ABSTRACT

The cubane molecule, in which eight carbon atoms are locked in a cubic framework, shows great potential for both military and pharmaceutical applications. Octanitrocubane, with a predicted density of 2.1 g/cc and strain energy of more than 165 kcal/mol, is considered to be the "super-explosive", while cubane derivatives submitted to the National Institutes of Health for preliminary biological activity screening have displayed promising anti-cancer and anti-HIV activity.

DUAL-USE PROGRAM

With the end of the cold war and the subsequent scaling down of American munitions manufacture, a need arises for novel, effective and inexpensive civilian applications of explosives technology.

Should it be possible to convert final products or some of the intermediates to materials of commercial value, the payoff to the civilian economy could be substantial. At a time when the use of tax dollars for research is increasingly questioned, such a dual use of explosives technology would demonstrate the spillover benefits of defense research into entirely different areas of science.

The cubane molecule shows great potential for both military and pharmaceutical applications. The cubane skeleton, in which eight carbon atoms are locked in a cubic framework, has a density almost 50% greater than its isomers, such as cyclooctatetraene. Octanitrocubane, with a predicted density of 2.1 g/cc and strain energy of more than 165 kcal/mole is considered to be the "super-explosive".

![Octanitrocubane](https://ntrs.nasa.gov/search.jsp?R=19940025949 2020-01-24T15:58:07+00:00Z)

Despite intensive interest in cubanes as energetic materials, other applications of this fascinating molecule have not been explored thoroughly, mainly due to the unavailability of
simple methodologies for functionalizing the cubane skeleton. Recently, we have developed new methods for functionalizing the cubane skeleton photochemically, which have enabled us to synthesize a large class of cubane compounds with variety of functional groups.

Cubane carboxylic acids are now readily available from commercially available starting materials. Cubane 1,3,5,7-tetraacid is a potential precursor to tetranitrocubane, a very powerful and stable energetic material. Meanwhile, cubane 1,2,3,5-tetraacid which has similar structural feature as Kemp's triacid, has been targeted for molecular recognition studies in the area of bioorganic chemistry.

A number of functionalized cage compounds, notably adamantyl amides, amines and sugars have shown antiviral and antitumor activity. The value of the cage substituent seems to lie in its increasing the lipophilicity of the rest of the molecule, allowing easier transport across membranes. Encouraged by these observations, we submitted a number of cubane derivatives to the National Institutes of Health for preliminary biological-activity screening. Dipivalylcubane showed moderate anti-HIV activity without affecting healthy cells and one of the phenylcubanes displayed moderate anti-cancer activity.

Perhaps most significantly, none of the submitted cubanes showed any toxicity. This suggests that the cubane moiety is, at worst, innocuous in pharmaceutical applications, while a number of adamantane derivatives exhibited toxicity. In military applications a cubane-based explosive should not constitute a pollution hazard in itself since, unlike TNT or RDX, it should be non-toxic.
Intensive efforts have been directed at finding potential anti-AIDS drugs under the National Cancer Institute's *In Vitro* Anti-AIDS Drug Discovery Program. Inhibition of the HIV virus in AIDS patients is most commonly achieved through the administration of azidothymidine (AZT). Although short-term treatment of AIDS patients with AZT leads to clinical, virological and immunological improvement, the long term use of AZT is associated with severe toxicity, in particular bone marrow suppression. Immunologic deterioration continues as well, despite continued administration of AZT. The other drugs which have been approved for AIDS treatment, ddC (2',3'-dideoxycytidine) and ddI (2',3'-dideoxyinosine) also have limitations imposed by side effects of peripheral neuropathy and pancreatitis, respectively.

Further search for effective inhibitors of HIV variants has led to the discovery of various carbocyclic nucleosides which hold promise for the treatment of retrovirus infections. Representative carbocyclic derivatives that are active against HIV are cyclobut-A and cyclobut-G. It is believed that the structural features of cyclobutyl rings attached to adenine or guanine play an important role in their activity.

The cubane nucleus consists of six cyclobutyl rings packed in a very stable frame. The recent availability of cubane derivatives, as well as their stability and non-toxicity, suggest that their therapeutic activities should be studied in greater depth. In the context of anti-AIDS drugs, one might readily envisage the synthesis of a cubyl analogue of Cyclobut-A, such as "Cubyl-A".
Molecular modeling studies predicted that special *cis* arrangements of the neighboring hydrogen atoms on the cubane frame, when replaced by amino groups, would lead to an intriguing analogue of *cis*-platin, an active anticancer drug.

![Cis-Platin](image1.png)  

**Cis-Platin**

![Diaminocubane Complex](image2.png)  

**Diaminocubane Complex**

In our initial plan, a large number of cubane derivatives such as aminocubanes and di(hydroxymethyl)cubanes will be prepared. From these compounds, analogs of *cis*-platin and cyclobut-A and cyclobut-G will be synthesized and submitted for biological evaluation. Meanwhile, we will conduct modeling studies and seek the collaboration of experts in pharmaceutical research to help us identify potential targets.

Major accomplishments have already been achieved in cubane chemistry under the "More Powerful Explosives Program" funded by the U.S. Army. Under the current administration policy of dual technology, redirection of the cubane program toward civilian use will be most rewarding.