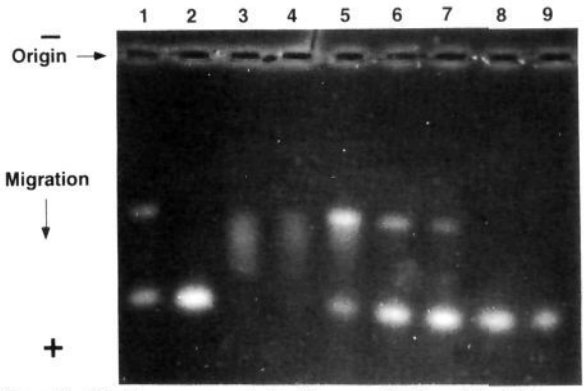

Figure 1. Alkaline agarose gel showing cross-linking of the 41-base-pair oligonucleotide by compound **3**. Each compound, in 5 μL of DMA, was incubated for 18 h at 37 °C with 1 μg of the 41-base-pair duplex oligonucleotide in 100 μL of TE buffer (15 μM in base pairs).[16] Samples were ethanol precipitated, resuspended in running buffer, loaded onto a 6% NuSieve (FMC Bioproducts, Rockland, ME) horizontal-bed alkaline agarose gel, and run for 2 h at 100 V. The gel was neutralized and stained as previously described.[1,17] Lane 1, trimethylpsoralen positive control, 17 μM irradiated for 10 s; lane 2, untreated DNA; lanes 3–7, DNA treated with **3** at 5, 1.5, 1.0, 0.5, and 0.15 μM, respectively; lane 8, DNA treated with adozelesin at 3 μM; lane 9, DNA treated with CC-1065 at 3 μM.

3 bound to oligonucleotide helices suggested that a binding-site size of six base pairs inclusive of the alkylated adenines matched the steric requirements dictated by the length and rigidity of compound **3**.

We have used the alkaline agarose cross-linking assay with a 41-base-pair oligonucleotide containing three separate but identical blocks of the sequence 5′-TAATTA-3′.[15] We selected 5′-TAATTA-3′ as the target binding and bonding sequence for compound **3** on the basis of the 5′-TTA-3′ alkylation sequence preferences seen for CC-1065 and other simplified analogues.[13b] Compound **3** readily forms DNA cross-links within this 41-base-pair duplex as shown in Figure 1.

The sites of alkylation within each strand of this duplex were assessed using the heat strand breakage assay previously utilized for monomeric CPI-containing compounds.[13a,b,18,19] Strand breakage occurs in each strand only at the 3′-terminal adenines of the 5′-TAATTA-3′ blocks (supplementary material). The results of the alkaline agarose gel assay together with the heat strand breakage assays indicate that compound **3** is capable of alkylating two distinct adenines on opposite strands separated by approximately one-half of a helical turn.

The incorporation of a rigid linker into dimeric CPI-based alkylating agents has yielded a class of dimeric compounds for which the DNA recognition site has been extended to six base pairs compared to the recognition-site size for monomeric CPI analogues. To our knowledge there are no other examples of interstrand cross-linking agents reported in the literature which possess a recognition site of this size. The biological implications of the increased size of the DNA recognition element are not known, but the increase in size may confer a greater absolute sequence selectivity upon these agents.[21]

Acknowledgment. We thank Dr. Li H. Li, Thomas F. DeKoning, and Joan W. Culp for the in vitro growth inhibition data and in vivo antitumor data.

Supplementary Material Available: Complete experimental details including analytical and spectral data for compounds **2a,b**, **3**, and **4**, alkaline agarose gel assay of ΦX174 restriction fragments treated with compound **3** and compound **4g** from ref 1, experimental methodology pertaining to the 41-base-pair oligonucleotide duplex, structures of CC-1065 and adozelesin, and the heat strand breakage gels of the 41-base-pair oligonucleotide duplex (10 pages). Ordering information is given on any current masthead page.

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(14) Warpehoski, M. A.; Hurley, L. H. *Chem. Res. Toxicol.* **1988**, *1*, 315–333.

(15) Sequence of the 41-base-pair duplex oligonucleotide:

5′-CGCTAATTAGGGGGCTAATTAGCGCGCGCTAATTAGGCCGC-3′

3′-GCGATTAATCCCCCGATTAATCGCGCGCGATTAATCCGGCG-5′

(16) The TE buffer composition is 10 mM Tris·HCl, 2 mM EDTA, pH 7.5.

(17) Cech, T. R. *Biochemistry* **1981**, *20*, 1431–1437.

(18) Maxam, A. M.; Gilbert, W. *Methods Enzymol.* **1980**, *65*, 499–560.

(19) We have found that incubation of the DNA modified with compound **3** for 18 h at 70 °C in 0.05 M *N*-(2-hydroxyethyl)piperazine-*N*′-2-ethanesulfonic acid–potassium hydroxide (HEPES-KOH), 0.1 M KCl, 0.05 M glycine, 0.5 mM EDTA, and 0.01 M putrescine reveals the strand breaks in DNA modified with compound **3** more effectively than standard methods.[20]

(20) Lindahl, T.; Andersson, A. *Biochemistry* **1972**, *11*, 3618–3623.

(21) Further studies are currently underway through collaborative efforts with L. H. Hurley at the University of Texas at Austin to more fully characterize the interaction of compound **3** with DNA.

Formation of [1.1.1]Propellane by Nucleophilic Attack on 1,3-Diiodobicyclo[1.1.1]pentane. Unrearranged Carbocation Intermediates in the Reaction of [1.1.1]Propellane with Electrophiles

Kenneth B. Wiberg* and Neil McMurdie

Department of Chemistry, Yale University
New Haven, Connecticut 06511

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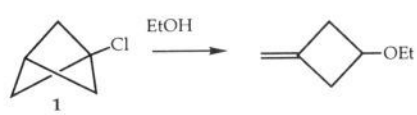
We have shown that 1-chlorobicyclo[1.1.1]pentane (**1**) undergoes solvolysis 3 times as rapidly as *tert*-butyl chloride,[1] despite the usually low reactivity of small bridgehead halides such as 1-norbornyl chloride.[2] The high reactivity of 1-bicyclo[1.1.1]-pentyl derivatives has recently been confirmed by Della and Taylor in their investigation of the solvolysis of 1-bromobicyclo[1.1.1]-pentane.[3]



1

Originally, we believed that the high reactivity resulted from a simultaneous carbon–carbon bond cleavage giving the 3-methylenecyclobutyl cation, which would lead to considerable strain relief. The products are derived from this cation. In view of the now well established bicyclobutonium ion intermediate in the solvolysis of cyclobutyl derivatives,[4] and RHF calculation on the 1-bicyclo[1.1.1]pentyl cation which suggests a similar interaction,[5] the structure of this ion was studied at the MP2/6-31G*

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(3) Della, E. W.; Taylor, D. K. *Aust. J. Chem.* **1990**, *43*, 945.

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(5) (a) Lehn, J. M.; Wipff, G. *Chem. Phys. Lett.* **1972**, *15*, 450. (b) Chandrasekhar, J.; Schleyer, P. v. R.; Schlegel, H. B. *Tetrahedron Lett.* **1978**, 3398. (c) Della, E. W.; Schiesser, C. H. *Tetrahedron Lett.* **1987**, *28*, 3869. (d) Della, E. W.; Schiesser, C. H. *J. Chem. Res. Synop.* **1989**, 172.

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Table I. Effect of Substituents on the Energies of Bicyclo[1.1.1]pentyl 1-Cations, MP2/6-31G*[a]

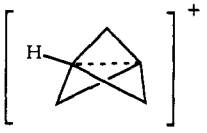
compound	hydrocarbon	cation	difference
1-fluorobicyclo[1.1.1]pentane	−293.612 86	−292.661 83	0.951 03
1-chlorobicyclo[1.1.1]pentane	−653.634 38	−652.711 25	0.923 13
bicyclo[1.1.1]pentane	−194.582 33	−193.702 07	0.880 26
1-methylbicyclo[1.1.1]pentane	−233.762 12	−232.885 81	0.876 31
1-silylbicyclo[1.1.1]pentane	−484.752 24	−483.904 40	0.847 84
isobutane	−157.847 77	−156.959 54	0.888 23

Energy Changes for Hydride Transfer Reactions (kcal/mol)

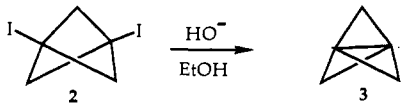
1-fluorobicyclopentane + (*tert*-butyl)$^+$ → 3-fluoro cation + isobutane	+39.4
1-chlorobicyclopentane + (*tert*-butyl)$^+$ → 3-chloro cation + isobutane	+21.9
bicyclopentane + (*tert*-butyl)$^+$ → bicyclopentyl cation + isobutane	−5.0
1-methylbicyclopentane + (*tert*-butyl)$^+$ → 3-methyl cation + isobutane	−7.5
1-silylbicyclopentane + (*tert*-butyl)$^+$ → 3-silyl cation + isobutane	−25.3

[a] Total energies are given in hartrees.

level. This level of theory generally gives good calculated structures,[6] even for highly strained compounds such as [1.1.1]-propellane.[7] The geometry-optimized structure had a 1.54-Å C1–C3 distance, indicating a strong stabilizing bridgehead–bridgehead interaction, and the ion was calculated to be more easily formed than *tert*-butyl cation (Table I). Therefore, the high reactivity of **1** may well arise from the formation of this bridged cationic species.[8]



In our earlier study of the solvolysis of 3-substituted cyclobutyl *p*-toluenesulfonates, we found that a chlorine effectively suppressed the S_N1 reaction, and only a very slow S_N2 reaction occurred.[9] This is presumably due to the destabilization of the bicyclobutonium ion by the electronegative substituent. The same would be expected in the bicyclo[1.1.1]pentane case, and calculations (Table I) suggest a similar strong effect of electronegative substituents. Therefore, as part of an investigation of the solvolysis of 3-substituted derivatives of **1**, we examined the reaction of 1,3-diiodobicyclo[1.1.1]pentane (**2**) with 80% ethanol. The reaction of **2** was initially very slow, but then became more rapid, presumably due to acid catalysis. The addition of base to eliminate the acid-catalyzed reaction led to the discovery of a new reaction, which has a first-order dependence on hydroxyl ion. The second-order rate constant at 25 °C was $(2.72 \pm 0.08) \times 10^{-3}$ L mol^{-1} s^{-1} in 100% ethanol. Using an internal standard, and following the reaction by NMR, a quantitative formation of [1.1.1]propellane (**3**) was found. The reaction must proceed via nucleophilic

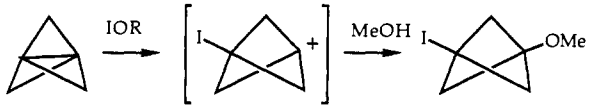


2 3

attack of the base on iodine. The hypoiodite formed in the reaction presumably attacks ethoxide ion, forming acetaldehyde, thereby preventing further reactions.

The thermochemistry of the elimination of halogen from 1,3-dihalobicyclo[1.1.1]pentanes to form **3** is about the same as that for eliminating halogen from 1,3-dihalopropanes to form cyclopropane.[10] However, 1,3-diiodopropane does not react with hydroxyl ion to give cyclopropane. Similarly, *cis*-1,3-diiodocyclobutane does not react with hydroxyl ion to give bicyclo[1.1.0]butane, but rather it gives elimination products. Thus, the close proximity of the bridgehead carbons in **2** (1.86 Å)[11] must be an important factor in the remarkable elimination reaction.

When **2** was treated with base in methanol, the final products were different. Some **3** was formed, but 1-iodo-3-methoxybicyclo[1.1.1]pentane (**5**) was a major product. It is probably formed by the reaction of **3** with hypoiodite, leading to the carbocation **4**, which picks up methanol from the solvent.[12] No



3 4 5

rearranged products were observed. In view of the high reactivity of **3** toward free radicals,[13] it is possible that **5** was formed by a free radical addition process. However, it is more likely to be a cationic process for the following reasons. The reactivity of **3** toward electrophiles is extraordinarily high, and a hypoiodite should be a good electrophile. When the reaction of **2** with base was carried out in the presence of a good carbocation trap, azide ion,[14] 1-azido-3-iodobicyclo[1.1.1]pentane became the major product.[15] These data strongly suggest that **4** can be an intermediate in the reaction and that it has a reasonable lifetime before rearranging. The increased lifetime as compared to that of the parent cation would presumably result from the iodine substituent, which would destabilize the rearranged cation. Another significant observation is that the reaction of the diiodide, **2**, with bromine in CCl_4 gave 3-bromo-1-iodobicyclo[1.1.1]pentane (30%) along with some rearranged products whereas 1,4-diiodobicyclo[2.1.1]hexane reacted with bromine to form only rearranged products,[16] presumably via a cationic process.

Further substituent studies are in progress along with attempts to observe the ion via ^{13}C NMR spectroscopy.

Acknowledgment. This investigation was supported by the Army Research, Development and Engineering Center via Geo-Centers, Inc., and by the National Science Foundation.

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(8) A calculation of the vibrational frequencies of the ion at the MP2/6-31G* level found one imaginary frequency (Wiberg, K. B.; Hadad, C. M.; Sieber, S.; Schleyer, P. v. R., to be published), suggesting that it may be a transition state. This does not affect the conclusions concerning the effect of substituents. It also was found to be a transition state at the HF/6-31G* level.[5d]
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(12) It seems likely that methyl hypoiodite is less reactive toward decomposition to form an aldehyde than is ethyl hypoiodite because of the higher energy of the carbonyl group in formaldehyde as compared to acetaldehyde: Wiberg, K. B.; Crocker, L. S.; Morgan, K. M. *J. Am. Chem. Soc.* **1991**, *113*, 3447. This would account for the difference between the reactions in methanol and ethanol.
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(15) In this case, it is likely that the initial reaction forming the hypoiodite is followed by its reaction with azide ion to give iodine azide (Hassner, A.; Levy, L. A. *J. Am. Chem. Soc.* **1965**, *87*, 4203) and that this is the source of "I$^+$" in the addition to [1.1.1]propellane. However, this does not affect any conclusions concerning the ion **4**.
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