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Cage opening and rearrangement of 1-iodocubane-4-carboxaldehyde

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ABSTRACT

Cubane is a highly strained unsaturated molecule that was first synthesized in 1964 by Philip E. Eaton. Since cubane's discovery, it has been researched in pharmaceuticals, explosives, and polymers. Due to its range of uses, we have explored the thermo-stability of a number of cubane derivatives. Some derivatives have revealed its propensity to undergo cage opening/rearrangement. In examining 1-iodocubane-4-carboxaldehyde, we observed that benzoic acid, benzaldehyde, benzyl alcohol, and benzyl benzoate were surprisingly formed in this thermo-decay.

Pentacyclo[4.2.0.0^{2,5}.0^{3,8}.0^{4,7}]octane, or more conventionally called cubane, was first synthesized in 1964 by Eaton and Cole.[1] The highly strained molecule and its derivatives have elicited great interest among various scientific fields. Although cubane is a highly strained molecule, it is remarkably stable.[2] This is because cubane has no kinetically viable pathways for thermal rearrangement. Two-bond ring-opening reactions (cycloreversions) are thermally disallowed by orbital symmetry considerations, and carbon–carbon bond homolysis leads to a high-energy biradical that releases very little strain.[3] It was however suggested that because octanitrocubane has a perfect oxygen balance, an estimated 20–25% greater release of energy than that of HMX would be obtained upon detonation.[4] In addition to the high detonation pressure it was also estimated that octanitrocubane would have an exceptionally high density of roughly 2.1–2.2 g/cm^3. These data suggest that it would be the most powerful nonnuclear explosive to be discovered[4] and in 2000 Eaton, Zhang, and Gilardi were able to successfully synthesize this explosive.[5]

Cubane and its derivatives have also been examined in the medical field. Cubylamides have been studied as P2X$_7$ receptor antagonists for their potential uses as an all-purpose analgesic or as in vivo radiotracers for positron emission tomography (PET).[6] Cubanes have also been examined as narcotic antagonists, and were tested against both the μ and κ receptors.[7] Cubane derivatives have been previously cited for their antiviral activity,[8] as well as a being monoamine oxidase (MAO) inactivators.[9] Beyond the medical realm, the cubane moiety has been incorporated into chiral ligands,[10] polymers,[11] and recently has been used as an internal NMR standard.[12]

The ability for cubane to undergo cage opening has been another area of interest. Cubanol[13] and cubanethiol[14] both undergo spontaneous cage opening, however the cubanethiol's oxidized derivatives are stable.[15] In 1970, Eaton reported that cubane and its derivatives can be converted to their corresponding *syn*-tricyclooctadiene isomers using certain transition metals, particularly rhodium(I).[16] In this case, a nonconcerted mechanism has been proposed where the rhodium(I) becomes rhodium(III) by forming two sigma bonds with two adjacent carbons on the cube, thus opening it. Eaton also reported the isomerization of cubane to cuneane using silver(I) and palladium(II) catalysts.[17] That cuneane arises from silver(I) catalyzed isomerization of cubane suggests that cuneane is more enthalpically stable. Bashir-Hashemi and co-workers calculated the enthalpy of formation for cubane to be 613.0 ± 9.5 kJ/mol and for cuneane to be 436.4 ± 8.8 kJ/mol.[18] Strain energies were also calculated for cubane and cuneane to be 681.0 ± 9.8 and 504.4 ± 9.1 kJ/mol, respectively.[18]

It has recently been reported that 4-iodo-1-vinylcubane (**1**) could be converted to a cyclooctatetraene derivative (**3**) without rhodium(I).[19] While attempting to polymerize **1**, it was discovered that the monomer was quantitatively converted to 4-vinyl-trans-β-iodostyrene (**5**).[19] This phenomenon was also observed when the vinylcubane, **1**, was evaluated under differential scanning calorimetry (DSC) studies.[20] Scheme 1 illustrates the proposed mechanisms for this conversion of 4-iodo-1-vinylcubane (**1**) to 4-vinyl-trans-β-iodostyrene (**5**).[19]

The initial proposed step involves the ylide resonance structure of the alkene (**2**) (which was substantiated, as the reaction is accelerated in the presence of a Lewis acid).[19] It was theorized that

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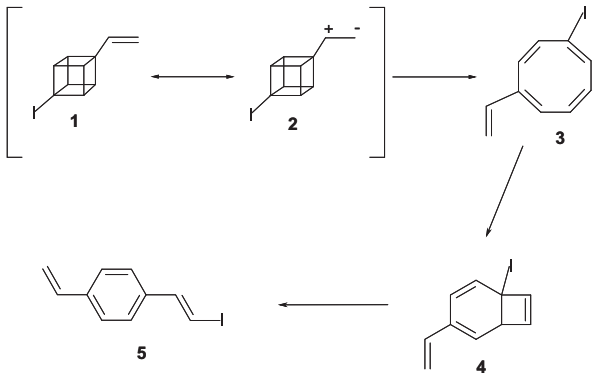
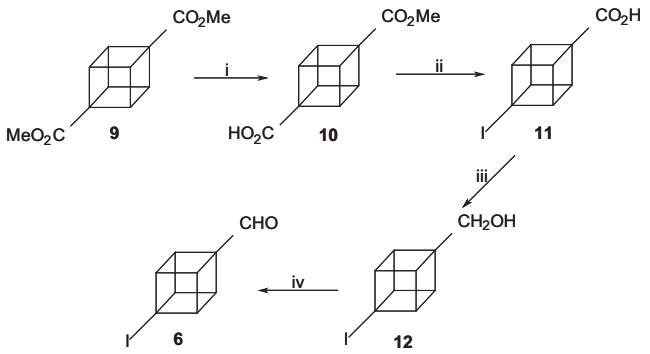


Scheme 1. Proposed mechanism of conversion of 4-iodo-1-vinylcubane (**1**) to 4-vinyl-trans-β-iodostyrene (**5**).[19]



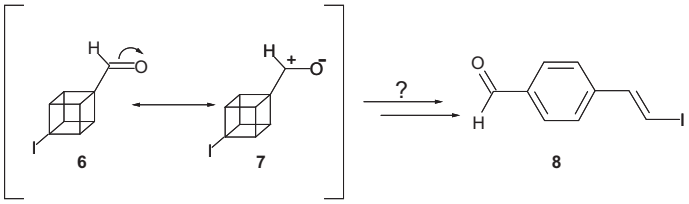
Scheme 3. Synthesis of 1-iodocubane-4-carboxaldehyde. Reagents and conditions: (i) (a) NaOH, MeOH, THF, (b) HCl; (ii) (a) IBDA, benzene, Δ, (b) NaOH, MeOH, (c) HCl; (iii) (a) $BH_3{\cdot}SMe_2$, THF, (b) HCl; (iv) oxalyl chloride, Et_3N, DMSO, CH_2Cl_2.

having the carbocation directly attached to the cubane scaffold allowed for the facile cage opening. We thus postulated that the aldehyde counterpart should also go through a similar cage-opening, as there exists a significant dipole moment (**6**→**7**) and in theory should form 4-carboxaldehyde-trans-β-iodostyrene, **8** (Scheme 2). Herein, we wish to report the results from the thermolytic study on 1-iodocubane-4-carboxaldehyde (**6**).

To synthesize our desired 1-iodocubane-4-carboxaldehyde (**6**), we began with dimethyl 1,4-cubanedicarboxylate (**9**). By reacting with 1 equiv of NaOH, we obtained the acid/ester, **10**.[21] A Moriarty reaction with iodobenzene diacetate, iodine, and ambient light yielded the iodo/ester, which was not isolated but immediately reacted with another equivalent of NaOH to afford the iodo/acid, **11**. Borane reduction provided the iodo/alcohol, **12**, which was subsequently oxidized under Swern conditions to afford our desired iodo/aldehyde, **6**, Scheme 3.[20]

With the 1-iodocubane-4-carboxaldehyde (**6**) in hand, we initially dissolved some in toluene and heated to reflux for one week. Upon evaporation of the solvent and subsequent NMR we were rather astonished with what we observed. Unlike the aforementioned 4-iodo-1-vinylcubane (**1**) which provided one clean product (i.e., 4-vinyl-trans-β-iodostyrene (**5**)) we observed no detectable 4-carboxaldehyde-trans-β-iodostyrene (**8**); but instead a collage of compounds, including benzyl benzoate. To attempt to ascertain what was being produced we re-preformed the reflux experiment but monitored progression using both GC–MS and NMR. At no time interval was the initially hypothesized 4-carboxaldehyde-trans-β-iodostyrene, **8** observed. Due to the similar amounts of 4-iodocubanecarboxylic acid (**11**) and 1-iodo-4-(hydroxymethyl)cubane (**12**) in the early stages of the reaction, we deduced that our 1-iodocubane-4-carboxaldehyde (**6**) was in equilibrium with its Cannizzaro products, thus affording **11** and **12**. The 1-iodocubane-4-carboxaldehyde (**6**) could however also go through some cage opening thus acting as a sink and shifting the equilibrium. Alternatively, it is possible that the initial Cannizzaro products, 4-iodocubanecarboxylic acid (**11**) and 1-iodo-4-(hydroxymethyl)cubane (**12**), independently undergo a cage-opening process eventually leading to benzoic acid and benzyl alcohol, respectively. To test this hypothesis, in separate experiments we heated 4-iodocubanecarboxylic acid (**11**) and 1-iodo-4-(hydroxymethyl)cubane (**12**) in refluxing toluene for two weeks. The carboxylic acid (**11**) was unchanged while the hydroxymethylcubane (**12**) eventually decomposed to intractable and unidentifiable charry residues. In addition, we heated a 1:1 mixture of 4-iodocubanecarboxylic acid (**11**) and 1-iodo-4-(hydroxymethyl)cubane (**12**) in refluxing toluene to see if indeed they existed in an equilibrium with the 1-iodocubane-4-carboxaldehyde (**6**). After 12 h of reflux, 5% of the cube aldehyde, **6** was observed with 7% of benzaldehyde (**16**). After 24 h, again only 5% of **6** was detected, however the benzaldehyde rose to 18% with traces of benzyl alcohol (**18**) and benzoic acid (**19**) (vide infra). This provides strong evidence that the cage-opening process through to aromatic products proceeds via the cube aldehyde (**6**).

There is a continual decrease in the amount of the cube aldehyde, **6**, with an initial increase then decrease in the both **11** and **12** (Fig. 1). Simultaneously, there was the formation of benzaldehyde (**16**). Benzaldehyde formation is most likely explained by the inability of the cyclooctatetraene intermediate, **13a** to go through a ring closure (**14a**) and liberation of I^- (Scheme 4) in a manner which was observed with 4-iodo-1-vinylcubane (**1**)[19] and described separately by both Cope[22] and Huisgen.[23] The strong electron-withdrawing nature of the carbonyl moiety would disfavor the pathway forming carbocation, **15**, that was seen in the rearrangement of the aforementioned 4-iodo-1-vinylcubane (**1**).[19] If cyclooctatetraene, **13b**, were to go through ring closure in a slightly different manner, **14b** would be formed, which could fragment to afford the observed benzaldehyde, **16** and iodoacetylene, **17**. As iodoacetylene has a boiling point of 32 °C, this would evaporate from the reaction vessel. However, we did observe the formation of iodoacetylene, **17** when we performed the thermo-studies in a sealed NMR tube. In addition, when the study was performed within a sealed NMR tube, the fragmentation was slower. For example, after 24 h, there existed a 29:25:27:14:2:3 ratio of **6**, **11**, **12**, **16**, **18**, and **19**; compared to 12:18:20:41:5:4 when



Scheme 2. Resonance of 1-iodocubane-4-carboxaldehyde (**6**) to possibly allow for the formation of 4-carboxaldehyde-trans-β-iodostyrene (**8**).

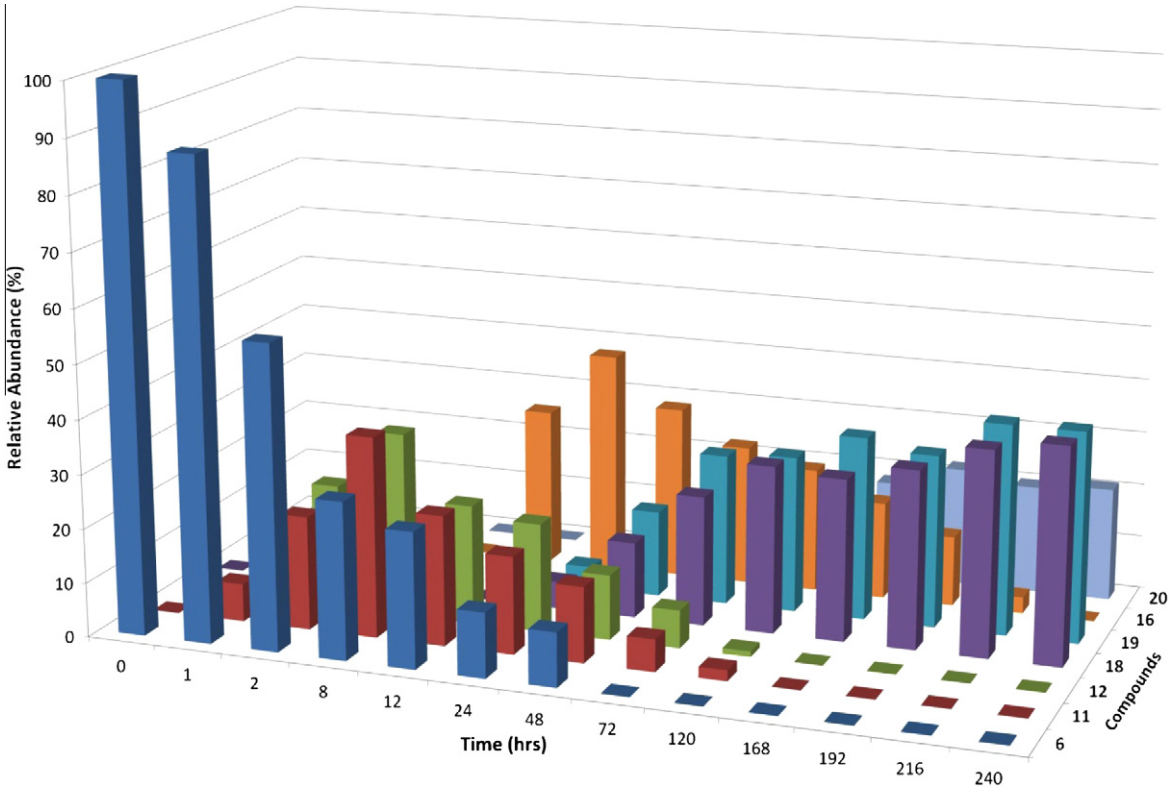
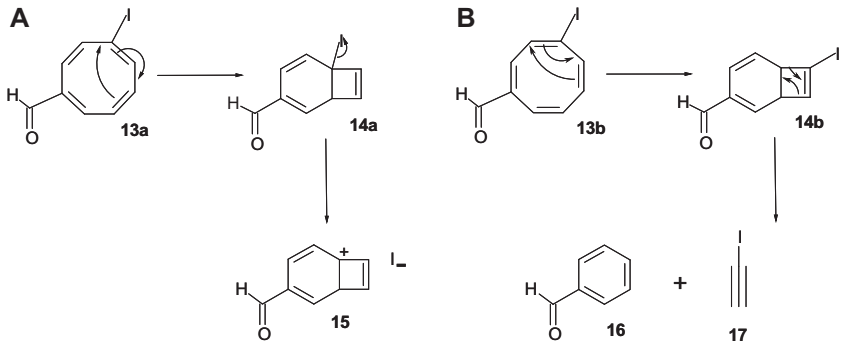


Figure 1. Relative percent abundance of the thermolytic decay of 1-iodocubane-4-carboxaldehyde (**6**).

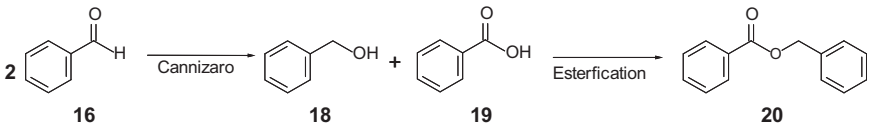


Scheme 4. Two routes for the closure of the cyclooctatetraene scaffold. (A) On left: the undetected path; (B) on right: the proposed mechanism.

performed in a larger scale. The disappearance of the iodoacetylene, **17** would drive the fragmentation process which explains the more rapid formation of benzaldehyde in the latter system.

The bond disassociation energy of the carbon–iodine bond is such that the homolysis of the 4-iodo substituent could not be immediately discounted in the cage-opening mechanism.[24] Cubyl radical formed in this way could conceivably be quenched by abstracting hydrogen from the toluene solvent. To probe this conjecture we conducted the thermolysis reaction in toluene-d_8. As no deuterium incorporation was observed into neither the cubane intermediates, nor the final aromatic products, this tends to refute the contribution of carbon–iodine homolysis to the cage-opening mechanism. In addition, if a radical cage-opening mechanism were involved, unsubstituted cubane carboxaldehyde and 4-iodocubane carboxaldehyde would be expected to behave similarly and have similar stabilities. We have observed that unsubstituted cubane carboxaldehyde is considerably less stable compared to 4-iodocubane carboxaldehyde, with the former tending to decompose during simple column chromatography.[25] The electron withdrawing iodo group would destabilize cation formation and hence stabilize the 1-iodocubane-4-carboxaldehyde (**6**). Finally, we performed the aforementioned studies in the presence of Lewis acids (i.e., $AlBr_3$, $AlCl_3$, BF_3, or BCl_3) and observed an accelerated rate of rearrangement, which is consistent with a cationic cage-opening versus free-radical mechanism, and which was also observed with the rearrangement of 4-iodo-1-vinylcubane (**1**).[19]

The newly formed benzaldehyde (**16**) could then undergo a Cannizzaro reaction yielding both the benzyl alcohol (**18**) and benzoic acid (**19**). In addition, the benzoic acid and benzyl alcohol could react with each other via simple esterification, affording the benzyl benzoate, **20**. The amounts of benzyl alcohol and benzoic acid continue to rise as the benzaldehyde is being converted. Likewise, the amount of benzyl benzoate seems to plateau, indicating equilibrium has been reached. To further confirm the latter



Scheme 5. Final formation of benzyl alcohol (**18**), benzoic acid (**19**), and benzyl benzoate (**20**).

steps, we have taken pure benzaldehyde in toluene and refluxed over one week. Indeed, we observed benzyl alcohol, benzoic acid, and benzyl benzoate, Scheme 5.

In summation, we have synthesized the 1-iodocubane-4-carboxaldehyde (**6**) in a four step process from dimethyl 1,4-cubanedicarboxylate (**9**). We subjected the aldehyde to refluxing toluene and monitored the formation and disappearance of compounds. Although the initially hypothesized 4-carboxaldehyde-trans-β-iodostyrene (**8**) was not observed we have proposed possible mechanistic explanations for the formation of the benzaldehyde, benzyl alcohol, benzoic acid, and benzyl benzoate.

Acknowledgments

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References and notes

1. Eaton, P. E.; Cole, T. W. *J. Am. Chem. Soc.* **1964**, *86*. pp 962 and 3157.
2. Eaton, P. E. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1421. and references cited therein.
3. Martin, H.-D.; Urbanek, T.; Pfohler, P.; Walsh, R. *J. Chem. Soc., Chem. Commun.* **1985**, 964.
4. Eaton, P. E.; Zhang, M. *Propell. Explos. Pyrot.* **2002**, *27*, 1.
5. Zhang, M.-X.; Eaton, P. E.; Gilardi, R. *Angew. Chem., Int. Ed.* **2000**, *39*, 401.
6. Gunosewoyo, H.; Guo, J. L.; Bennett, M. R.; Coster, M. J.; Kassiou, M. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 3720.
7. Cheng, C. Y.; Hsin, L. W.; Lin, Y. P.; Tao, P. L.; Jong, T. T. *Bioorg. Med. Chem.* **1996**, *4*, 73.
8. Camps, P.; Duque, M. D.; Vazquez, S.; Naesens, L.; Clercq, E. D.; Sureda, F. X.; Lopez-Querol, M.; Camins, A.; Pallas, M.; Prathalingam, S. R.; Kelly, J. M.; Romero, V.; Ivorra, D.; Cortes, D. *Bioorg. Med. Chem.* **2008**, *16*, 9925.
9. (a) Zhou, J. J. P.; Li, J.; Upadhyaya, S.; Eaton, P. E.; Silverman, R. B. *J. Med. Chem.* **1997**, *40*, 1165; (b) Silverman, R. B.; Zhou, J. J. P.; Eaton, P. E. *J. Am. Chem. Soc.* **1993**, *115*, 8841; (c) Silverman, R. B. *Acc. Chem. Res.* **1995**, *28*, 335.
10. (a) Ingalsbe, M. L.; St. Denis, J. D.; Gleason, J. L.; Savage, G. P.; Priefer, R. *Synthesis* **2010**, 98; (b) McGonagle, A. E.; Savage, G. P. *Aust. J. Chem.* **2009**, *62*, 145.
11. Priefer, R.; Nguyen, S.; Farrell, P. G.; Harpp, D. N. *Macromolecules* **2003**, *36*, 5435.
12. Chalmers, B. A.; Chen, A. P.-J.; Savage, G. P.; Williams, C. M. *Aust. J. Chem.* **2010**, *63*, 1108.
13. Cole Jr., T. W. Ph.D. Dissertation, University of Chicago, 1966.; Hormann, R. E. Ph.D. Dissertation, University of Chicago, 1987.
14. Priefer, R.; Lee, Y. J.; Barrios, F.; Wosnick, J. H.; Lebuis, A.-M.; Farrell, P. G.; Harpp, D. N.; Sun, A.; Wu, S.; Snyder, J. P. *J. Am. Chem. Soc.* **2002**, *124*, 5626.
15. Priefer, R.; Martineau, E.; Harpp, D. N. *J. Sulfur Chem.* **2007**, *28*, 529.
16. Cassar, L.; Eaton, P. E.; Halpern, J. *J. Am. Chem. Soc.* **1970**, *92*, 3515.
17. Cassar, L.; Eaton, P. E.; Halpern, J. *J. Am. Chem. Soc.* **1970**, *92*, 6366.
18. Roux, M. V.; Davalos, J. Z.; Jimenez, P.; Notario, R.; Castano, O.; Chickos, J. S.; Hanshaw, W.; Zhao, H.; Rath, N.; Liebman, J. F.; Farivar, B. S.; Bashir-Hashemi, A. *J. Org. Chem.* **2005**, *70*, 5461.
19. Carroll, V. M.; Harpp, D. N.; Priefer, R. *Tetrahedron Lett.* **2008**, *49*, 2677.
20. Griffiths, J. R.; Savage, G. P.; Tsanaktsidis, J.; Priefer, R. *Thermochim. Acta* **2010**, *499*, 15.
21. Priefer, R.; Farrell, P. G.; Harpp, D. N. *Synthesis* **2002**, 2671.
22. Cope, A. C.; Burg, M. *J. Am. Chem. Soc.* **1952**, *74*, 168.
23. Huisgen, R.; Konz, W. E. *J. Am. Chem. Soc.* **1970**, *92*. pp 4102 and 4104.
24. Kropp, P. J.; Adkins, R. L. *J. Am. Chem. Soc.* **1991**, *113*, 2709.
25. Priefer, R. Ph.D. Dissertation, McGill University, **2003**.