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Reactions of Some Bicycloalkyl Iodides with Bromine

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The reactions of normally unreactive bicyclic iodides such as 1- and 7-iodonorbornane with bromine has been found to occur readily with the formation of the corresponding bromide. The reaction involves the formation of the complex $RI{\cdot}X_2$ as an intermediate and is accelerated by polar solvents. The reaction of 1-iodobicyclo[2.1.1]hexane with bromine led to rearranged products, showing that a cationic intermediate is involved. The data indicate that the IBr_2^- ion is one of the best of the known leaving groups for S_N1 or S_N2 reactions. The observation of a rapid reaction of the bridgehead bicyclo[2.2.2]octyl iodides with bromine has led to a reexamination of the reaction of 1,4-diiodobicyclo[2.2.2]octane with butyllithium. The previous report of the formation and trapping of the [2.2.2]propellane in this reaction was found to be incorrect.

In 1905, Thiele and Peters[2] reported that simple alkyl iodides react with chlorine or bromine to give the corresponding alkyl halides. They were able to show that an intermediate, $RI{\cdot}X_2$, was formed and then decomposed to give the products. Since then, several groups have reported studies of this reaction.[3–6]

It is generally agreed that the reactions of saturated alkyl iodides with halogens proceeds via the $RI{\cdot}X_2$ complex. A study of the reaction of optically active 2-octyl iodide with chlorine or bromine found predominent inversion with considerable racemization.[4,6] When the reaction was carried out in the presence of chloride ion, essentially complete inversion was obtained.[6] The reaction of neopentyl iodide with bromine gave *tert*-amyl bromide along with 2,3-dibromo-2-methylbutane.[4] The reaction of *tert*-butyl iodide with iodine in solvents having some polarity was found to involve a unimolecular decomposition of the complex, and the rate of reaction was found to be markedly dependent on the ionizing power of the solvent.[3]

In the course of other studies, it was found that this reaction also occurred with some normally very unreactive bridgehead iodides. These observations have some bearing on the mechanism of the reaction and are reported herein. The cases which were studied are summarized in Scheme I. The reaction of 7-iodonorbornane (**1**) proceeded at a conveniently measured rate at 0–25 °C in methylene chloride solution and could be studied via NMR spectroscopy. Spectra obtained shortly after **1** was treated with a 50-fold excess of bromine showed that no **1** remained, and no bromide had been formed. Thus, the initial complex between **1** and bromine was formed rapidly and quantitatively under these conditions. As time passed, the spectrum of the intermediate was replaced by that of 7-bromonorbornane via a first-order process. The rate constants are summarized in Table I. The reaction was characterized by $\Delta H^{\ddagger} = 10.5$ kcal/mol and $\Delta S^{\ddagger} = -36$ eu.

The reaction of 1-iodonorbornane (**2**) could not be followed by NMR spectroscopy because of the similarity in spectra between **2** and 1-bromonorbornane. In this case, aliquots were removed periodically, quenched with sodium bisulfite, and analyzed by VPC. The rate of reaction was significantly less than that of **1**. 1-Iodobicyclo[2.2.2]octane (**3**), on the other hand, was much more reactive. When small quantities of bromine were added to a solution of **3** in methylene chloride at 25 °C, the formation of iodine was virtually instantaneous. At −44 °C the rate of reaction was still too fast to measure. A rough estimate of the minimum rate of reaction was made, and on the assumption of the same activation energy as for **1**, a rough estimate of the relative rate could be made. These values are recorded in Table I.

Scheme I

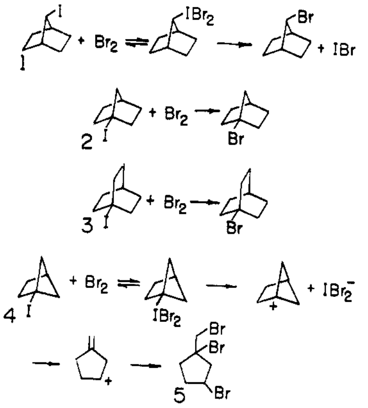

Table I. Rates of Reaction of Bicyclic Iodides with Bromine[a]

compd	temp, °C	10^4k_1, s^{-1}	k_{rel}
7-iodonorbornane (**1**)	0	2.68	
	10	5.91	
	20	11.2	
	25	14.6	
	40.8	39.0	13.0
1-iodonorbornane (**2**)	40.8	3.00	1.0
1-iodobicyclo[2.2.2]octane (**3**)	−44	>100[b]	$>10^5$

[a] Methylene chloride solutions. [b] Estimated minimum rate of reaction.

The relative rates of reaction of **1**–**3** are quite similar to the relative rates of solvolyses of the corresponding bromides (10^2:1:10^6).[7] The reaction clearly involves the ionic dissociation of IBr_2^-. Further evidence for this mode of reaction is found in the observation that whereas **2** reacts with bromine in methylene chloride at 40 °C, the temperature must be raised to 77 °C to achieve a reaction in carbon tetrachloride, and no reaction is obtained in refluxing cyclohexane. The solvent effect is consistent with the formation of an ion-pair intermediate in the reaction.[3]

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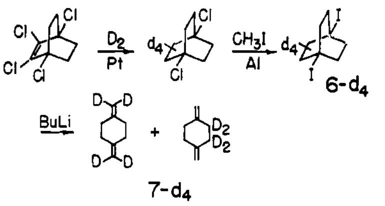
Scheme II



Another test for the formation of a carbocation intermediate may be found in the reaction of 1-iodobicyclo[2.1.1]hexane (4) with bromine. None of the corresponding bromide was formed, but rather the principal product was 1,3-dibromo-1-bromomethylcyclopentane (5). It is known that the solvolysis of 1-halobicyclo[2.1.1]hexanes leads to the 3-methylenecyclopentyl cation.[8] This would lead to the observed product by capturing bromide ion and adding bromine to the double bond. The formation of rearranged products is consistent only with an ionic process.

These results show that the IBr_2 group is one of the most effective leaving groups. The rate constant for the reaction of bromine with 1-iodonorbornane in methylene chloride is 10^{10} times greater than the rate of solvolysis of 1-iodonorbornane in 80% ethanol.[9]

The present observations are in good accord with the previous investigations of this reaction. The reaction of the tertiary bridgehead iodides, as well as neopentyl iodide,[4] must proceed via the formation of the $RI{\cdot}X_2$ complex which undergoes a unimolecular formation of the ion pair $R^+\ IX_2^-$. This, in turn, leads to the products expected for a carbocation. In primary and secondary cases, both S_N2 and S_N1 processes may occur in the decomposition of $RI{\cdot}X_2$, and the reaction conditions determine the proportions of the two modes of reaction.

We previously reported that 1,4-diiodobicyclo[2.2.2]octane (6) reacts with butyllithium, followed by trapping with chlorine to give 1,4-dichlorobicyclo[2.2.2]octane.[10] This was considered as evidence for the formation of the [2.2.2]propellane as an intermediate. In view of the rapid reaction of the bridgehead iodides with halogens to give the corresponding halide, this reaction was reinvestigated.

The lack of reaction of 1,4-dibromobicyclo[2.2.2]octane with chlorine,[11] led us to assume, incorrectly, that the normally quite unreactive diiodide would be equally unreactive. This, coupled with the initial observation that all of the diiodide was consumed in its reaction with butyllithium, led us to believe that the formation of the dichlorobicyclo[2.2.2]octane indicated the presence of the [2.2.2]propellane in the reaction mixture. A reexamination of the process showed that the reaction of the diiodide with butyllithium was very sensitive to reaction conditions and frequently led to considerable unreacted diiodide. The diiodide, in turn, reacted with chlorine to give the dichloride.

In order to determine the course of the reaction in an unambiguous manner, we have prepared deuterium-labeled 6 as shown in Scheme II. It was alllowed to react with *tert*-butyllithium in hexane at -78 °C, and the ^2H NMR spectrum was examined at -20 °C.[12] Only bands due to the deuterium-labeled isomers of 1,4-dimethylenecyclohexane (7) were observed. If the propellane were formed, its NMR signal would have to coincide with one of the bands of 7. When 6 was treated with a 5-fold excess of *tert*-butyllithium, a quantitative yield of 7 was obtained, and no diiodide was recovered. A repetition of the experiment, followed by quenching with bromine at low temperature, gave a 98.7% yield of 1,4-dibromo-1,4-bis(bromomethyl)cyclohexane (8) and less than 1% of 1,4-dibromobicyclo[2.2.2]octane. These results indicate that our earlier report was in error and that the propellane is not formed under these conditions. The reported conversion of 1,5-diiodobicyclo[3.2.1]octane to the [3.2.1]-propellane is, on the other hand, correct.

Experimental Section

Iodides. The preparations of 7-iodonorbornane,[13] 1-iodonorbornane,[14] 1-iodobicyclo[2.2.2]octane,[13] and 1,4-diiodobicyclo[2.2.2]octane[10] have been described.

1-Iodobicyclo[2.1.1]hexane. Powdered lithium containing 2% sodium (1.75 g, 0.25 mol) was added to 50 mL of cyclohexane distilled from calcium hydride under dry nitrogen, and the mixture was brought to reflux with stirring. Lithium was obtained as a dispersion in mineral oil (Ventron), and the latter was removed by washing with pentane followed by drying on a vacuum line. Potassium (0.2 g, 5 mmol) was added, followed by the dropwise addition of 10.2 g (63 mmol) of 1-bromobicyclo[2.1.1]hexane in 20 mL of dry cyclohexane. The mixture was heated to reflux for 15 h.

Anhydrous ether (150 mL) and 23 g (91 mmol) of iodine were placed in a second flask which was cooled in an ice bath. The cooled reaction solution was transferred to the ether solution over a 15-min period. After 30 min, the ether solution was filtered though Celite and washed with two 15-mL portions of 10% sodium bisulfite solution, 15 mL of water, and 15 mL of brine. After being dried over magnesium sulfate, the solution was concentrated by using a 20-cm packed distillation column. The residue was distilled, giving 6.8 g (52%) of the iodide: bp 39–40 °C (5 mm); ^1H NMR (270 MHz, $CDCl_3$) δ 2.51 (1 H, 7 lines), 2.06 (4 H, m), 1.72 (2 H, m), 1.58 (2 H, m); mass spectrum, molecular ion at *m/e* 207.9766, calc for C_6H_9I *m/e* 207.9748. Anal. C, H, I.

Reaction of 7-Iodonorbornane with Bromine. To a solution of 1.0 g of 7-iodonorbornane in 5 mL of dichloromethane was added a 0.5 M solution of bromine in 10 mL of dichloromethane. It was heated to reflux for 5 h. After cooling, the solution was worked up with 5 mL of saturated sodium bicarbonate and 5 mL of brine. The solvent was removed by distillation through a packed column. The residue (0.79 g, 99%) was found to be >97% pure by GC. The NMR spectrum was identical with that of an authentic sample of 7-bromonorbornane.[13]

Reaction of 1-Iodonorbornane with Bromine. The reaction of 1.0 g of 1-iodonorbornane with 0.8 g of bromine in 20 mL of dichloromethane was effected at room temperature for 20 h. After a workup as described above, the product was found to be 1-bromonorbornane,[15] and no (>1%) 1-iodonorbornane was obtained. When carbon tetrachloride was used as the solvent, the reaction was very slow at 40 °C, but after 15 h at the reflux temperature (77 °C), complete conversion was effected. The reaction in cyclohexane solvent gave no 1-bromonorbornane after 24 h at reflux (80 °C).

Reaction of 1-Iodobicyclo[2.2.2]octane with Bromine. The reaction of 1.0 g of 1-iodobicyclo[2.2.2]octane in 5 mL of methylene chloride with 4.2 mL of 0.5 M bromine in methylene chloride occured in a few minutes. After 30 min, the solution was worked

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[9] The rate constant for the solvolysis of 1-bromonorbornane has been estimted by Schleyer and Nicholas,[7] and they found that several tertiary iodides reacted 2–3 times as fast as the corresponding bromines. This led to an estimated rate of solvolysis of the iodide of 3×10^{-14} s at 40.8 °C.

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[11] Wiberg, K. B.; Epling, G. A.; Jason, M. *J. Am. Chem. Soc.* **1974**, *96*, 912.

[12] It is known that the [2.2.2]propellane would be thermally stable under these reaction conditions: Eaton, P. E.; Temme, G. H., III, *J. Am. Chem. Soc.* **1973**, *95*, 7508.

[13] Wiberg, K. B.; Pratt, W. E.; Bailey, W. F. *J. Org. Chem.* **1980**, *45*, 4936.

[14] Lansbury, P. T.; Pattison, V. A.; Sidler, J. D.; Bieber, J. B. *J. Am. Chem. Soc.* **1966**, *88*, 78.

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up as described above, giving 0.85 g of a semisolid which contained 90% 1-bromobicyclo[2.2.2]octane and 10% 1-iodobicyclo-[2.2.2]octane.

1,4-Diiodobicyclo[2.2.2]octane-*2,2,3,3*-d_4. To a solution of 25 g (0.1 mol) of 1,2,3,4-tetrachlorobicyclo[2.2.2]oct-2-ene[16] in 150 mL of ethanol-*d* were added 41 g of dry triethylamine and 1.0 g of 10% palladium on carbon. The solution was reduced by deuterium by using a Parr apparatus (15 h). The solvent was removed by distillation under reduced pressure. The residue was diluted with 500 mL of methylene chloride, filtered through Celite, and washed with water, 10% hydrochloric acid, saturated sodium bisulfite, and brine. The solution was dried over sodium sulfate and concentrated, giving brown crystals. Recrystallization from ethanol gave 16.8 g (92%) of 1,4-dichlorobicyclo[2.2.2]octane-*2,2,3,3*-d_4. Mass spectral analysis indicated 86% d_4 and 14% d_3. The dichloride was converted to the diiodide as previously described.[10]

Reacton of 1,4-Diiodobicyclo[2.2.2]octane with Bromine. A solution of 3.5 g (9.7 mmol) of 1,4-diiodobicyclo[2.2.2]octane in 100 mL of methylene chloride was treated with a solution of 3.3 g (21 mmol) of bromine in 25 mL of methylene chloride. After 1.25 h at room temperature, the reaction mixture was worked up as described above, giving 2.5 g (96%) of 1,4-dibromobicyclo[2.2.2]octane, mp 252–254 °C.[11]

Reaction of 1,4-Diiodobicyclo[2.2.2]octane-d_4 with *tert*-Butyllithium. A solution of 0.72 g (1.96 mmol) of the diiodide in 64 mL of dry pentane–ether (3:1) was cooled to −77 °C and treated with 1.26 mL (2.1 mmol) of 1.7 M *tert*-butyllithium with stirring. After 14 min, the stirring was stopped, and the solid matter was allowed to settle. A portion of the solution was studied at −21 °C by ^{2}H NMR at 41.4 MHz. The spectrum contained bands of the starting material and those of the two deuterium-labeled isomers of 1,4-dimethylenecyclohexane.

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Registry No. 1, 70279-05-9; 2, 930-80-3; 3, 931-98-6; 4, 74725-75-0; 5, 81389-50-6; 6, 10364-05-3; 4-d_4, 81389-51-7; 7, 4982-20-1; 7-d_4, 81389-52-8; 8, 81389-53-9; cyclohexane, 110-82-7; 1-bromobicyclo-[2.1.1]hexane, 77379-00-1; 7-bromonorbornane, 13237-88-2; 1-bromonorbornane, 13474-70-9; 1-bromobicyclo[2.2.2]octane, 7697-09-8; 1,2,3,4-tetrachlorobicyclo[2.2.2]oct-2-ene, 1197-74-6; 1,4-diiodobicyclo[2.2.2]octane-d_4, 10364-05-3.

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Mechanism of Asymmetric Hydrogenation. Rhodium Complexes Formed by Unsaturated Carboxylic Acids, Carboxylates, and Carboxamides

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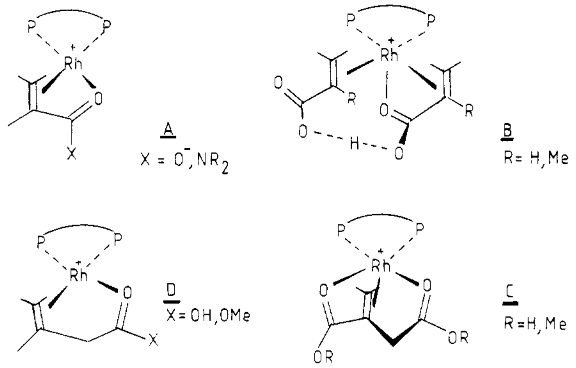
α,β-Unsaturated acids displace solvent from (*RR*)-[4,5-bis[(diphenylphosphino)methyl]-2,2-dimethyldioxolan]bis(methanol)rhodium cation, forming chelate complexes in which olefin and carboxylate are bound to the metal. The strength of complexation is enhanced in basic media and propenoic or 2-methylpropenoic acid form a different type of species with 2:1 stoichiometry in the absence of base. α,β- and β,γ-unsaturated amides likewise form complexes in which olefin and carboxamide oxygen are bound to rhodium. The ratio of diastereomers observed by ^{31}P NMR does not correlate with optical yields in hydrogenation of these precursors. In related experiments with (*RR*)-[1,2-bis(*o*-anisylphenylphosphino)ethane]bis(methanol)rhodium cation, 2-methylenesuccinic acid and its methyl esters gave a variety of complexes, including tridentate species where both carboxyl groups and olefin were concomitantly bound.

As a general rule, asymmetric hydrogenation is rarely used other than in the synthesis of amino acids and very closely related species.[1] Its extension will require new types of catalyst and perhaps a better understanding of reaction mechanism to assist their design. For this latter reason we have studied the complexes formed by representative α,β-unsaturated carboxylic acids and their congeners with bis(phosphine)rhodium(I) procatalysts, employing ^{31}P NMR in the manner of earlier work.[2-5] Four distinct types of complexes have been observed, depending on the system, shown as A–D in Chart I.[6] Each of these is associated with a characteristic set of PRh and PP coupling constants. Much of the survey was conducted

Chart I. Types of Rhodium Bis(phosphine) Complex Formed by Carboxylic Acids and Carboxamides



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