Review Article

Thermal Cage Opening/Rearrangement of Novel Cubyl Styrene Derivatives

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Abstract

Recently, it was observed that 4-iodo-1-vinylcubane underwent cage-opening/rearrangement under elevated temperature conditions to yield 4-vinyl-trans-β-iodostyrene. As this process was unique, other known iodinated cubane derivatives were evaluated and it was observed that 1-iodocubane-4-carboxaldehyde was also unstable under elevated temperatures. However, in the latter instance a cage-opening/fragmentation process occurred yielding benzaldehyde and iodoacetylene. It was theorized that both the iodine and the "para" sp^2-hydrized carbon play a role in these different paths. Therefore, novel cubyl styrene derivatives were synthesized, and their thermal behaviors were assessed. Indeed, α-cubyl styrene and its "para" iodinated analogue, 1-(4'-iodocubyl) vinyl)benzene were synthesized and thermally analyzed. Under refluxing conditions α-cubyl styrene undergoes complete cage-opening to α-cyclooctatetraene styrene after 17 days. In contrast, 1-(4'-iodocubyl)vinyl)benzene underwent cage-opening/rearrangement to 4-(1-phenylethenyl)-trans-β-iodostyrene in just 5 hours. In both instances, a polar versus radical mechanism appears to be the path to cage-opening.

Keywords: Cubane; Cape Opening; Rearrangement; Styrene

Introduction

Since the initial synthesis of cubane [1] by Eaton and Cole in 1964, numerous publications dealing with the special qualities of its derivatives have been reported [1]. Some nitrated cubanes are classified as the most powerful non-nuclear explosives [2-4]. In a quite different area, cubylamines have been reported to be antiviral [5]. Cubanes also have a tendency to behave as quasi-aromatic molecules, participating in reactions that are typically associated with benzene[6]. Cubane derivatives have also been studied regarding their tendency to undergo spontaneous cage-opening (Figure 1); for example, cubanol (2) will open to form vinylcyclobutenylketene (3) [7,8]. Cubane (1) has also been reported to rearrange via metal induced pathways. When cubane is treated with rhodium (I), syn-tricyclooctadiene (4) is obtained [9], but in the presence of silver (I) ions, cuneane (5) is formed [10].

Additionally, it has been reported that iodinated cubane derivatives undergo a unique cage-opening/rearrangement or cage-opening/fragmentation process when a sp^2-hybridized carbon is "para" to the halide [11-13]. It was observed that 4-iodo-1-vinylcubane (6) went through cage-opening/rearrangement to form 4-vinyl-trans-β-iodostyrene (8) via the cyclooctatetraene intermediate, 7 [11]. However, with 1-iodocubane-4-carboxaldehyde (9), cage-opening/fragmentation occurred to yield benzaldehyde (10) and iodoacetylene (11) [13]. The unpredictable thermal behavior of iodinated cubane derivatives in conjunction with the "para" sp^2-hybridized carbon is an area that requires further exploration, in particular since the proposed two-bond ring-opening reaction (cycloreversions) is theoretically thermally disallowed by orbital symmetry considerations.
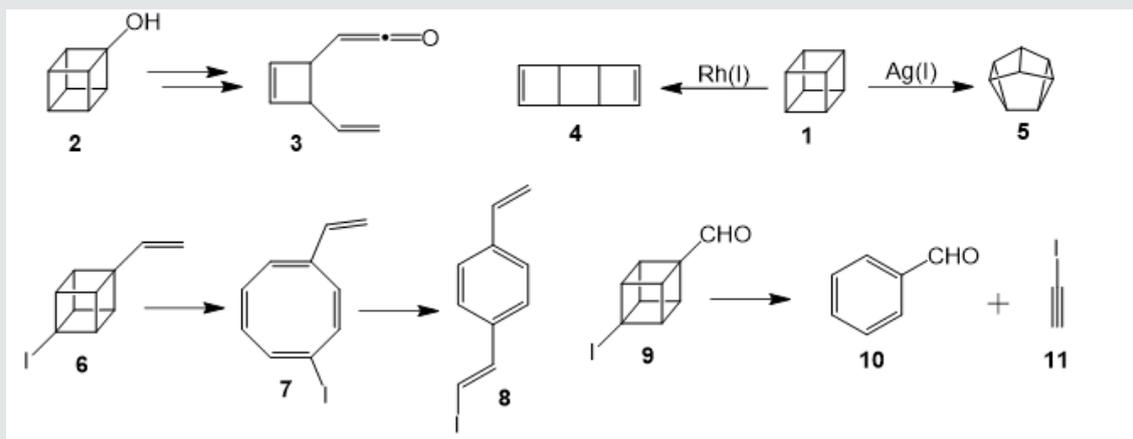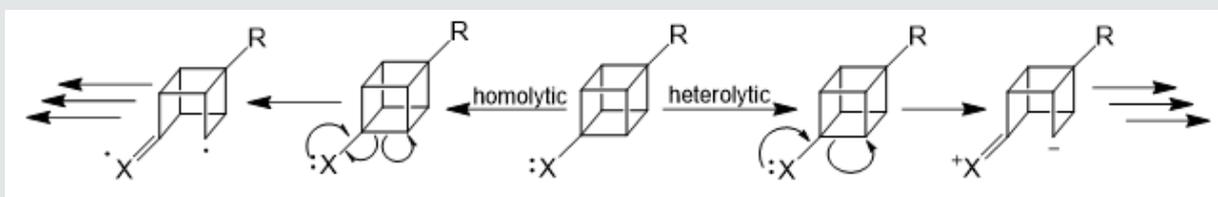
Figure 1: Cage-opening of cubanol (2); cage-opening of cubane (1) with rhodium to syn-tricyclooctadiene (4) and rearrangement to cuneane (5) with silver; cage-opening/rearrangement of 4-iodo-1-vinylcubane (6) to 4-vinyl-trans-β-iodostyrene (8); cage-opening/fragmentation of 1-iodocubane-4-carboxaldehyde (9) to benzaldehyde (10) and iodoacetylene (11).

Scheme 1: Possible fragmentation pathways for heteroatom attached cubane derivatives.
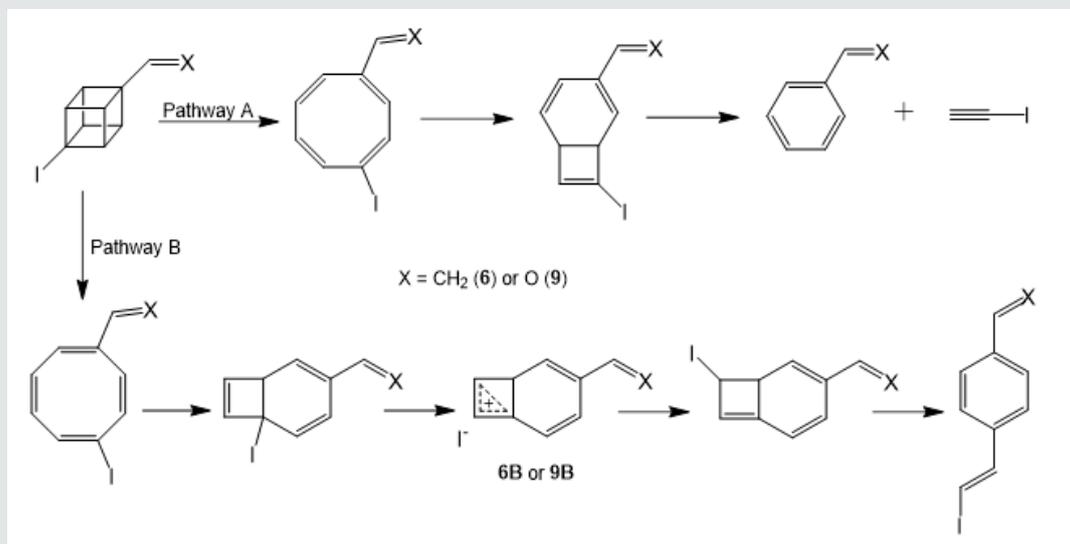
**Scheme 2:** Proposed pathways for cage-opening/rearrangement and cage-opening fragmentation.

We attribute the observed cage-opening/rearrangement and/or fragmentation of the above iodinated cubane derivatives, as well as the instability of cubanols [7,8], cubanethiols [14], and cubylamines [2] to the presence of the lone pair of electrons on the adjacent heteroatom. We propose that this electron pair significantly disrupts the integrity of cubane analogues by donating into the cage and inducing instability via either a homolytic or heterolytic

pathway (Scheme 1). Although simple cubyl iodides had not been previously reported to possess any thermal instability, the unusual structural isomerization of 4-iodo-1-vinylcubane (6) to 4-vinyl-trans-β-iodostyrene (8) under simple refluxing in toluene added a new dimension [11]. During differential scanning calorimetry studies on iodinated cubane derivatives this cage-opening/rearrangement process was again detected [12]. Likewise, the

cage-opening/fragmentation of cubane-4-carboxaldehyde (9) [13], suggests that there is a connection with having a sp²-hybridized carbon directly attached to the cage with an iodine "para" to it, and stability. We hypothesized alternate routes for the cage-opening/ rearrangement or cage-opening/fragmentation (Scheme 2) [13]. For example, starting with 1-iodocubane-4-carboxaldehyde (9), Pathway B would be unlikely because the strong electron-withdrawing nature of the carbonyl moiety would disfavor the formation of the carbocation intermediate, 9B. Therefore, Pathway A is the more likely route to achieve aromaticity [13]. However, with 4-iodo-1-vinylcubane (6), which underwent a quantitative cage-opening/rearrangement [11], presumably Pathway B, where intermediate 6B would be a possibility, is the likely route.

Results and Discussion

To further understand this phenomenon, we looked at synthesizing and thermally analyzing 1-(4'-iodocubyl)vinyl) benzene (12) and α-cubyl styrene (13). The formation of the 12 was accomplished in six steps (Scheme 3). An initial base hydrolysis with one equivalent of NaOH on dimethyl-1,4-cubanedicarboxylate (14) gave the acid/ester, 15 [15]. A Moriarty reaction yielded the iodo/ester, 16 [15], followed by another base hydrolysis afforded the iodo/acid, 17 [15]. Conversion to the iodo/acid chloride (18) under Vilsmeier conditions [16] and subsequent addition of phenyl magnesium bromide gave 1-(4'-iodocubyl) phenyl ketone (19), which after a Wittig afforded 1-(4'-iodocubyl)vinyl)benzene (12) in 38% overall yield.
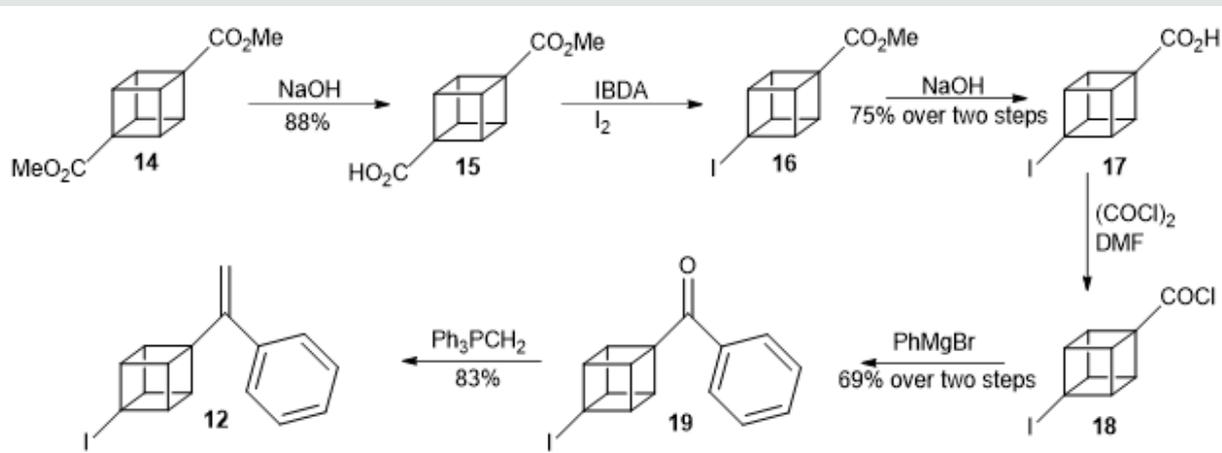
Scheme 3: Synthesis of 1-(4'-iodocubyl)vinyl)benzene (12) from dimethyl-1,4-cubanedicarboxylate (14).
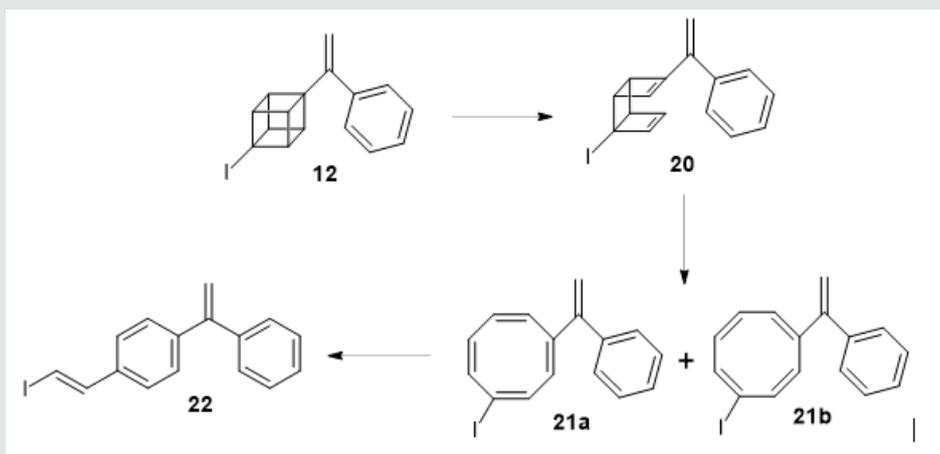
Scheme 4: Cage-opening/rearrangement of 1-(4'-iodocubyl)vinyl)benzene (12) to 4-(1-phenylethenyl)-trans-β-iodostyrene (22).

With 1-(4'-iodocubyl)vinyl)benzene (12) in hand we examined to see whether this iodinated cubane compound would undergo the cage-opening/rearrangement or cage-opening/fragmentation pathway or be stable at elevated temperatures to possibly allow for polymerization. Upon refluxing 1-(4'-iodocubyl)vinyl)benzene (12) in toluene (110 °C), we observed cage-opening/rearrangement (Scheme 4); not in the days that was seen in the previous two examples [11-13], but a complete conversion in only 5 hours. We also observed, with ¹H-NMR, the syn-tricyclooctadiene intermediate 20 as well as the two conformers of cyclooctatetraene (21a and 21b)

within a half an hour. The 1,4-isomer of cyclooctatetraene (21a) is less prevalent than the 1,6-isomer (21b) (Figure 2a & b) which is what has been observed on other cyclooctatetraene systems [17]. The final styrene derivative, 4-(1-phenylethenyl)-trans-β-iodostyrene (22), was also observed within the first half hour of the study (Figure 2a & b). The cage-opening/rearrangement was moderately accelerated in the presence of a Lewis acid (Figure 2b) which was also observed with 4-iodo-1-vinylcubane (6) [11] and 1-iodocubane-4-carboxaldehyde (9) [13], suggesting that the process may be polar in nature as proposed in Scheme 1.
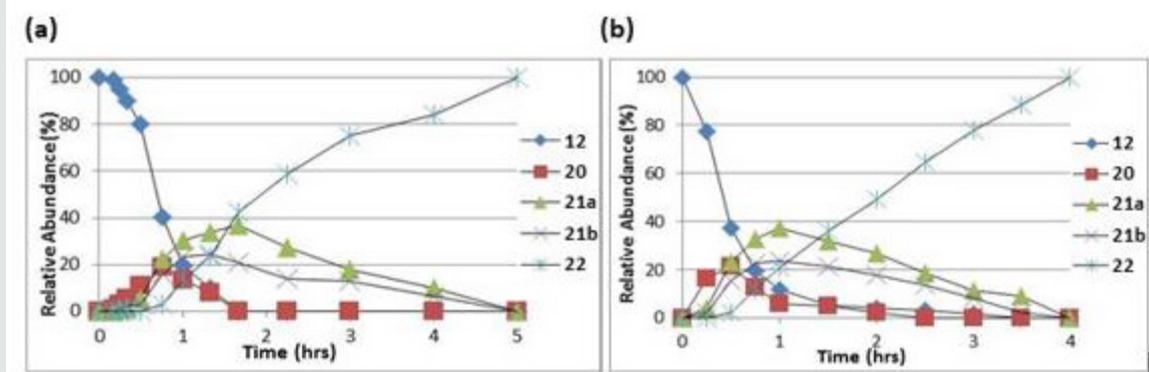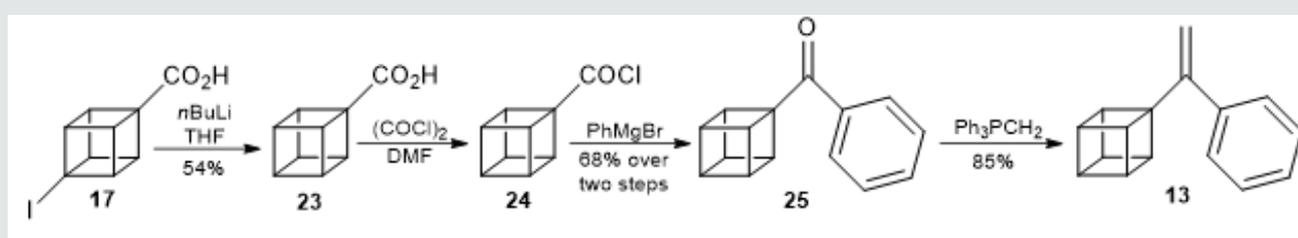

Figure 2: (a) Cage-opening/rearrangement (12: 5mg/0.5mL) in refluxing d_8-toluene. (b) Cage-opening/rearrangement (12: 5mg/0.5mL) in refluxing d_8-toluene with 0.25eq of BCl_3.

Also, in an attempt to determine whether the cage-opening/rearrangement was due to the presence of the sp^2-hybridized carbon, the "para" iodine, or both; we synthesized α-cubyl styrene (13). Utilizing the iodo/acid intermediate from Scheme 3, we initially de-iodinated with n-BuLi to yield cubanecarboxylic acid (23),15 followed by conversion to the acid chloride, 24,16 attack by phenyl magnesium bromide to provide the ketone, 25, and concluding with a Wittig reaction to obtain α-cubyl α-cubyl styrene (13) in 21% overall yield from starting cubane 14 after 7 total steps (Scheme 5). Compound 13 is a solid at just above room temperature and is non-polymerizable in an oxygen deficient environment. As with the iodinated analogue, 12, we set out to test the stability of this vinyl cubane, 13, under thermal conditions. Within a sealed NMR tube, 5mg of 13 was dissolved in 0.5mL d8-toluene and heated to 110 °C. The observed rearrangement of 13 was drastically different from that of the iodinated form (12). With 13, the cage-opening required 17 days (Figure 3) as opposed to only 5 hours for both cage-opening and rearrangement for compound 13 (Figure 2). The opening did proceed as anticipated, stopping at the cyclooctatetraene, 26. The lack of the iodine does prevent the rearrangement to any possible benzene product which have been reported in the past. Decomposition occurred when the solvent was changed to d_4-AcOH. However, when the solvent was changed to d_6-DMSO and heated to 110 °C, the rearrangement was completed at an accelerated rate of 3 days. This suggests that this cage-opening is solvent dependent and may likely be polar versus radical in nature. The dramatic decrease in the rate of cage opening when iodine was not present provides confidence in our initial hypothesis that a lone pair of electrons on this heteroatom does indeed provide a donating effect into the cage system, thus destabilizing it. These results suggest that other cubane derivatives possessing both a sp^2-hybridized carbon and a "para" heteroatom should have decreased barriers to cage-opening.

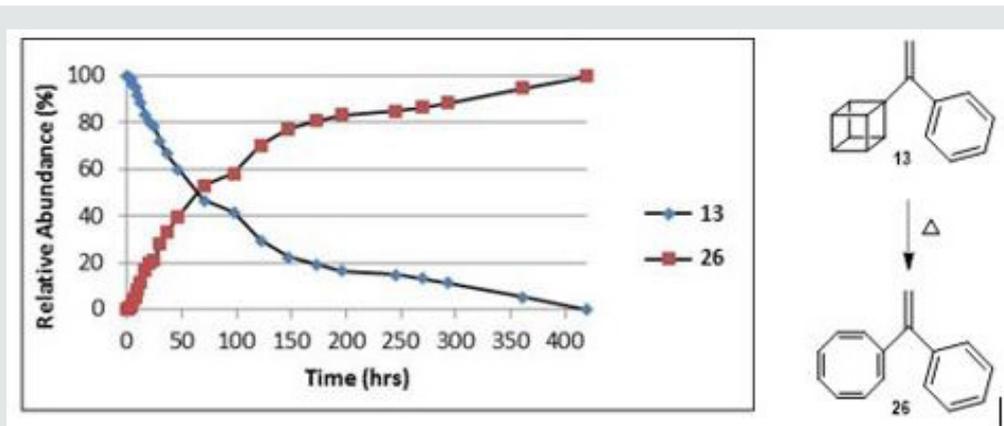**Scheme 5:** Synthesis of the α-cubyl styrene (13).

Figure 3: Cage-opening/rearrangement (13: 5mg/0.5mL) in refluxing d$_8$-toluene.

Conclusion

We have been able to synthesize 1-(4'-iodocubyl)vinyl) benzene (12) and α-cubyl styrene (13) and conduct thermal cage opening experiments on both. The former showed complete cage open/rearrangement after only 4 hours with both the syn-tricyclooctadiene (20) as well as both conformers of cyclooctatetraene (21a and b) intermediates being observed on the path to the final 4-(1-phenylethenyl)-trans-β-iodostyrene (22) product. The thermal cage opening of α-cubyl styrene (13) was accomplished after approximately 400hrs stopping at the cyclooctatetraene derivative, 26.

Acknowledgments

References

1. Biegasiewicz KF, Griffiths JR, Savage GP, Tsanaktsidis J, Priefer R (2015) Cubane: 50 Years Later. Chemical Reviews 115(14): 6719-6745.

2. Eaton PE, Shankar BKR, Price GD, Pluth JJ, Gilbert EE, et al. (1984) Synthesis of 1,4-dinitrocubane. J Org Chem 49(1): 185-186.

3. Eaton PE, Wicks GE (1988) Conversion of isocyanates to nitro compounds with dimethyl dioxirane in wet acetone. J Org Chem 53(22): 5353-5555.

4. Eaton PE, Xiong Y, Gilardi R (1993) Systematic substitution on the cubane nucleus. Synthesis and properties of 1,3,5-trinitrocubane and 1,3,5,7-tetranitrocubane. J Am Chem Soc 115(22): 10195-10202.

5. Gregory WA (E I du Pont de Nemours and Co.) US Patent 3558704.

6. Eaton PE (1992) Cubanes: starting materials for the chemistry of the 1990s and the next century. Angew Chem 104: 1447.

7. Cole Jr, TW PhD (1966) Dissertation, University of Chicago, USA.

8. Hormann RE PhD (1987) Dissertation University of Chicago, USA.

9. Cassar L, Eaton PE, Halpern J (1970) Catalysis of symmetry-restricted reactions by transition metal compounds. Valence isomerization of cubane. J Am Chem Soc 92(11): 3515-3518.

10. Cassar L, Eaton PE, Halpern J (1970) Silver(I)- and palladium(II)-catalyzed isomerizations of cubane. Synthesis and characterization of cuneane. J Am Chem Soc 92(21): 6366-6368.

11. Carroll VM, Harpp DN, Priefer R (2008) Thermo-cage opening of 4-iodo-1-vinylcubane to a novel styrene derivative. Tetrahedron Lett 49(17): 2677-2680.

12. Griffiths JR, Tsanaktsidis J, Savage GP, Priefer R (2010) Thermochemical properties of iodinated cubane derivatives. Thermochim Acta 499(1-2): 15-20.

13. Heaphy PJ, Griffiths JR, Dietz CJ, Paul Savage G, Priefer R (2011) Cage opening and rearrangement of 1-iodocubane-4-carboxaldehyde. Tetrahedron Lett 52(48): 6359-6362.

14. Priefer R, Lee YJ, Barrios F, Wosnick JH, Lebuis AM (2002) Dicubyl Disulfide. J Am Chem Soc 124(20): 5626-5627.

15. Priefer R, Farrell PG, Harpp DN (2002) Effective synthetic routes to cubylcarbinol derivatives. Synthesis 2671-2673.

16. Priefer R, Nguyen S, Farrell PG, Harpp DN (2003) Synthesis of Novel, Cubane-Containing Norbornene-Based Polymers. Macromolecules 36(15): 5435-5436.

17. Allinger NL, Frierson M, Van-Catledge FA (1982) The importance of van der Waals attractions in determining the equilibrium between 1,4- and 1,6-dialkylcyclooctatetraenes. J Am Chem Soc 104: 4592-4593.

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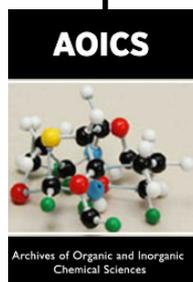
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