Trapping the 3-Halobicyclo[1.1.1]pent-1-yl Cation. Mechanistic Implications and Synthesis of Mixed 1,3-Dihalobicyclo[1.1.1]pentanes

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Chart 1

Solvolysis of bridgehead-substituted bicyclo- and polycycloalkanes generally proceed at a much reduced rate compared to that of their open-chain analogues.[1] This has been ascribed to the increased difficulty of the system in achieving a planar configuration about the developing positive charge. As a result, the usual stabilizing factors, in particular β-C−H hyperconjugation, are no longer available to the cation. Müller and his associates demonstrated this by showing that there is a linear correlation between the free energy of activation of solvolysis ($\Delta G^{\ddagger}$) of numerous caged substrates and the calculated strain energy difference between the intermediate bridgehead cation and the parent hydrocarbon ($\Delta E_S(R^+ - R - H)$).[2] In addition, recent correlations between MP2/6-31G* cation energies of related caged cations and the solvolysis rates of their precursor triflates also support the above argument.[3]

The 1-bromobicyclo[n.1.1]alkanes ($n = 1-3$) represent a family of bicycloalkanes which display aberrant solvolytic behavior. Thus, the 1-bicyclo[3.1.1]heptyl **1**, 1-bicyclo[2.1.1]hexyl **2**, and 1-bicyclo[1.1.1]pentyl **3** bromides (Chart 1) undergo S_N1 processes at extraordinary rapid rates, the substrates **1** and **3** reacting even faster than the classical system, *tert*-butyl bromide.[4−6] These three systems have been the focus of attention over recent years. For example, 1-bromobicyclo[3.1.1]heptane and 3-methoxycarbonylbicyclo[2.1.1]hexyl triflate have been shown unequivocally to solvolyze via the corresponding cations **4a** (R = H) and **4b** (R = CO₂CH₃) and the remarkably fast reaction has been attributed to the enhanced stability of **4a** (R = H) and **4b** (R = CO₂CH₃), which is accounted for by the phenomenon of homohyperconjugation as depicted in **5a** (R = H) and **5b** (R = CO₂CH₃).[4,5]

The formation and reactions of various 3-R-substituted bicyclo[1.1.1]pent-1-yl cations have been the subject of several major studies;[6,7] however, the intermediacy of the parent bicyclo[1.1.1]pent-1-yl cation **4c** (R = H) and all
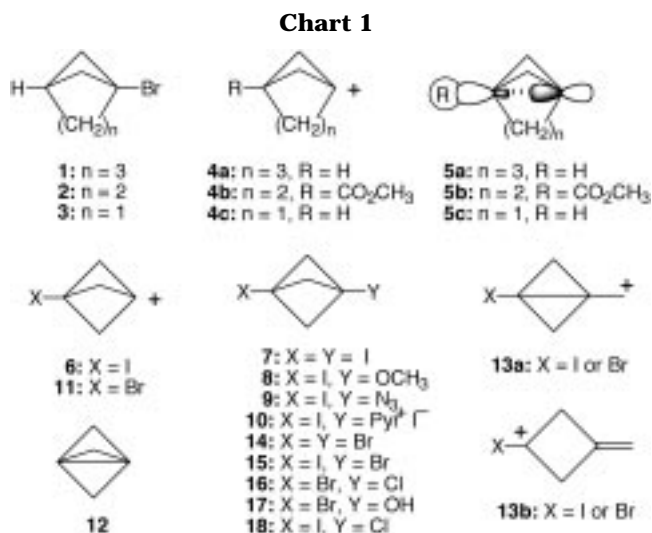
but one of the 3-R-substituted bicyclo[1.1.1]pent-1-yl derivatives studied has remained contentious. Recently, two groups have reported observations which strongly suggest the intermediacy of the substituted species, 3-iodobicyclo[1.1.1]pent-1-yl cation **6**. Thus, Wiberg reports that treatment of 1,3-diiodobicyclo[1.1.1]pentane **7** with methanolic KOH leads to 3-methoxybicyclo-[1.1.1]pent-1-yl iodide **8** while similar treatment of **7** in the presence of azide ion afforded 3-iodobicyclo[1.1.1]pent-1-yl azide (**9**),[7] and Adcock and associates have isolated the pyridinium salt **10** from treatment of the diiodide **7** with the weak nucleophile, pyridine.[8]

We report now the successful trapping by external nucleophiles of the 3-iodo- and 3-bromobicyclo[1.1.1]pent-1-yl cations (**6** and **11**) and its application to the synthesis of several mixed dihalides which have been otherwise difficult, if not impossible, to generate by other means. The trapping of the 3-bromobicyclo[1.1.1]pent-1-yl cation **11** is significant as this represents the second example of the intermediacy of a discrete 3-substituted bicyclo-[1.1.1]pent-1-yl cation.

It is known that treatment of [1.1.1]propellane **12** with iodine results in quantitative diiodide **7** formation. No rearrangement products resulting from ring opening of cation **6** with concomitant formation of cation **13** are detectable.[9] This was originally taken as evidence that iodine adds to **12** in a radical manner;[9] however, recent studies[7] clearly contradict this. To gauge the extent of [1.1.1]propellane production in our experiments, we first allowed an aliquot of our stock [1.1.1]propellane solution (in ether/pentane), prepared in the usual fashion[10] from 1,1-dibromo-2,2-bis(chloromethyl)cyclopropane, to react with excess iodine. As expected, no rearranged products were detectable and **7** was formed in 67% yield from the propellane precursor as depicted in Table 1. Formation of the dibromide (**14**) by the addition of bromine to **12** is

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Table 1. Product(s) from Addition of Halogens to [1.1.1]Propellane in the Presence of External Nucleophiles[a]

halo-gen	addi-tive	product(s) and (ratio)[b]	product yield (%)
I$_2$		**7**	**7** (67)
Br$_2$		**14** (1) + **19/20** (3.5)	**14** (24)
Br$_2$	LiBr	**14** (10) + **19/20** (1)	**14** (66)
I$_2$	LiBr	**7** (1) + **15** (10) + **19/20** (1)	**15** (49)
I$_2$	LiBr[c]	**7** (1) + **15** (2) + **19/20** (6)	
Br$_2$	LiCl	**14** (1.2) + **16** (1.5) + **17** (1) + **19/20** (1)	
Br$_2$	LiCl[c]	**14** (16) + **16** (1) + **16** (1) + **19/20** (15)	
I$_2$	LiCl	**7** (3) + **18** (1) + **19/20** (6)	
Br$_2$	LiI	**7** (15) + **15** (5) + **14** (8) + **19/20** (1)	
I$_2$	NaN$_3$	**7** (5) + **9** (1)	
I-Cl		**7** (1) + **18** (1) + **19/20** (80)	
I-Cl	LiCl	**7** (1) + **18** (1) + **19/20** (4)	

[a] See Experimental Section for details. [b] Determined from ¹H NMR analysis of crude mixtures utilizing benzene as an internal standard. [c] 15 equiv of salt utilized as compared to the usual 10 equiv.

known to proceed in poor yield (31%);[11] however, it can be raised to 36% if external irradiation is utilized.[6] The remaining poly-brominated material arrises from the facile rearrangement (**11** → **13a** and/or **13b**) confirming the intermediacy of the short-lived bridgehead cation. Thus, assuming that both iodine and bromine add to **12** with initial formation of their respective 3-halobicyclo-[1.1.1]pent-1-yl cations, we felt that addition of external nucleophiles should allow for the trapping of the bridge-head cations. Indeed, addition of bromine to **12** in the presence of excess lithium bromide afforded the dibro-mide **14** in 66% isolated yield with formation of only a trace (<5%) of rearranged products.[12] Considering that the expected yield could be no more than 67% on the basis of the trapping experiment with iodine, this remarkable result essentially represents complete trapping of the bridgehead cation **11**.

Similarly, addition of iodine to **12** in the presence of excess lithium bromide resulted in the formation of the mixed dihalide **15** as the major product (49%, 73% based on 67% propellane production) along with a small quan-tity of diiodide **7** and rearrangement products as collated in Table 1. The only other synthetic routes to this particular mixed dihalide (**15**) are the reaction of diiodide **7** with bromine and radical iododecarboxylation of the 3-bromobicyclo[1.1.1]pent-1-yl thiohydroxamic ester. These approaches are low yielding (14% and 45% respec-tively) due to competing rearrangement or elimination processes.[6,7,13] These reactions could be performed on a scale which provided up to 5 g of the desired dihaloge-nated bicyclo[1.1.1]pentyl system. Small scale prepara-tions should be avoided and due care utilized during solvent removal and recrystalization/sublimation due to the volatility of the bicyclo[1.1.1]pentyl system. Ad-

ditionally, the extent of rearranged products was found to be highly dependent on salt concentration and reaction duration. For example, attempting to prepare the mixed dihalide **15** utilizing a higher concentration of lithium bromide under identical reaction conditions to those above resulted in a significant increase in rearrangement products at the expense of the dihalide as revealed in Table 1. This can be attributed to both the polarity of the solvent mixture and salt concentrations (dielectric constant increased by salt effect) assisting ionization of the initially formed dihalides and thus causing facile rearrangement. The best results were obtained utilizing no more than a 10-fold excess of external nucleophile. Finally, the tetrahydrofuran/ether/pentane ternary mix-tures utilized in these trapping experiments were chosen for the following reasons: (a) they allow for the easy preparation and utilization of the [1.1.1]propellane pre-cursor; (b) they allow for the ready dissolution of a wide range of ionic salts, thus maximizing capture of the carbocationic intermediates; (c) the low overall polarity maximizes the possibility for capture of the bridgehead cations since more polar solvents such as acetonitrile would favor facile rearrangement of the bridgehead cations.

A similar effect was observed during the addition of bromine to **12** in the presence of lithium chloride. Unfortunately, product composition and volatility pre-cluded the isolation of significant quantities of pure mixed dihalide[14] **16**. In a similar fashion addition of iodine to **12** in the presence of excess lithium chloride afforded a mixture of diiodide **7**, mixed halide[13,15] **18**, and rearranged products in a ratio of 3:1:6. Formation of mixed dihalide **15** is not advisable utilizing the bromine/lithium iodide system as this leads to significant diiodide **7** and dibromide **14** formation. Dissolution of lithium iodide affords significant release of "free" iodine, thus resulting in competitive diiodide formation. Reaction of **12** with iodine in the presence of sodium azide resulted in the formation of the diiodide **7** and the known 1-azido-3-iodobicyclo[1.1.1]pentane[7] **9** in a 5:1 ratio with no accompanying rearrangement. Finally, addition of neat iodine monochloride to [1.1.1]propellane **12** essentially resulted in complete rearrangement with only traces of the desired mixed dihalides being detectable. The pres-ence of excess lithium chloride increased the yield of the desired mixed dihalide; however, product composition precluded isolation of a pure sample.

In conclusion, the aforementioned trapping experi-ments clearly demonstrate that both iodine and bromine add to [1.1.1]propellane **12** to afford the discrete 3-halo-bicyclo[1.1.1]pent-1-yl cations (**6** and **11**) which can be intercepted by the presence of external nucleophiles. In competition with this process is the usual facile ring opening of the bridgehead cations. The stability of the 3-iodo- and 3-bromobicyclo[1.1.1]pent-1-yl cations can be attributed to a delicate tradeoff between relief of ring strain and stabilizing through-space inductive effects as depicted in **5c**.[6,7] Trapping of the 3-bromobicyclo-[1.1.1]pent-1-yl cation **11** is significant as this represents only the second example of the intermediacy of a discrete 3-substituted bicyclo[1.1.1]pent-1-yl cation. Further-more, trapping of the intermediate bridgehead cations by external nucleophiles has allowed the synthesis of

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(12) The rearranged products were easily identified from ¹H NMR analysis of the crude reaction mixtures and could be assigned to either dihalide **19** or tetrahalide **20** as depicted below.

19 **20**

X or Y = I, Br or Cl
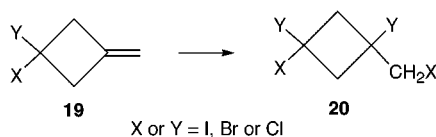
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several mixed dihalides which have been otherwise difficult, if not impossible, to generate by other means.

Experimental Section

General. Stock solutions of [1.1.1]propellane **12** in ether/pentane were prepared from 1,1-dibromo-2,2-bis(chloromethyl)-cyclopropane according to the known procedure and used as is.[10] All solvents were dried according to standard procedures while salts were dried by applying gentle heating under vacuum overnight. Both bromine and iodine monochloride were added neat in a slow dropwise manner to the reaction mixtures while iodine was added as a pentane solution until the typical halogen color persisted. All salts were dissolved in THF except for sodium azide which was dissolved in DMF. All reactions were carried out under an inert atmosphere. All pure compounds and product mixtures were characterized by comparison of their ^{1}H and ^{13}C NMR spectra and melting points to those reported for the known compounds. Further structure confirmation was achieved utilizing GCMS. The following two typical procedures serve as examples.

1,3-Dibromobicyclo[1.1.1]pentane (14). To a mixture of lithium bromide (26 g, 0.3 mol) dissolved in anhydrous THF (100 mL) at −5 °C was added an aliquot (65 mL) of **12** (prepared from 9 g of 1,1-dibromo-2,2-bis(chloromethyl)cyclopropane) in ether/pentane. Bromine was then added in a slow dropwise manner until the color persisted. After 1 h, the solution was washed with a saturated sodium metabisulfite solution (2 × 50 mL) and then dried (MgSO$_4$) and carefully concentrated in vacuo. Recrystallization from methanol afforded pure dibromide **14** (4.5 g, 66%) as needles: mp 121−122 °C (lit.[11] mp 119.5−120.5 °C).

1-Bromo-3-iodobicyclo[1.1.1]pentane (15). To a mixture of lithium bromide (23.4 g, 0.27 mol) dissolved in anhydrous THF (100 mL) at −5 °C was added an aliquot (60 mL) of **12** (prepared from **8** g of 1,1-dibromo-2,2-bis(chloromethyl)cyclopropane) in ether/pentane. Iodine was then added in a slow dropwise manner until the color persisted. After 1 h, the solution was washed with a saturated sodium metabisulfite solution (2 × 50 mL) and then dried (MgSO$_4$) and carefully concentrated in vacuo. Sublimation (100 °C/80 mmHg) resulted in the initial removal of the diiodide **7** and continuation then afforded pure mixed dihalide **15** (3.62 g, 49%) as a volatile colorless solid, mp 140−141 °C (lit.[7] mp 141−142 °C).