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Energetic Materials

Cubane, Bicyclo[1.1.1]pentane and Bicyclo[2.2.2]octane: Impact and Thermal Sensitiveness of Carboxyl-, Hydroxymethyl- and Iodo-substituents

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Abstract: With the burgeoning interest in cage motifs for bioactive molecule discovery, and the recent disclosure of 1,4-cubane-dicarboxylic acid impact sensitivity, more research into the safety profiles of cage scaffolds is required. Therefore, the impact sensitivity and thermal decomposition behavior of judiciously selected starting materials and synthetic intermediates of cubane, bicyclo[1.1.1]pentane (BCP), and bicyclo[2.2.2]octane (BCO) were evaluated via hammer test and sealed cell differential scanning calorimetry, respectively. Iodo-substituted systems were found to be more impact sensitive, whereas hydroxymethyl substitution led to more rapid thermodecomposition. Cubane was more likely to be impact sensitive with these substituents, followed by BCP, whereas all BCOs were unresponsive. The majority of derivatives were placed substantially above Yoshida thresholds—a computational indicator of sensitivity.

Exploration of chemical space by the application of bioisosteres continues to attract considerable interest from medicinal chemists.[1] Especially since the introduction of the concept "escaping from flatland" in 2009,[2] when interest in enhancing the drug-like properties of lead candidates through the use of saturated cage hydrocarbons has seen sharp uptake.[3] Cubane (**1**, Figure 1)[4] and bicyclo[1.1.1]pentane (BCP, **2**),[5] in particular, are gaining increased popularity as structural motifs, bioisosteres, and scaffolds to explore structure activity relationships (SAR).[6] Cubane is particularly suitable for this operation, given the similarity of the body diagonal distance to that of benzene.[7]

Investigation of the BCP motif as a phenyl ring bioisostere stems back to at least 1996, when Pellicciari et al. undertook an SAR study comparing the mGlu receptor agonist, carboxyphenylglycine, with BCP[8] and cubane derivatives.[9] In contrast, the bicyclo[2.2.2]octane scaffold (BCO, **3**) has not enjoyed the same level of popularity as cubane nor BCP, however, it is still deployed on occasion.[10] BCO is significantly less strained (7.4–11.6 kcal mol^{-1})[11] than both cubane (161.5–169.1 kcal mol^{-1})[12] and BCP (67.0–68.0 kcal mol^{-1}),[11] making this scaffold a useful comparator in any cubane or BCP associated campaign.

Certain functional groups are well known to substantially activate cubane derivatives. For example, 1,4-cubane-dicarboxylic acid (**1 c**, Figure 2) and 4-carbamoylcubane-1-carboxylic acid (**4**),[13] were recently disclosed by the authors to be thermally and impact sensitive. 1,4-Diisocyanocubane (**5**)[14] and azidocubanes (e.g., **6**)[15] are observed to be highly thermally unstable and exceedingly shock sensitive. 4-[(Nitrooxy)methyl]cubane-1-carboxylic acid (**7**), dimethyl cubane-1,4-dicarboxylate (**1 a**), and cubane-1,4-dicarboxylic acid (**1 c**) have also been reported to exhibit sensitiveness to impact,[16] whereas octanitro- (**8**) and heptanitrocubane (**9**) are described as insensitive to hammer taps.[17] Additionally, (4-iodocuban-1-yl)methanol (**1 g**) was shown to undergo particularly rapid thermodecomposition in thermogravimetric analysis (TGA), while the decomposition of other iodinated cubanes was not as notably rapid,[18] apart from an iodinated norbornene based polymer (**10**).[19] This led to the question of whether the hydroxymethyl group may also

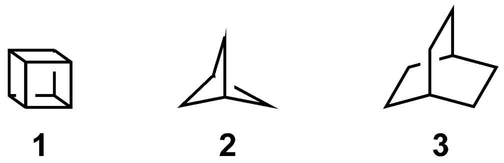

Figure 1. Cubane (**1**), bicylco[1.1.1]pentane (**2**), and bicyclo[2.2.2]octane (**3**) scaffolds.

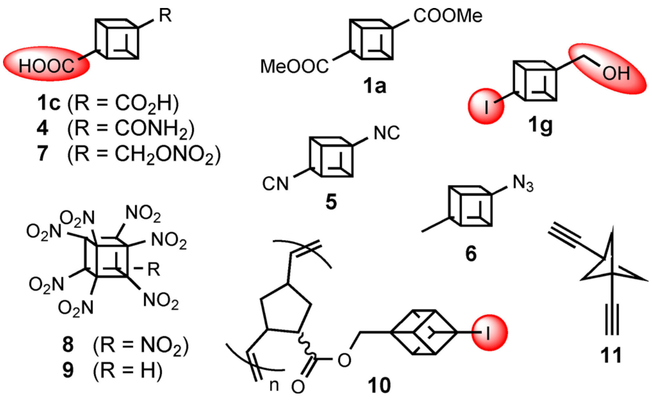

Figure 2. Cubanes (**4**–**10**) which are known to be impact and/or thermally sensitive, in addition to BCP **11**.

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contribute to thermal instability and decomposition behavior of cubane and other cage systems. Together, iodinated and carboxylic acid derivatives raise concerns, as many of these are common synthetic intermediates within the cubane, BCP, and BCO classes.

In addition to cubane examples, the BCP framework is also known to be thermally sensitive. Namely 1,3-diethynyl[1.1.1]bicyclopentane (**11**), of which a sample exploded during attempted sublimation.[20] Subsequently, others have successfully sublimed **11** at 50 °C with no incident, however cautious handling of this BCP was strongly recommend.[21]

In light of the emerging and increasing popularity of these cage motifs, it is timely to review and investigate key functional groups used in synthesis that potentially instill sensitivity. Especially, in terms of increasing practitioner awareness and enhancing general safety (e.g., handling and scale up).

Reported herein are the results of impact sensitiveness testing, as well as thermal sensitiveness and behavior of selectively substituted cubane, BCP and BCO systems involving carboxyl-, hydroxymethyl- and iodo-substituents (Table 1), as evaluated through hammer test and sealed cell differential scanning calorimetry (scDSC). These results build a safety perspective, unobtainable through commonly deployed in silico methods, around key functional groups such that informed precautions can be taken.

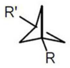
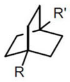
Impact Sensitiveness: Hammer tests were performed on all system derivatives listed in Table 1. This test is commonly used in high energy density materials research, and provides information about any precautions that should be taken with storage, handling, and reaction scale up.[22] The two possible outcomes of a hammer test are 1) a go event, which is defined as any one of: an audible report, flame or visible light, smoke, or definite evidence of discoloration of the sample due to decomposition (e.g., charring); or 2) a no-go event, which is the absence of any of the above. Sample size for this type of assessment is generally in the range of 5 mg.

Most cage derivatives investigated were not sensitive to impact and none of the BCO compounds displayed go events. 1,4-Diiodocubane (**1 d**) was by far the most impact sensitive material observed in this study, requiring only a light tap to reliably and repeatedly give a go event, which consisted of a loud crack, smoke, and charring. 4-Iodocubane-1-carboxylic acid (**1 f**) also displayed a go event, consisting of charring and an audible pop. Overall, both iodinated cubanes **1 d** and **1 f** were markedly easier to initiate than diacid **1 c** (Table 1).[23]

Of the BCP derivatives it was again the diiodo **2 d** which displayed the most obvious go event, consisting of a popping noise and visible charring. This is in keeping with the high impact sensitivity of **1 d** and suggests that iodinated cages may be particularly susceptible to impact initiation. Acid-methanol **2 j** also gave a go event, albeit only consisting of a color change (slight charring) (Table 1).

The occurrence of a go event for BCP **2 j**, but not for the cubane equivalent **1 j**, was slightly surprising, given the higher energy of the cubyl system and the tendency for cubanes to be more sensitive to impact. It should be noted, however, that many factors affect impact sensitivity (e.g., particle size), and that results can vary from batch to batch. Diacid **1 c**, for example, was quantitatively determined to have an impact sensitiveness similar to a secondary explosive,[13] but did not always display a go event in our hands, that is, depending on the batch, impurities, and the experimenter.

Table 1. Summary of hammer test results and exotherms observed in scDSC (endotherms not listed).[a,b]

		R	R'	Hammer	T_{DSC} [°C]	Q_{DSC} $[cal\ g^{-1}]$	Thermal Potential	Ref.
	**1a**	COOMe	COOMe	No-go	169	1581	Very high	[28]
	1b	COOMe	COOH	No-go	146	1739	Very high	[13]
	1c	COOH	COOH	Go	180	1657	Very high	[13]
	1d	I	I	Go	222	9918	Very high	[29]
	1e	I	COOMe	No-go	152 242	6961 961	Very high High	[18]
	1f	I	COOH	Go	150 178	27 11101	Low Very high	[4h]
	1g	I	CH_2OH	No-go	111 164	3783 9139	Very high Very high	[18]
	1h	CH_2OH	CH_2OH	No-go	106 170	4909 8192	Very high Very high	[30]
	1i	CH_2OH	COOMe	No-go	99	13872	Very high	[4i]
	1j	CH_2OH	COOH	No-go	142	1415	Very high	[31]
	**2a**	COOMe	COOMe	No-go	252		[d]	[5a]
	2b	COOMe	COOH	No-go	218		[d]	[5g]
	2c	COOH	COOH	No-go	289		[d]	[5g]
	2d	I	I	Go	111	920	High	[32]
	2e	I	COOMe	No-go	163	4657	Very high	[33]
	2f	I	COOH	No-go	102	6554	Very high	
	2g	I	CH_2OH	No-go	66	7340	Very high	
	2h	CH_2OH	CH_2OH	n/a[c]	110 245	256	Medium [d]	[34]
	2i	CH_2OH	COOMe	n/a[c]	244		[d]	[34]
	2j	CH_2OH	COOH	Go	217		[d]	
	**3d**	I	I	No-go	248	2383	Very high	[35]
	3e	I	COOMe	No-go	66	46	Low	[36]
	3f	I	COOH	No-go	276		[d]	[37]
	3g	I	CH_2OH	No-go	198	2984	Very high	[38]

[a] The synthesis of the carboxyl-, hydroxymethyl- and iodo-substituted cubane, BCP and BCO systems followed standard literature procedures, which afforded known and novel cubanes (**1 a**–**j**), BCPs (**2 a**–**j**) and BCOs (**3 d**–**g**) (See Supporting Information); [b] Each entry represents one exothermic event in the heatflow curve, compounds with two exotherms displayed two exotherms; [c] Liquids at room temperature were not impact tested; [d] Exotherm was ongoing at 300 °C so Q_{DSC} and thermal potential could not be determined.

Thermal testing: Sealed cell differential scanning calorimetry was employed to investigate the thermal sensitiveness and behavior of all derivatives, using the method described by Sperry et al.[24] Surprisingly, the interpretation and reporting of DSC data is currently not standardized, although the technique is gaining popularity due to its utility as an early indication of thermal sensitivity.[25] Herein, the onset temperature (T_{DSC}) referred to is the left limit onset temperature rather than the extrapolated onset temperature, as this is a more useful parameter in thermal hazard assessments (See Supporting Information).

All iodinated cages, other than BCO-iodo-acid (**3 f**) and BCO-iodo-ester (**3 e**), underwent exotherms with at least high ($>$500 cal g^{-1}) thermal potential, and as a result flagged substantially above the Yoshida thresholds for impact sensitivity and explosivity (see Table 1 and further below). The iodo-alcohols **1 g** and **2 g**, displayed unusual hook shaped heatflow curves when heated at 5 K min^{-1} (Figures S7 and S18 respectively, Supporting Information). A similar shape was seen previously when the oxidants IBX, MTP3, and ATP3 were examined for impact sensitivity,[26] and was attributed to thermal lagging (i.e., the instrument being unable to accurately measure the extremely rapid thermal decomposition). Decreasing the heating rate to 1 K min^{-1} allowed the instrument to more accurately record the decomposition energy (Q_{DSC}). As can be seen in Figure 3, at 1 K min^{-1} the onset of the exotherm for these two compounds is still very rapid—almost vertical. The rapid onset of the exotherm in scDSC supports the previous finding that (4-iodocuban-1-yl)methanol (**1 g**) underwent extremely rapid thermodecomposition in TGA.[18] Cubane acid-alcohol **1 j** also displayed an extremely sharp heat flow curve, suggesting that this material also undergoes rapid thermodecomposition. Conversely, cubane ester-alcohol **1 i** displayed a wide, gentle exotherm curve indicating that the ester substituent either retards the decomposition rate or simply does not contribute to accelerating decomposition. Cubane iodo-acid (**1 f**), which gave a go event in the hammer test, also underwent rapid exothermic decomposition (Figure S6). The onset is steep, and at least two large exothermic events are visible, however these overlap to give the measured exotherm with $T_{DSC}=178\,^{\circ}C$ and $Q_{DSC}=11101$ cal g^{-1} (very high thermal potential). While the onset is rapid, it is not as rapid as the alcohol **1 g**, further supporting the hypothesis that hydroxymethyl substitution of the cage increases thermodecomposition rate. See Supporting Information for all scDSC heatflow curves.

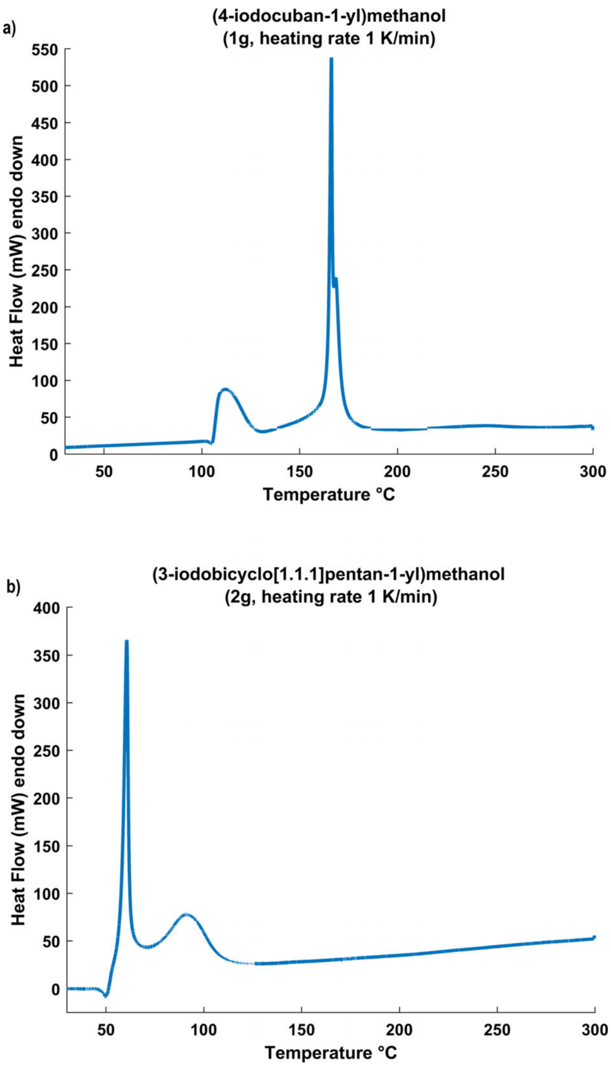


Figure 3. scDSC heatflow curves at 1 K min^{-1} heating rates. a) (4-iodocuban-1-yl)methanol (**1 g**) heated at 1 K min^{-1} b) (3-iodobicyclo[1.1.1]pentan-1-yl)-methanol (**2 g**) heated at 1 K min^{-1}.

When comparing the three scaffolds with identical substituents (e.g, **1 e**, **2 e**, and **3 e**, Figure 4), the cubane derivatives displayed the highest exotherm, followed by BCP then BCO, except in the case of the diiodo compounds (**1**–**3 d**) where BCP **2 d** had a lower exotherm than BCO **3 d**. These findings support the theory that the exothermic nature of decomposition stems primarily from the strain energy within the cage. Cubane has the highest strain energy, followed by BCP, and then BCO (see above).

Yoshida correlations were initially considered as a reinforcing method to flag substituted cages as potentially explosive and/or impact sensitive; that is, plotting the energy of the exotherm (Q_{DSC}) against the onset temperature (T_{DSC}).[24,27] However, almost all the derivatives examined were placed substantially above the thresholds. The exceptions were those systems whose exotherms were still ongoing at 300 °C, so a Q_{DSC} could not be determined (i.e., **2 a**, **2 b**, **2 c**, **2 i**, **2 j**, and **3 f**), and BCO-iodo-ester (**3 e**) for which a small exotherm was observed which fell below the thresholds.

Beyond the sensitivity of the carboxylic acid residue being reinforced herein, the combination of iodo- and hydroxymethyl substituents on the three cage scaffolds examined leads to extremely rapid thermodecomposition (i.e., presumably through loss of iodine and formaldehyde) as evidenced by the vertical onset for iodo-alcohols **1 g** and **2 g** in the scDSC analyses. Therefore, care should be taken if using cubane iodo-alcohol **1 g** and BCP iodo-alcohol **2 g**, especially if heating (the onset

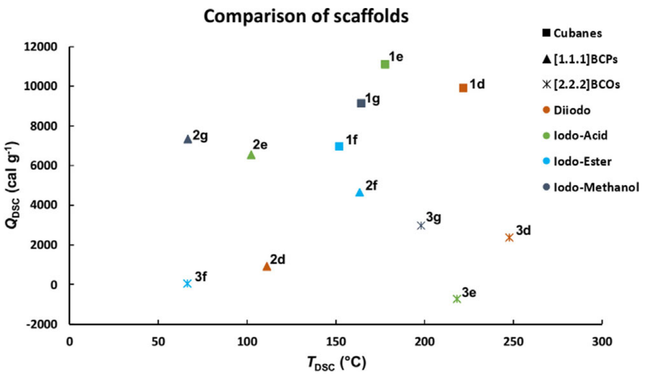


Figure 4. Comparison of iodinated scaffolds.

for **1 g** decomposition can be as low as 50 °C) or scaling up. Iodo substituents appear to increase sensitivity to impact, with 1,4-diiodocubane (**1 d**) being particularly sensitive.

In fact, a general warning about the use of iodocubanes and iodoBCPs is warranted.[23] Ester substituents appear to have a stabilizing effect against impact, with no ester derivatives showing go events in a hammer test. In general, cubanes displayed the largest exotherms in this study, and were the most sensitive to impact, followed by BCPs, and BCOs, although no BCO was observed to be sensitive to impact.

With the current high interest of synthetic chemists in rigid alkane scaffolds (e.g., new skeletons, methodology, drug and materials development),[5d,39] it is important to consider the safety aspects of handling and storing these sometimes high energy materials. Scale up and processing (e.g., ball milling) should be especially considered in the context of manufacturing. In concert with this advice, Yoshida calculations often struggle to accurately predict the sensitiveness of these systems, with most of the cages studied flagging well above the threshold for impact sensitivity, yet not displaying go events in a hammer test. Furthermore, as evidenced by conflicting reports in the literature, the sensitivity of any one compound can vary from batch to batch. Indeed, even well-known impact and thermally sensitive reagents such as IBX[26,40] are commonly used in laboratory settings quite often without incident.[41]

It is therefore our hope that this report will encourage chemists to be mindful of the potential risks associated with these kinetically stable yet highly strained scaffolds, and to carefully consider and investigate the safety profiles of such compounds at every stage of synthesis. With that said, however, our experience in the context of working with the cubane scaffold has revealed it to be generally robust and tolerant to a wide range of synthetic conditions.[4] Indeed, many cubanes and BCPs have been prepared without incident, and many are available commercially.

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Conflict of interest

C.M.W has a formal relationship with Boron Molecular Pty Ltd. A supplier of cubane products.

Keywords: bicyclo[1.1.1]pentane · bicyclo[2.2.2]octane · cubane · sensitiveness · Yoshida

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COMMUNICATION

Energetic Materials

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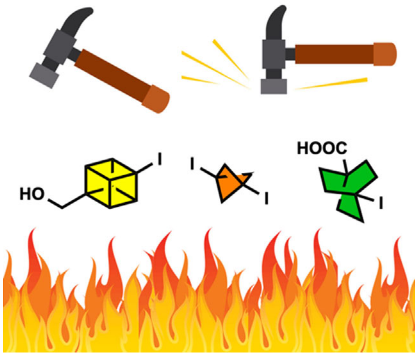
Cubane, Bicyclo[1.1.1]pentane and Bicyclo[2.2.2]octane: Impact and Thermal Sensitiveness of Carboxyl-, Hydroxymethyl- and Iodo-substituents



Fire and bicy: The thermal and impact sensitiveness of a series of carboxy-, hydroxymethyl-, and iodo-substituted cages were examined through sealed cell differential scanning calorimetry and hammer impact tests. The results reveal that these often-popular synthetic intermediates and functional groups can present some safety issues if not handled, stored, or used with care.