dynamics simulation on HIV-1 protease (HIV-1 PR), a protein dimer that exhibits a diversity of secondary structural motifs.

I. Introduction

The general presence of domain substructures in globular proteins has long been recognized and used to systematize our understanding of protein structure[1] and folding.[2,3] We propose herein a new theoretical method for the investigation of domains in proteins based on the analysis of molecular dynamics simulations. The method also provides the possibility of new insight into the study of domain–domain communication in the dynamical structure and functional energetics of the protein. Our approach is illustrated here with an analysis of a molecular dynamics sim-

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