Diamantane. III[1] Preparation and Solvolysis of Diamantyl Bromides

Tamara M. Gund,[2a,b] P. v. R. Schleyer,*[2b] Gerald D. Unruh,[2c] and Gerald J. Gleicher[2c]

Department of Chemistry, Princeton University, Princeton, New Jersey 08540, and Department of Chemistry, Oregon State University, Corvallis, Oregon 97331

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The bromination of diamantane (I) may be controlled to give mono-, di-, or polybrominated derivatives. At 25° in neat bromine, 1-bromodiamantane (III) is obtained in high yield. In refluxing bromine, 1,6- and 1,4-dibromodiamantane (V and VI) predominate. 4-Bromodiamantane (IV) is best prepared as a 59:41 equilibrium mixture with III, by reaction of I with *tert*-butyl bromide–aluminum bromide at 0°. Reaction of I in neat bromine with trace amounts of $AlBr_3$ gives 4,9-dibromodiamantane (VII) as the major product together with dibromides V and VI. Addition of larger quantities of Lewis acid produces 1,4,9-tribromodiamantane (VIII) and 1,4,6,9-tetrabromodiamantane (IX). The structure of the various bromides can be determined from their nmr spectra, as a chemical shift additivity relationship holds. The monobromides and dibromides were solvolyzed in 80% aqueous ethanol. The relative rates at 75° follow: III, 1.0; IV, 3.2×10^{-2}; V, 2×10^{-3}; VI, 8×10^{-3}; VII, 7×10^{-4}. 1-Bromodiamantane (III) solvolyzes eight times faster than 1-bromoadamantane (II), and IV three times slower. Although carbocation strain is less favorable for III and IV than for II, III is accelerated by relief of axial leaving group strain and by the greater stability of the 1-cation owing to β-chain branching. No detectable hydroxy bromide intermediates formed during solvolysis of V and VI. The solvolysis rates of dibromides V, VI, and VII were analyzed in terms of two limiting models for the transmission of nonconjugative substituent effects—σ inductive (through bond) and field models. The field effect contribution was evaluated by calculations based on the Tanford modification of the Kirkwood–Westheimer ellipsoidal model. The magnitude of each transmission mode is independent on the geometrical relationship between the two bromines. Through-bond coupling is favored by the parallel arrangements found in V and VII, and contributes factors in the range of ½–1/45 to the rate depressions observed.

Diamantane (I), first prepared[3] in 1965, became readily available in 1970.[4,5] Initial chemical studies of this second member of the diamondoid family centered on methods of functionalization,[6-10] substituent interchange,[7-10] relative reactivity of the two bridgehead positions,[6] and equilibration studies of substituent preferences for the three different positions.[11]

Ionic bromination of adamantane proceeds in a relatively uncomplicated manner to give only the bridgehead monosubstituted derivative;[12] no polybrominated compounds are obtained even after prolonged reflux.[12,13] However, by addition of greater amounts of Lewis acid catalysts and increasing the severity of the reaction conditions, adamantane may be selectively di-, tri-, or tetrabrominated at the bridgehead positions.[13-16] The reaction is thought to proceed by an ionic pathway with intermediate formation of bridgehead carbocations.[12,13,17] These adamantane bromides are versatile starting materials for a variety of syntheses leading both to substituted adamantanes and to unusual ring skeletons.[13-15,18-20] It was expected that diamantane also might be selectively brominated. However, owing to its lower symmetry, two types of bridgehead positions, termed "medial" [21] (C-1, -2, -6, -7, -10, -11) and "apical" (C-4, -9) are available for substitution. We have found that the bromination of diamantane may be controlled to give a variety of mono- and polybromides. The solvolysis rates of these compounds provide insight into relative reactivities of the substituent positions.[6]

Results

Preparation of Diamantyl Bromides. Scheme I summarizes the bromination results and Table I provides greater detail. In neat bromine, after only 2 hr at room temperature, diamantane gives 1-bromodiamantane (III) in 80% yield. Refluxing I in bromine for longer periods results in mixture of the 1,6- and 1,4-dibromides (V and VI). Addition of catalytic amounts of aluminum bromide to a diamantane–bromine solution gives mixtures of 1- and 4-bromodiamantane (III and IV) and 1,6- 1,4- and 4,9-dibromodiamantane (V, VI, and VII). The monobromide/dibromide ratio is determined by the amount of catalyst, the temperature, and the reaction time. It is difficult to control the bromine–aluminum bromide reactions to obtain 4-bromodiamantane but the dibromo derivatives VI and VII are best prepared in this manner. The optimum preparation of 1,6-dibromodiamantane (V) utilized refluxing bromine without added $AlBr_3$ catalyst. By successively increasing the amount of aluminum bromide added to the reaction mixture, 1,4,9-tribromodiamantane (VIII) and 1,4,6,9-tetrabromodiamantane (IX) were obtained selectively as major

Scheme I

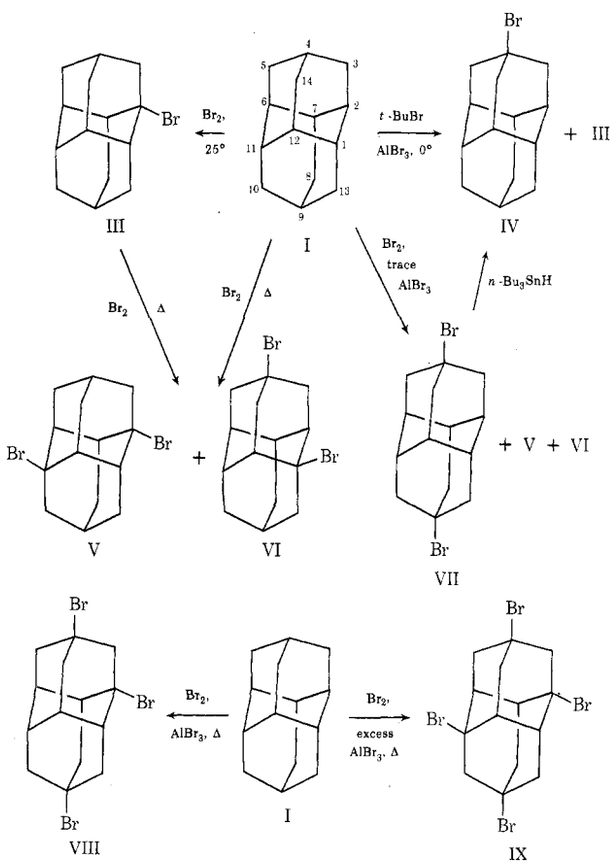


Table I
Bromination of Diamantane. Effect of Temperature, Catalyst, and Brominating Agent on Product Distribution

I, g	Br_2, ml	*t*-BuBr, g	$AlBr_3$, g	Temp, °C	Time, hr	Products, % III	IV	V	VI	VII	VIII	IX	Unidentified products, %
2.0	10			25	2	80[a]		*b*	*b*				
10.0	50			Reflux	16	19[c]		48[c]	7.7[c]				25.3[c]
1.0	5		0.10	0	5		4[c]	6[c]	38[c]	48[c]			*b*
2.0	10		0.08	Reflux	2			40[d]			53[a]		*b*
2.0	10		2.0	Reflux	1	*b*	*b*	*b*	*b*	*b*	*b*	41[a]	*b*
2.0		2.0	0.1	0	24	40[e]	58[e]	*b*	*b*	*b*			

[a] Per cent yield, determined after work-up and purification. [b] Present, but amounts were not determined. [c] Composition of product determined by glc before separation. [d] Mixture was not separated. [e] Composition of product determined by glc analysis of the hydrolyzed mixture.

Table II
Solvolysis Rate Constants of Adamantyl and Diamantyl Bromides in 80% (v/v) Aqueous Ethanol

Compd	Temp, °C	k, sec^{-1} [a]	k_{rel} 75°	ΔH^*, kcal/mol	ΔS^*, eu	Ref	Registry No.
1-Bromoadamantane (II)	25.0	5.1×10^{-7} [b]		22.4	−12.3	*d*	768-90-1
	70.0	8.3×10^{-5} [b]					
	75.0	1.35×10^{-4} [b]					
2-Bromo-2-methyladamantane (XVII)	75.0	7.4×10^{-1}				*e*	27852-61-5
1-Bromo-3-methyladamantane (XVIII)	75.0	9.76×10^{-5}		24.0	−10.1	*f*	702-77-2
1-Bromodiamantane (III)	25.0	3.67×10^{-6} [b]					30545-17-6
	49.8	$7.64 \pm 0.025 \times 10^{-5}$		22.8	−6.8	*g*	
	70.0	6.62×10^{-4} [b]					
	75.0	1.09×10^{-3} [b]	1				
	75.4	$1.13 \pm 0.025 \times 10^{-3}$					
4-Bromodiamantane (IV)	25.0	$1.05 \times 10^{-}$ [b]					30545-30-3
	70.0	2.16×10^{-5} [b]					
	75.0	3.60×10^{-5} [b]	3.2×10^{-2}	23.4	−11.9	*g*	
	75.3	$3.69 \pm 0.13 \times 10^{-2}$					
	100.8	4.29×10^{-4}					
	103.0	4.53×10^{-4}					
1,6-Dibromodiamantane (V)	25.0	1.13×10^{-8} [b]					32401-10-8
	70.0	2.18×10^{-6} [b]					
	75.0	4.51×10^{-6} [b]	2×10^{-3} [i]				
	88.9	$1.97 \pm 0.11 \times 10^{-5}$		24.1	−14.2	*g*	
	100.2	$4.39 \pm 0.025 \times 10^{-5}$					
	123.5	3.14×10^{-4} [c]					
	125.8	5.42×10^{-4}					
1,4-Dibromodiamantane (VI)	25.0	1.91×10^{-8} [b]					32401-09-5
	70.0	5.17×10^{-6} [b]					
	75.0	8.82×10^{-6} [b]	8×10^{-3}	24.7	−11.1	*g*	
	75.2	$8.98 \pm 0.10 \times 10^{-6}$					
	100.4	$1.08 \pm 0.10 \times 10^{-4}$ [h]					
4,9-Dibromodiamantane (VII)	25.0	4.41×10^{-9} [b]					30651-02-6
	70.0	9.11×10^{-7} [b]					
	75.0	1.51×10^{-6} [b]	7×10^{-4}	23.5	−18.1	*g*	
	100.20	$1.60 \pm 0.01 \times 10^{-5}$					
	115.50	$5.78 \pm 0.10 \times 10^{-5}$					
1,3-Dibromoadamantane (X)	25.0	3.20×10^{-10} [b]					876-53-9
	70.0	9.22×10^{-8} [b]					
	75.0	1.58×10^{-7} [b]					
	100.4	$1.98 \pm 0.05 \times 10^{-6}$		25.0	−18.3	*g*	
	125.1	1.70×10^{-5} [c]					
	126.0	1.82×10^{-5} [c]					

[a] Determined conductometrically unless otherwise noted. Average of duplicate determinations. [b] Calculated from other temperatures. [c] Determined titrimetrically. [d] Reference 28c. [e] Rate constant determined by Dr. J. L. Fry. [f] Reference 37. [g] This work. [h] Average of three runs. [i] Statistically corrected.

reaction products. All the bromo and polybromo derivatives are readily separable by column chromatography on alumina.

Alternatively, bromination can be achieved by reaction of diamantane with a slight excess of *tert*-butyl bromide and catalytic amounts of aluminum bromide. After 24 hr at 0°, a mixture of monobromides (40% III, and 58% IV) and trace amounts of dibromides V, VI, and VII were obtained. 4-Bromodiamantane (IV) was also prepared by selective reduction of 4,9-dibromodiamantane (VII) with 1 mol of tri-*n*-butyltin hydride,[6] but this is less convenient than the preparation of the III–IV mixture from *tert*-butyl bromide–aluminum bromide isomerization, and separation of the two components either directly or after conversion to alcohols by column chromatography on alumina.

Solvolysis Reactions. Solvolysis rate constants for III, IV, V, VI, VII, and 1,3-dibromoadamantane (X) were measured in 80% ethanol either conductometrically or titrimetrically (Table II). Product studies to detect the presence of monobromo intermediates were undertaken for dibrom-

ides V and VI. In both cases, solvolyses were carried out in 60% acetone for half of one half-life. The products were analyzed by gas chromatography but no evidence for the build-up of intermediates was found.

Discussion

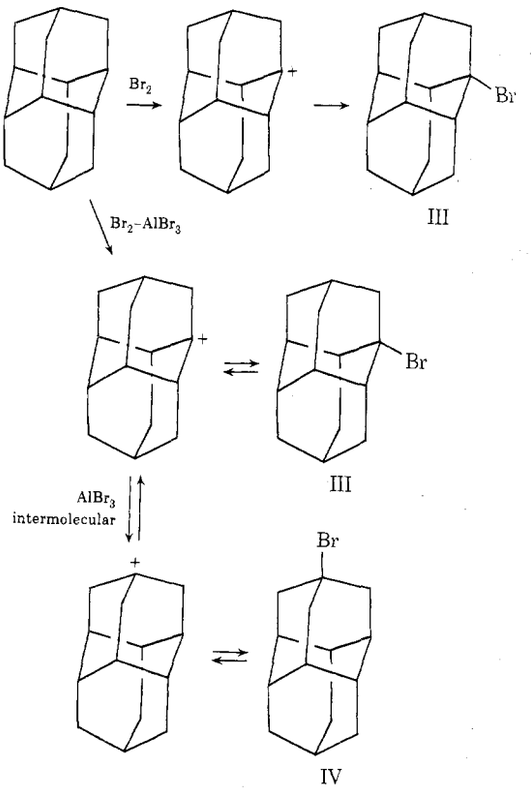
Preparation of Monobromides. Diamantane (I) is more reactive toward bromination than adamantane, since I reacts rapidly at room temperature. Furthermore, the medial bridgehead (C-1) is substituted more readily than the apical (C-4); in the absence of Lewis acid catalyst the 4-monobromo derivative is not formed in significant amounts. This is quite understandable when one considers the 3:1 statistical advantage for medial over apical attack and the inherently greater stability of the medial over the apical cation.

The 24-fold greater solvolysis rate of 1-bromodiamantane (III) over 4-bromodiamantane (IV) at 25° (Table II) provides documentation for the greater stability of the 1 cation. The solvolysis rate of 1-diamantyl bromide (III) also is eight times faster than that of 1-adamantyl bromide (II), consonant with the greater ease of bromination of diamantane than that of adamantane. Furthermore, diamantane in SbF_5–FSO_3H at −78° gives the 1- and not the 4-diamantyl cation, the structure being readily assigned from the proton nmr spectrum.[22]

Apical (4) derivatives are expected to be thermodynamically more stable owing to their equatorial character and more favorable enthalpy; however, medial (1) derivatives, while axial, nonetheless have a statistical advantage (greater entropy owing to lower symmetry, $\Delta\Delta S = R \ln 3/1$), but this effect is of lesser magnitude except when the substituents are small. Apical products would thus tend to result from thermodynamic control by equilibration.[5c]

Addition of trace amounts of $AlBr_3$ to the diamantane bromination produces much 4-substituted product by equilibration of the first formed 1-bromodiamantane (III) (Scheme II). Primary formation of 1-bromodiamantane

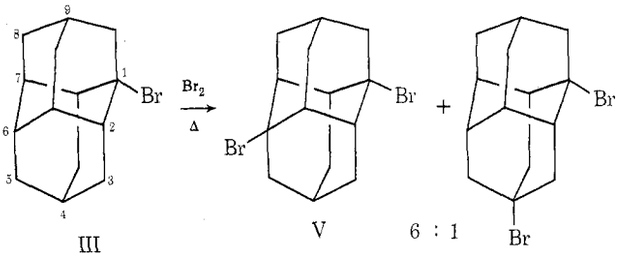
Scheme II



(III) was indicated by following the reaction of I with *tert*-butyl bromide–aluminum bromide at 0° for 24 hr. After 1 hr, III predominated, but at the end, the reaction mixture was richer in IV than III (59:41). This ratio is in agreement with that obtained by McKervey by direct equilibration of III and IV.[5c]

4-Bromodiamantane (point group C_{3v}) has symmetry number 3, which lowers its entropy by $R \ln 3$ or 2.18 cal/deg mol relative to 1-bromodiamantane (point group C_s, symmetry number 1). This would contribute −0.65 kcal/mol ($-T\Delta S$) to the equilibration free energy at 25°.[23] The enthalpy difference between axial and equatorial cyclohexyl halides is rather small (0.28–0.53 kcal/mol)[23] and the entropy term is of comparable importance in the III ⇄ IV equilibration. The entropy term becomes more important at higher temperatures and the formation of the 1 isomer is favored under such conditions.[5c,11,24]

Preparation of Dibromides. Formation of the dibromo derivatives is governed not only by the relative reactivity of the apical and medial positions but also by the position of attachment and the inductive effect of the bromine already present in the precursor monobromide. For 1-bromodiamantane (III) further uncatalyzed bromination occurs at C-4 and C-6 (ratio VI:V 1:6) since both are four carbon atoms away (eq 1). The greater amount of C-6 attack is due to the greater reactivity at the medial position. We expected 4-bromodiamantane (IV) to react preferentially at C-9, since it is the only available bridgehead six carbons removed. In fact, uncatalyzed bromination of IV gave a mixture of 1,4-dibromide (VI) and 4,9-dibromide (VII) in an 8:1 ratio (eq 2) instead of the statistical 3:1. Here the me-



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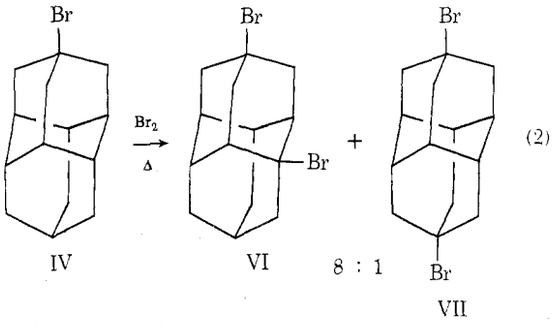


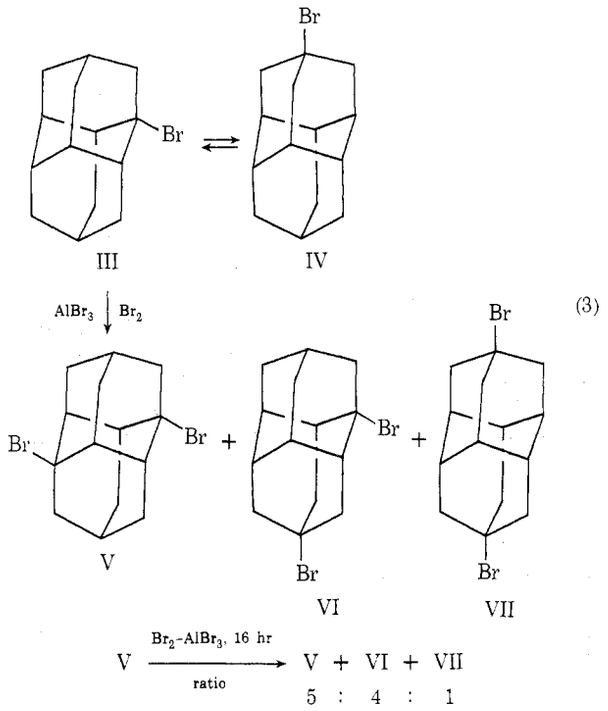
(2)

dial position was again preferentially attacked despite its smaller separation from the 4-bromine originally present. This suggests the possibility of the operation of a specific ("through-bond")[25] net effect enhancing the inductive interaction between the 4 and 9 positions (see below).

In the presence of aluminum bromide, equilibration of the initially formed monobromides or product dibromides may occur. This is shown most directly by the obtention of VII as one of the products from III (eq 3).

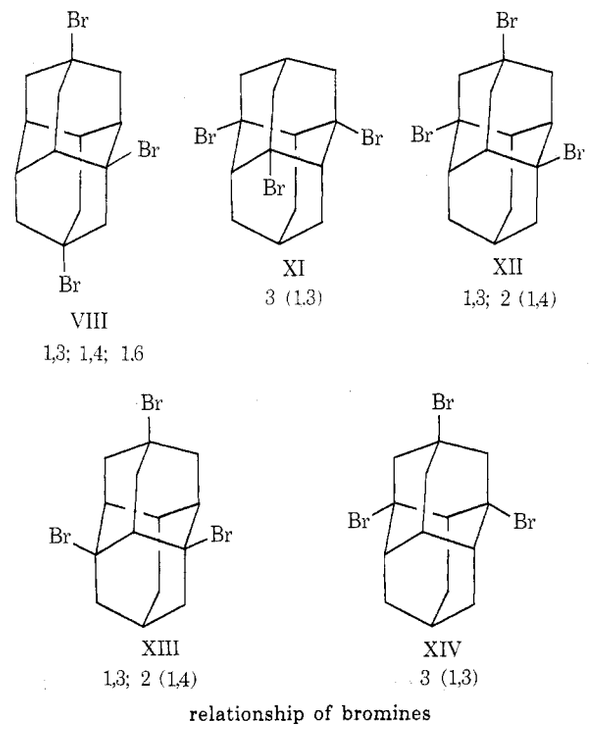
1,6-Dibromodiamantane (V) when treated with traces of aluminum bromide in bromine gives a mixture of V, VI, and VII, but it is not clear that complete equilibration was obtained under the conditions employed.

Preparation of Polybromides. By increasing the severity of the bromination conditions, a tribromide (VIII) and



tetrabromide (IX) were obtained from diamantane (I). Assignment of structures was made by nmr analysis (discussed below) and by synthesis from dibromides.

Excluding unlikely vicinal dibromides, five bridgehead tribromides, VIII and XI–XIV, are possible. Tribromides

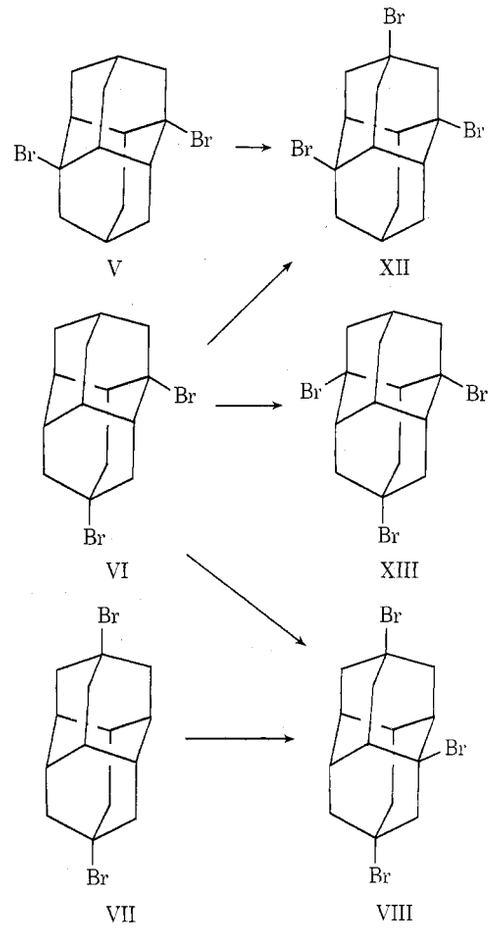


relationship of bromines

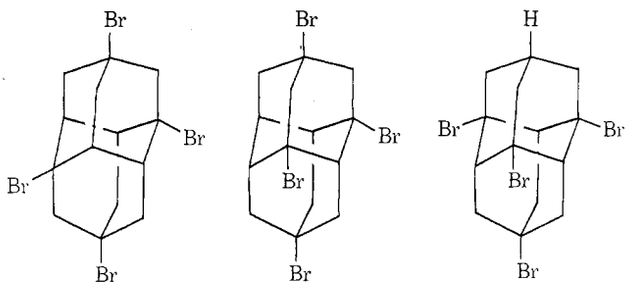
XI and XIV are less likely candidates however, owing to the three 1,3 bromide–bromine relationships. No vicinal or 1,3-type dibromodiamantanes have ever been observed as bromination or even as rearrangement products, suggesting that substitution is strongly inhibited at positions close to bromines already present.

Of the remaining three isomers (VIII, XII, and XIII), VIII seemed most likely since two of the bromines have a 1,6 relationship. Furthermore, the observed nmr spectrum was in closest agreement to that calculated for VIII. Isomer VIII could result directly from bromination of VI and VII; XII can be produced from V and VI but XIII only from VI (Chart I). Bromination of VII in the presence of aluminum bromide gave a product identical by nmr, ir, and melting point with the tribromide VIII isolated by direct polybromination of I (Chart I). Gas chromatographic analysis of the progress of the reaction revealed that equilibration of VII prior to reaction with bromine did not occur. Moreover, bromination of V under similar conditions produced after 16 hr only an equilibrium mixture of V, VI, and VII with only a small amount of tribromide.

Chart I



The tetrabromide isolated by addition of large quantities of aluminum bromide to bromination of I seemed likely to have one of the structures IX, XV, or XVI.



relationship of bromines

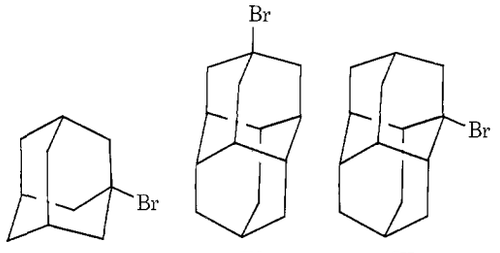
The observed nmr spectrum was in closest agreement to that calculated for IX (see below). Furthermore, IX was

produced by bromination of VII with larger quantities of aluminum bromide. Equilibration of VII prior to reaction with bromine and equilibration of tetrabromide after reaction were excluded by careful glc monitoring of reaction progress.

Solvolysis of Monobromo Derivatives. Since elimination and back-side solvent attack do not occur, diamantane derivatives, like their adamantane analogs,[15,28] undergo mechanistically uncomplicated solvolysis. It might be expected that the apical 4-bromodiamantane (IV) would be about as reactive as 1-bromoadamantane (II) and the medial isomer (III) two to three times faster owing to relief of 1,3-diaxial Br···H interactions destabilizing the starting material.[5c,23,29]

In actual fact, the diamantyl bromides exhibit a 24-fold rate difference between the bridgehead positions, favoring the "medial" isomer. Apical 4-bromodiamantane (IV) solvolyzes three times slower and the medial isomer (III) eight times faster than 1-bromoadamantane (II) (Chart II).

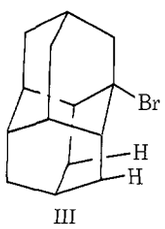
Chart II



	II	IV	III
k_{rel}, 75°, 80% EtOH	1	0.34	8.0

Molecular mechanics calculations[30-32] were carried out to assess the steric contributions to these rate differences (Table V).[33] The method utilizes the hydrocarbon as a model for the ground-state strain, and the free carbocation as a model for strain in the transition state.[33-36] This approach has been applied successfully to other bridgehead systems whose solvolysis rates vary nearly 20 powers of ten; the average deviation is only a factor of 3.[33-36]

From these calculations, the effect of strain on solvolysis was expected to be a small rate deceleration for both 1- and 4-bromodiamantane (*ca.* 0.5 and 0.4) compared to 1-bromoadamantane[33] (Table V). Diamantane is more rigid than adamantane, and resistance toward flattening of the bridgehead cations is greater. Agreement of calculations and experiment for the apical isomer (IV) is excellent, but the higher reactivity of III is not explained.



III

These calculations neglect the greater steric requirement of bromine compared to hydrogen. Winstein[29] has invoked ground-state steric strain relief to explain the three- to fourfold solvolysis rate difference between *cis*- and *trans*-4-*tert*-butylcyclohexane *p*-toluenesulfonate; despite mechanistic differences, these appear to be reasonable models for axial and equatorial substrates. This effect may be neglected for 1-bromoadamantane (II) with 4-bromodiamantane (IV), since in both cases the bromines are equatorial with respect to all composite cyclohexane rings. However, for 1-bromodiamantane (III) the bromine is axial with respect to one cyclohexane ring. Consequently, the diamantane is inaccurate as a model for the ground state. The effect of the diaxial interactions may be estimated from the enthalpy difference between 1- and 4-bromodiamantane, 0.6 kcal/mol[5c,11b] (slightly larger than the axial strain in the more flexible bromocyclohexane, 0.5 kcal/mol).[23]

This ground-state steric effect, not taken into account in the calculations of Table V, should result in a ~2.8-fold rate enhancement for medial bromide (III) if the strain is completely relieved in the transition state. On this basis, III should be 1.4 times more reactive than 1-adamantyl bromide (II), still less than the experimental eightfold effect. We attribute the remaining difference, a factor of 5.7 (8/1.4), to electronic effects (inductive and hyperconjugative) due to differences in chain branching, particularly on two at the β carbons.

The magnitude of this effect is in agreement with that observed experimentally in acyclic compounds. Streitwieser has shown that the 80% ethanolyses of tertiary halides correlate with $\Sigma\sigma^*_{CH_2}$ of the substituents with $\rho^* = -3.29$.[37] Assuming that the difference between III and IV is equivalent to substitution by two ethyl groups ($\Sigma\sigma^*_{CH_2} = 0.230$), a rate enhancement of 5.7 is calculated. Table VI summarizes our rate analysis. That β branching is capable of preferentially stabilizing diamondoid carbocations is shown by the obtention in superacid media of only the 1-diamantyl cation from diamantane[22] or either 1- and 4-bromodiamantane;[38] triamantane (XVII)[39] similarly gives the 2-triamantyl cation. In both cases, the most highly β-branched cation is formed (eq 4-6).

Table V
Calculated Steric Energies of Adamantane and Diamantane and Their Bridgehead Carbocations[a,b]

	Hydrocarbon	Cation	Δ strain	k_{rel} (calcd)[c]	k_{rel} (obsd)
Adamantane	8.91	21.18	12.27	1	1
Diamantane	13.50	26.93 (apical)	13.43	0.4	0.3
		26.51 (medial)	13.01	0.5	8.0

[a] In kilocalories per mole. Reference 33. [b] Calculations with a revised force field. *Cf.* J. L. Fry, E. M. Engler, and P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **94,** 4628 (1972); and E. M. Engler, J. D. Andose, and P. v. R. Schleyer, *ibid.*, **95,** 8005 (1973), give comparable results. [c] Calculated from the linear free energy relationship $-\log k$ bromide (80% EtOH, 70°) = 0.41Δ strain − 0.12; *cf.* ref 35.

Table VI
Contributions to Solvolysis of Monobromides

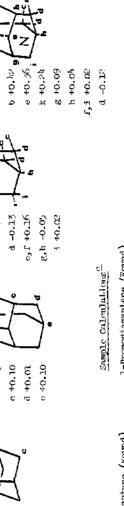
	1-Adamantyl (II)	4-Diamantyl (IV)	1-Diamantyl (III)
Δ strain effect relative rates	1	0.4	0.5
Relief of leaving group strain factor	1	1	2.8[b]
β-Alkyl branching factor	1	1	5.7[c]
Total k_{rel} (calcd)[d]	1	0.4	8.0
Experimental k_{rel} (25°)	1	0.34	8.0

[a] Molecular mechanics calculations (Table V). [b] Corresponds to an enthalpy difference of 0.6 kcal/mol for IV and III.[5c] [c] Based on acyclic models; see ref 37 and text. [d] Product of the three factors.

Nmr Spectra of Diamantyl Bromides. Adamantane derivatives have been shown to obey additivity relationships which make their nmr spectra readily interpretable.[26,27] From 1- and 2-substituted adamantanes, sets of substituent shielding and deshielding parameters have been derived which can be used to accurately predict the spectra of di and polysubstituted adamantanes (Table III). We have found that these shift parameters may also be used to predict diamantane spectra to a first approximation. As illustrated in Table III, the method simply equates the 4-position (apical) of diamantane with an adamantane bridgehead, but the diamantane 1-position (medial) is treated as a bridgehead with respect to one adamantane unit (M) and as a secondary position with respect to the other adamantane moiety, N. Although this approximate procedure is useful for structure elucidation of di- and even polysubstituted diamantanes, better agreement between calculated and observed spectra may be obtained by using a refined set of shift parameters derived from the 220 MHz nmr spectra of 4- and 1-bromodiamantane (Table III). As illustrated in Table IV, superior agreement is found for di and polysubstituted diamantyl bromides using these refined parameters, and isomers are readily differentiated.

In general, 4- (apical) diamantane derivatives give simpler nmr spectra than 1- (medial) isomers and therefore are easier to interpret. 4-Bromodiamantane (IV) behaves like 1-adamantyl bromide, with deshielding effects caused by the bromine substituent generally decreasing with increasing distance. However, the remote C-9 bridgehead hydrogen is deshielded more than the adjacent secondary hydrogens at C-8. The 1-bromodiamantane (III) displays a more complicated spectrum; however, interpretation is facilitated by characteristic AB quartets (at δ 2.38 and 1.56, $J \cong 12$ Hz, C_3 and C_{14} methylene H's) due to 1,3-diaxial and 1,3-axial-equatorial interactions between the axial bromine and corresponding protons.

TABLE III. COMPARISON OF ADAMANTANE NMR SHIFT INCREMENTS WITH REFINED DIAMANTANE SHIFT INCREMENTS FOR BROMINE SUBSTITUTION AND SAMPLE CALCULATIONS OF BROMODIAMANTANE SPECTRA USING ADAMANTANE INCREMENTS.



1-Bromoadamantane[a,b]	4-Bromodiamantane[b,c]	2-Bromoadamantane[b,d]	1-Bromodiamantane[b,c]
a +0.52	a +0.62	b +0.28	j +0.74
b +0.20	b +0.19	c +0.58	e +0.70
c −0.05	c +0.10	d −0.13	b +0.42
	d +0.01	e,f +0.16	e +0.36
	e +0.10	g,h −0.05	k +0.24
		i +0.02	g +0.09
			h +0.04
			f,i +0.02
			d −0.12

Sample Calculations[c]

4-Bromodiamantane (Found)	1-Bromodiamantane (Found)	
a 1.68+0.52 − 2.20 (2.30)[f](2.30)[g]	j 1.68+0.52 − 2.20 (2.50)[f](2.42)[g]	i 1.68+0.02 − 1.70 (1.58)[f](1.70)[g]
b 1.68+0.20 − 1.88 (1.85)(1.87)	e 1.68+0.52 = 2.26 (2.40) (2.38)	f 1.68−0.05 = 1.63 (1.58) (1.70)
c 1.68−0.05 − 1.63 (1.73)(1.78)	b 1.68+0.28 − 1.96 (2.10) (2.10)	g 1.68−0.05 = 1.63 (1.58) (1.77)
d 1.68+0.00 − 1.68 (1.73)(1.69)	c 1.68+0.20 − 1.88 (1.75) (2.04)	h 1.68−0.05 − 1.63 (1.58) (1.70)
e 1.68+0.00 − 1.68 (1.73)(1.78)	k 1.68+0.20 − 1.88 (1.75) (1.92)	d 1.68−0.13 − 1.55 (1.58) (1.56)

[a] Reference 23a. [b] A positive value represents a downfield shift from the methylene and bridgehead adamantane resonances at δ1.88 and 1.78, and from the single diamantane absorption at δ1.68 for all three kinds of protons. [c] Values derived by calculation from observed 220 MHz nmr spectrum. [d] Reference 24a. [e] 1- and 2-bromoadamantane increments. [f] Observed 60 MHz spectra. [g] Observed 220 MHz spectra taken by E. Hagaman, Indiana University.

Of the three dibromides, diapical VII gave the simplest spectrum consisting of two lines at 60 MHz in a 12:6 downfield:upfield ratio. Dimedial-1,6-dibromide (V) displayed AB quartets at δ 2.50 and 1.69, while medial-apical, 1,4-dibromide (VI) displayed AB patterns further downfield (δ 3.00 and 1.91) than those of V. Of the three most probable tribromide structures, VIII, XII, and XIII, the observed 220 MHz nmr spectrum was most consistent with that calculated for VIII. Tribromide XII would be expected to exhibit two downfield (δ 3.02 and 2.41) and two upfield (δ 2.20 and 1.59) AB patterns, while only one AB pattern (δ 3.00 and 1.91) is actually observed. Similarly tribromide XIII should have three AB protons absorbing at about δ 3.02 and near δ 2.20, while only two protons actually appear at δ 3.02. Also, the proton singlet at δ 1.90 is in better agreement with structure VIII (calc. 2.06-2.21), than XII (calc. 2.11-2.19); XIII is not expected to display such an upfield absorption.

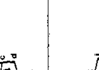
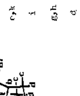
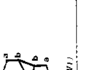
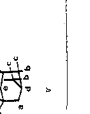
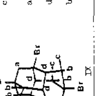
Similar arguments lead to the assignment of structure IX to the tetrabromide.

Experimental Section

Microanalyses were performed at Hoffmann-La Roche, Nutley, N.J., and Robertson Laboratories, Florham Park, N.J. Infrared spectra (Table IX) were taken on a Perkin Elmer 337-B spectrophotometer. Nmr spectra were recorded on Varian A-60-A or HA-100 spectrometers. Chemical shifts are recorded in δ units (parts per million) relative to tetramethylsilane. Gas chromatographic analysis and separations were performed on either a Varian-Aerograph 90-P or a Perkin Elmer 820 flame ionization gas chromatograph unit.

Preparation of Monobromides. A. In Neat Bromine at Room Temperature. Bromine (10 ml) was added dropwise to 2.0 g (0.011 mole) of diamantane with stirring and cooling in an ice bath. After addition was completed, the ice bath was removed and the reaction mixture was stirred about two hours at room temperature. The bromine solution was diluted with CCl_4 or $CHCl_3$ and poured onto ice. Excess bromine was decomposed by addition of solid sodium

TABLE IV. CALCULATED AND OBSERVED 60 AND 220 MHz Nmr SPECTRA OF MONO-, DI-, AND POLYBROMODIAMANTANES

Compd	Proton Type	Area	δ (Calc)[a]	δ (Calc)[b]	δ Found[c] 60 MHz (Type)	Area	Appearance	δ Found[c,d] 220 MHz (Type)	Area	Appearance
 IV	a	6	2.20		2.30 (a)	6	s	2.30 (a)	6	d
	b	3	1.88		1.85 (b)			1.87 (b)	3	s
	c,e	3,1	1.68		1.73	13		1.78 (c,e)	4	s
	d	6	1.63					1.69 (d)	6	d
 III	j	2	2.20		2.50	2		2.42 (j)	2	d
	e	2	2.26		2.40	2	AB, J ≅ 12	2.38 (e)	2	AB, J ≅ 12 Hz
	b	2	1.96		2.10			2.10 (b)	2	s
	c,k	3	1.88		1.75	15		2.04 (c)	2	s
	i	2	1.66		1.58		AB, J ≅ 12 Hz	1.92 (k)	1	s
								1.77 (g)		
	g,h	6	1.63					1.72 (h)	1	s
	d	2	1.55					1.70 (f,i)	6	s
								1.56 (d)	2	AB, J ≅ 12 Hz
 VII	a	12	2.20	2.30	2.30	12	s			
	b	6	1.83	1.87	1.99	6	s			
 VI	e	2	2.78	3.00	3.03	2	d	3.00 (e)	2	AB J ≅ 12
	a	2	2.20	2.44	2.43	2	d	2.41 (a)	2	d J ≅ 5
	g	2	2.18	2.33	2.25		m	2.30 (g)	2	m
	b	2	2.16	2.29	2.05	10		2.24 (b,h)	3	s
	f	2	2.07	2.18	1.79	4	m	2.14 (c,d)	3	m
	c	2	1.88	2.14			d	1.91 (f)	2	AB J ≅ 12
	h	1		2.02						
	d	1	1.83	1.96				1.73 (i)	4	d J ≅ 5
	i	4	1.63	1.71						
 V	e	4	2.21	2.44	2.62	4	AB J ≅ 12Hz	2.50 (e)	4	AB J ≅ 12
	a	4	2.20	2.40	2.42	4	d	2.48 (a)	4	d
	c	4	2.12	2.46	2.28	4	br	2.33 (c)	4	s
	d	2	1.83	1.96	1.78	2	br	1.94 (d)	2	s
	b	4	1.50	1.58	1.58	4	AB J ≅ 12Hz	1.69 (b)	4	AB J ≅ 12
 VIII	e	2	2.78	3.00	3.0	2	AB J ≅ 12Hz	3.03 (e)	2	AB J ≅ 12
	a	2	2.72	3.05	2.92	2	s	2.92 (a)	2	s
	f	2	2.11	2.39				2.30 (d,c)	6	s
	d	2	2.20	2.33	2.28					
	g	2	2.07	2.33	2.25	13		2.18 (f,g)	4	s
	e	4	2.15	2.33	2.15		AB J ≅ 12			
	b	2	2.07	2.34				2.14 (b)	2	AB J ≅ 12
	h	1	1.78	2.06				1.90 (h)	1	s
 IX	c	4	2.73	3.03	3.10	4	AB J ≅ 12Hz			
	a	4	2.72	3.07	2.90	4	s			
	d	4	2.31	2.75	2.25	4	s			
	b	4	2.02	2.21	2.10	4	AB J ≅ 12Hz			

[a] Calculated using adamantane increments, see Table III. [b] Calculated using refined diamantane values, see Table III. [c] In $CDCl_3$. [d] Taken by E. Hagaman, Indiana University.

TABLE IX

MP, IR, AND ANALYTICAL DATA OF DIAMANTYL BROMIDES

Compound	mp, °C	IR Bands, cm^{-1}	Calculated % C	Calculated % H	Calculated % Br	Found % C	Found % H	Found % Br
III	222 - 224	1340, 1280, 1070, 1050, 970, 880, 800, 740, 710	62.92	7.17		62.62	7.25	
IV	127 - 128.2	1325, 1260, 1060, 980, 825, 762	62.92	7.17	29.91	63.16	7.47	30.07
V	272 - 273	1335, 1295, 1280, 1218, 1170, 1110, 1068, 980, 940, 810, 792 690	48.58	5.24	46.18	48.59	5.31	46.26
VI	107.4 - 109.1	1340, 1320, 1280, 1250, 1225, 1090, 1080, 1040, 980, 955 880, 815, 795, 715, 700	48.58	5.24	46.18	48.65	5.50	46.45
VII	324 - 326	1330, 1320, 1260, 1240, 1015, 980, 825, 712	48.58	5.24		48.21	5.37	
VIII	193.2 - 194.8	1332, 1302, 1291, 1265, 1250, 1221, 1118, 1080, 1055, 995, 972, 960, 895, 825, 725	39.50	4.04	56.41	39.76	4.01	56.32
IX	354 - 356	1330, 1290, 1265, 1120, 1050, 1000, 960, 830, 808, 728	33.35	3.17	63.46	33.58	3.22	63.69

bisulfite in small portions and stirring until the bromine color disappeared and the solution turned light yellow or colorless. The carbon tetrachloride (or chloroform) solution was then washed with water, dried over $MgSO_4$ and evaporated under reduced pressure. The semi-solid which was obtained was sublimed and recrystallized from pentane; 2.4 g (80%) of white crystalline 1-bromodiamantane (III), mp 217.5-220° were obtained. Further recrystallization from hexane gave white crystals, mp 222-224°. See Table IX for further data.

B. With t-Butyl Bromide-Aluminum Bromide at 0°C. Freshly sublimed aluminum bromide (0.1 g) was added to a mixture of 2.0 g (0.011 mole) diamantane and 2.0 g (0.015 mole) t-butyl bromide in 10 ml of anhydrous cyclohexane at 0°. After stirring overnight at the same temperature, the reaction mixture was added to ice and extracted with 3 x 100 ml of hexane. The hexane layers were combined, washed with water and dried over $MgSO_4$. Evaporation of solvent left 3.0 g of semi-solid material which was 98% a mixture of monobromodiamantanes III and IV. The rest was comprised of dibromides V, VI and VII. A sample of this material (1.0 g) was hydrolyzed by refluxing in 100 ml of a solution of 10% K_2CO_3, 50 ml acetone, and 0.5 g $AgNO_3$. Gas chromatographic analysis on a 1.5 m X 3 mm 5% DC 710 column, at 190° indicated a mixture of hydrolysis products to be 41% 1-hydroxy and 59% 4-hydroxy diamantane (retention times 3.5 and 4.25 min respectively). 1- and 4-bromodiamantanes III and IV are separable by column chromatography on Woelm neutral alumina or silica gel. The first to elute with hexane was III; IV followed. Recrystallization of IV from hexane yielded white crystals, mp 127-128.2° (lit.[5] 127-129°).

Preparation of Dibromides. A. In Neat Bromine at Reflux. Diamantane (10.0 g, 0.054 mole) was refluxed in 50 ml of bromine overnight. Workup as in A (above) gave 19.0 g of semi-solid crude product which was shown by gas chromatographic analysis on a (5% carbowax 20 M, 3 m x 3 mm column at 220°) to be a mixture of III (15%), V (48%), VI (9%), and other non-bromide products 28%. Pure white crystalline 1,6-dibromodiamantane (V), mp 272-273°, was obtained by recrystallization from chloroform.

B. In Neat Bromine With Added Aluminum Bromide. Ratio of Diamantane: Aluminum Bromide (10:1) at 0°C. To 1.0 g (0.0054 mole) diamantane mixed with 0.05 g of aluminum bromide was added with ice-cooling 5 ml of bromine slowly. After 3 hours, another 0.05 g of aluminum bromide was added and the reaction mixture left at 0° for an additional two hours. The excess bromine was decomposed and the reaction worked up in the usual manner. A white solid, 2.0 g was obtained. Gas chromatographic analysis (5% DC 710, 3 m x 3 mm, 200°, He = 1.3 atm), indicated a mixture of VII (48%), VI (38%), V (6%) monobromide III and IV (4%) and other unidentified materials (4%). A small amount of petroleum ether was added, and the insoluble 4,9 dibromodiamantane (VII), 0.6 g was collected. The soluble portion was chromatographed on silica gel and eluted with hexane. The order of elution was as follows: monobromides III and IV, followed by dibromides V, VI and VII. Analytically pure white crystalline VI, mp 107.4-109.1°, was obtained by recrystallization of the chromatographed material from hexane. Pure VII, also white and crystalline, mp 324-326°, was obtained by recrystallization from hexane: benzene (1:1).

Preparation of 1,4,9-tribromodiamantane (VIII). To a mixture of 10 ml bromine and 80 mg aluminum bromide was added in small portions 2.0 g (0.011 mole) diamantane. After stirring at reflux for two hours, the usual workup procedure was employed. Evaporation of solvent ($CHCl_3$) left 3.7 g of solid. Addition of a small amount of pentane left 2.5 g (53%) of insoluble material characterized as 1,4,9-tribromodiamantane (VIII). The soluble fraction contained a mixture of mono and dibromodiamantanes which were not separated. The crude, insoluble VIII was chromatographed on 200 g of alumina and eluted first with hexane and then benzene. Pure VIII (2.0 g) was obtained by evaporating the benzene fractions. Recrystallization from benzene-acetone (1:1) gave white crystals, mp 194-195.5°.

Preparation of 1,4,6,9-tetrabromodiamantane (IX). Diamantane (2.0 g, 0.011 mole) was added in small portions to 10 ml of bromine containing 2.0 g

aluminum bromide. An exothermic reaction ensued. Refluxing was continued for an additional hour after which the usual workup procedure was followed. The crude solid thus obtained was washed with pentane leaving 8.25 g (41%) of crude 1,4,6,9-tetrabromodiamantane (IX). The soluble fraction, a mixture of mono- di- and tribromides, was not separated. IX was recrystallized from chloroform: white crystals, mp 358–356° were obtained. IX may also be prepared by adding about 20 mg of aluminum bromide to 100 mg of 1,9-dibromodiamantane (VII) in 1 ml of refluxing neat bromine.

Tri-n-butyltin Hydride Reduction of 1,9-Dibromodiamantane (VII). To 4.9 g of VII dissolved in 95 ml of benzene was added through a dropping funnel 9.5 g of tri-n-butyltin hydride[6] in 10 ml of benzene. The reaction mixture was refluxed for 96 hrs. Evaporation of the solvent left an oily residue. Upon addition of a small amount of hexane, 690 mg of unreacted 1,9-dibromodiamantane (VII) precipitated. The filtrate, a mixture of diamantane, 4-bromodiamantane (IV), 1,9-dibromodiamantane (VII) and tri-n-butyltin bromide, was separated by preparative thin layer chromatography. Three bands were observed by ultraviolet light upon elution with hexane. The first band contained diamantane and tri-n-butyltin bromide, the second was extracted with hexane and gave 565 mg of IV, and the third fraction contained VII.

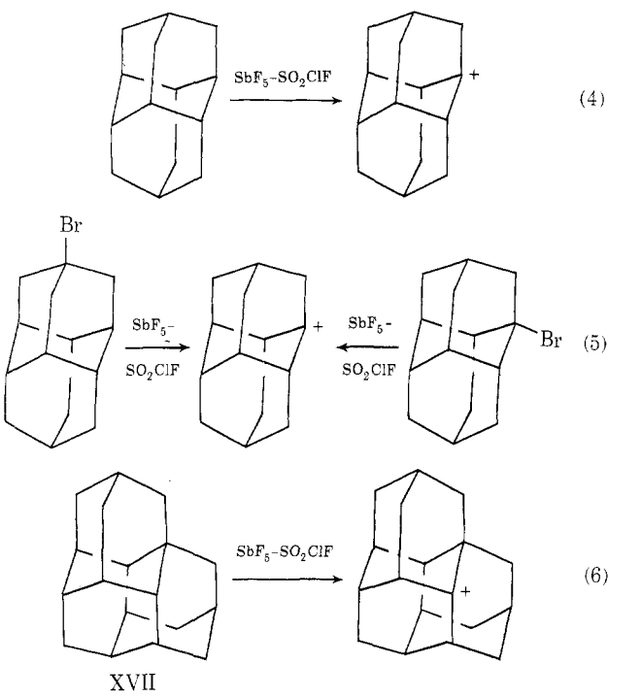
Solvolysis Reactions. A. Kinetic Measurements. Rate measurements were performed in 80% aqueous ethanol (by volume). The ethanol was purified by standard procedures. Conductimetric rates were followed using either a recording conductivity bridge or a Wayne-Kerr Universal Conductance bridge B-641. In each case, the sample was made about 10^{-3} M in a conductance cell having bright platinum electrodes and a capacity of about 20 ml. Titrimetric rates were determined using a Beckman automatic titrator. At least two runs per sample were made, and good first-order rate plots were obtained in all cases.

B. Product Studies from Solvolysis of 1,4-Dibromodiamantane (V). Dibromide V (2.0 g) was partially dissolved in 125 ml of 60% aqueous acetone and heated in a sealed ampoule at 102.5°[7] for 76.3 minutes (one half life at 102.5° is 81.3 minutes). The reaction was quenched and diluted with water and extracted with chloroform and ether. Gas chromatographic analysis of the product mixture on a glass column (5% SE710, 3 m x 6 mm) did not indicate build up of intermediate 1-hydroxy-4-bromodiamantane. Authentic 1,4-dihydroxy compound was prepared by solvolysis to 99% reaction and had retention time of 11 min. Unreacted dibromide had retention time of 30 min. The intermediate, if present, would be expected to show a peak between 11 and 30 minutes.

C. Product Studies from Solvolysis of 1,4-Dibromodiamantane (VI). As above, 2.0 g of VI was partially dissolved in 125 ml of 60% aqueous acetone and heated at 102.6° (solution was complete at this temperature) for 10.5 min (one half life at 100.82° is 18.5 minutes). Following the same workup procedures as above, glc analysis on a 3% carbowax 3 m x 3 mm column did not reveal any significant build up of intermediate. Authentic 1,4-dihydroxydiamantane (retention time 7 min) was prepared by solvolysis to 99% reaction, for product identification. Unreacted 1,4-dibromide had retention time 19.5 min. The intermediate (1-hydroxy-4-bromodiamantane) would be expected to have a retention time between the two. A very small peak (< 1% of retention time 18 min)was observed, but not isolated.

Kirkwood-Westheimer Calculations. The method used has been described in general.[48] Both sets of calculations used point charge models for the carbonic centers and the leaving groups were ignored. In the first set, a diamantane structure with tetrahedral angles, C-C bond lengths of 1.535 Å and normal aliphatic C-H and C-Br bond lengths were employed. The second set assumed a flattened carbocation site; distances were reduced accordingly. Standard bond or group moments were employed.[50]

(50) C.P. Smyth, "Dielectric Behavior and Structure," McGraw-Hill Book Co., Inc., New York, N.Y., 1955 p. 411.



XVII

Solvolysis of Dibromides. Rate-Determining Step. Solvolyses of compounds containing two leaving groups can well be expected to be complicated. Nevertheless, all of the diamantane dibromides solvolyzed exhibited apparent first-order behavior over at least 2.5 half-lives. Product analyses after partial solvolysis (0.5 half-life) of V and VI did not reveal significant build-up of intermediates; very small glc peaks (<1%) believed to be due to hydroxybromodiamantanes were observed, but isolation attempts failed.

A large build-up of hydroxyl bromide intermediate is not to be expected during solvolysis of the symmetrical dibromides V and VII. Replacing one bromine ($\sigma^*_{CH_2Br}$ = 1.0)[40-42] by a less electron-withdrawing hydroxyl group ($\sigma^*_{CH_2OH}$ = 0.555)[40-42] should result in a hydroxy bromide more reactive than the original dibromide, despite the statistical advantage of the latter. Analysis of such sequential processes[43] show that if loss of the first bromine (k_1) is ten times slower than loss of the second (k_2), then the maximum build-up of intermediate should only be 8%. The kinetics are complex, but the observed rate approximates k_1. If $k_2 > 10k_1$, then the concentration of intermediate would be undetectable by the methods employed.

To assess the rate enhancement to be expected from replacement of one bromine by a hydroxy substituent, we applied a rough two-point (H and Br) Taft–Hammett treatment[44] to experimental data of VII, V, and X, and interpolated a relative rate for the hydroxy bromo intermediate (Table VII). For a check, we also supplied a Taft–Hammett treatment to published data of some 1,3-disubstituted adamantanes[37,45] and interpolated a relative rate for the hydroxy substituent (Table VII); satisfactory agreement was obtained.

Table VII

Relative Rates of Hydroxy Bromo Compounds Extrapolated from Graph of Log k_R/k_H vs. Taft $\sigma^*_{CH_2}$ Constants

Positions of substitution	Dibromide	Bromo alcohol	Temp, °C	Ref
4,9-Diamantane (VII)	1	5.6	70	*a*
1,6-Diamantane (V)	1	17.4	70	*a*
1,3-Adamantane (X)	1	28.6	70	*a*
	1	36	75	*b*
	1	51	100	*c*

[a] This work; two points used, H and Br; OH derived from graphical interpolation. [b] Extrapolated from data of P. v. R. Schleyer and C. W. Woodworth, *J. Amer. Chem. Soc.*, **90,** 6528 (1968); $\rho^*_{CH_2}$ = −2.70 from plot of log k_R/k_H vs. $\sigma^*_{CH_2}$. [c] Data were taken from ref 45.

The hydroxy substituent retards the rate less than bromine. The roughly estimated 5.6 rate acceleration for 9-OH relative to 9-Br and VII indicates that ~14% maximum build-up of intermediate should have occurred and the measured rate constant should be complicated by contributions from k_2. In V, the calculated rate acceleration for OH is >10 (17.4) and therefore build-up of intermediate is expected to be negligible and k_1 should be the rate-determining step. Solvolysis of VI is the most complicated, since the bromines are at two different types of bridgeheads, which differ 24-fold in reactivity. The medial bromine should solvolyze first, to yield a 1-hydroxy-4-bromodiamantane. A two-point Taft–Hammett treatment here is not possible, and is difficult to assess the exact acceleration for an OH. Although VI is like V in that the two polar substituents are separated by four carbons, the orientations are different. We did not experimentally observe an intermediate from VI, suggesting that the first step (k_1) is rate determining.

Application to Polar Effects Models. Marked rate decelerations with respect to the monobromides were observed for all four dibromides with the effect generally falling off with the distance between the substituents (Table VIII). The decrease is caused by the diminishing electron-withdrawing polar effect of the second bromine.

Two propagation mechanisms for the polar effect are believed to operate. *Through-bond induction* is dependent on the number and orientations of paths between the substituent and reaction site.[25,46] Alternatively, in the *through-space field effect model,*[46] the polar effect is

Table VIII
Calculated and Experimental Solvolysis Rates of Diamantane Dibromides Relative to Diamantane Monobromides in 80% Ethanol (by Volume) at 70°

Compd	Calcd[a] (normal model)	Calcd[b] (flattened model)	Calcd rate deceleration range—normal and flattened models	Obsd
IV	1.0	1.0	1.0	1.0
VII	2.85×10^{-1}	7.46×10^{-2}	1/4–13	2.0×10^{-2} [c] (1/50)
VI		1.66×10^{-2} [d]	1/60	
III	1.0	1.0	1.0	1.0
V	7.23×10^{-2}	2.26×10^{-3}	1/14–442	1.6×10^{-3} [e] (1/625)
VI	1.03×10^{-2} [f]	1.76×10^{-3} [f]	1/98–562	5.2×10^{-3} [e] (1/193)

[a] Kirkwood–Westheimer model with tetrahedral carbons. [b] Kirkwood–Westheimer model with distance between center of cavity and reaction site decreased by flattening to the extent of an adamantane bridgehead carbocation. [c] Statistically corrected by dividing original value by 2. [d] For solvolysis of apical bromine [e] Statistically uncorrected. [f] For solvolysis of medial bromine.

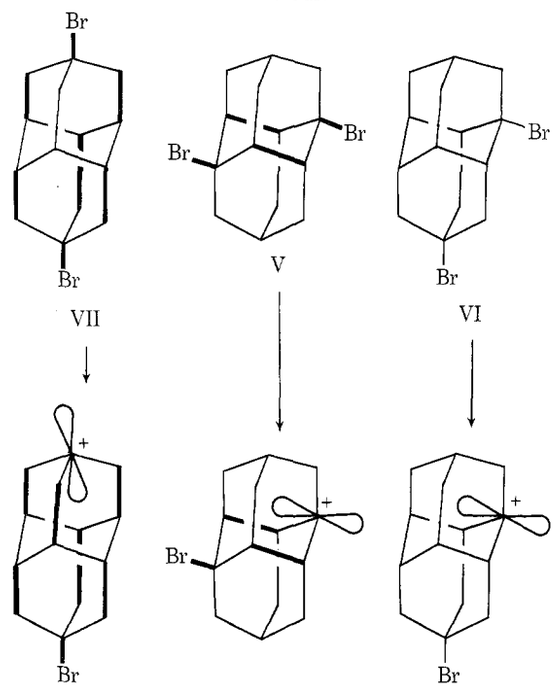
transmitted according to the classical laws of electrostatics, the magnitude being dependent on distance, the angular relationship between the reaction site and substituent, and the nature of the medium between and around them. Most studies of propagation mechanisms have dealt with substituent effects on pK_a's, *e.g.*, of carboxylic acids in rigid systems.[46] Carbonium ion processes would appear to provide even better tests, since charge is created directly upon the molecular framework.[46b]

The rigid diamantyl bromides are ideally constituted for investigation of the two polar mechanisms. Calculations based on the Tanford modification[47] of the Kirkwood–Westheimer elipsoidal cavity model[48] were employed to evaluate the contribution of the field effect to the dibromide rate depressions (Table VIII).[49] Two sets of calculations were performed, both employing the point-charge approximation for the carbocation (the leaving group was ignored). The first set used ground-state geometries but in the second the distance between the reaction site and center of the diamantane molecule was shortened to simulate the flattening expected in such bridgehead cation systems. The calculations predict rate decelerations of 4 (ground-state geometry) to 13 (flattened model) for VII compared to IV, 14–442 for V compared to III, and 98–562 for VI compared to III. These calculations suggest that the rate depressions due to a field effect should be small for VII, and comparable for V and VI. Solvolysis of VI exhibits a 193-fold rate depression relative to III, a magnitude bracketed by the two field model calculations. This is to be expected, since the unsymmetrical dibromide VI does not possess the favorable parallel alignment of bonds and orbitals necessary for optimum operations of the through-bond effect[25] (Chart III).

In contrast, the observed 50-fold rate depression for VII is appreciably larger than that calculated even with the flattened model. We attribute the discrepancy (3–13) to the operation of the through-bond inductive effect.[46] Although the interaction appears to be remarkably large for such a long distance, multiple pathways are available which possess the favorable parallel alignment of the "vacant" cation orbital with the C–C bonds (darkened in Chart III) and the bromine substituent.[25] The inductive model also seems able to account for the 625-fold rate depression of V compared to III which exceeds by 1.4–45 times that calculated by the field effect model. V also possesses a favorable alignment of the "vacant" carbocation orbital with the C–C and C–Br bonds (Chart III).

In summary, it appears that transmission of substituent effects in these diamantyl dibromides may occur by both the through-bond and through-space mechanisms. This is evident in the solvolysis of dibromides V and VII, both of

Chart III



which display rate depressions much greater than that calculated for a direct through-space interaction. The necessary criterion for a strong σ-inductive interaction appears to be a parallel arrangement of orbitals. Effects of other substituents are currently being studied and will be reported later.

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Bufadienolides. 28. Marinobufotoxin[1]

George R. Pettit* and Yoshiaki Kamano

Cancer Research Laboratory and Department of Chemistry, Arizona State University, Tempe, Arizona 85281

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Syntheses of marinobufagin (**5b**) and marinobufotoxin (**5e**) have been achieved. The principal synthetic transformations involved selective dehydration of telocinobufagin (**2**) and addition of hypohalous acid to the resulting olefin (**2** → **3** → **4**) followed by dehydrohalogenation to yield marinobufagin (**5b**). Application of a carefully developed mixed carbonic anhydride reaction to the condensation of marinobufagin suberate (**5c**) with arginine monohydrochloride provided marinobufotoxin (**5e**).

Almost 50 years elapsed between isolation[2] of marinobufagin (**5b**) from the American toad, *Bufo marinus*, and assignment[3] of structure **5b**. Nearly 40 years passed before the structure of marinobufotoxin (**5e**)[4] was firmly estab-