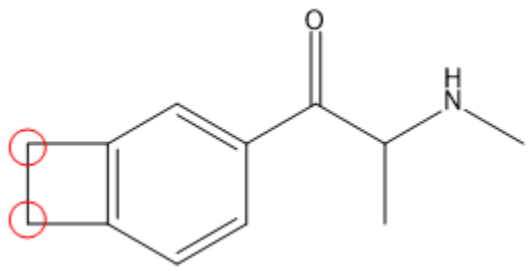
Computational Analysis of a Novel Cathinone Analog

Preface and Introduction

This analysis was done "back of the envelope" style. In other words, as far as properly conducted studies go, this analysis is full of flaws, and not worthy of being cited as real data. The purpose of this is to get an idea of how the structural differences between 3-methylmethcathinone (3-mmc) and the novel cathinone 1-(bicyclo[4.2.0]octa-1(6),2,4-trien-3-yl)-2-(methylamino)propan-1-one (hereafter referred to as 3,4-boxmmc for simplicity) offer credence to the theory that the novel cathinone may act as a prodrug for other known cathinone analogs.

Hypothesis and Background Theory

The angle of the bond between the highlighted carbon atoms below is forced to be around 90 degrees (Gaussain calculated an optimized angle of 93.43 degrees). Carbon, when sp^3 hybridized, has bond angles of 109.5 degrees. The significant reduction in bond angles observed in 3,4-boxmmc suggests the bond in question is not as stable as other bonds in the molecule, indicating that it is potentially more susceptible to being broken (by some undetermined mechanism) when introduced into the human body. If this is the case, the novel cathinone analog would most likely act as a prodrug to several other cathinone analogs, the most probable of which being 3,4-dimethylmethcathinone if the bond in question is broken. It is worth noting that the bonds to the benzene ring would also be susceptible to breakage, leading to a variety of other similar cathinone analogs such as 3-ethylmethcathinone or 4-ethylmethcathinone.



Methods

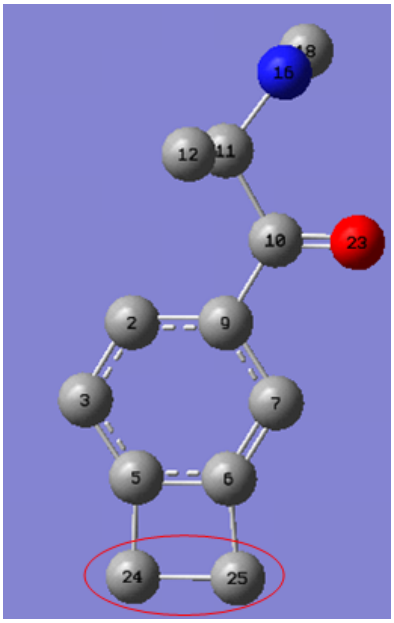
The Gaussian 03W suite of programs was used for computational analysis. Avogadro was used to quickly build non-geometrically optimized Z-matrices. The "back-of-the-envelope" nature of this analysis is evident in the process-flow, and it went as follows: construct the molecule of interest in Avogadro, run the auto geometry optimization function within the program several times until the structure is nearly unchanged, extract the Z-matrix, optimize the geometry again in Gaussian, then use the optimized parameters in a Gaussian NBO calculation. The NBO summary at the bottom of the output file gives energy of the bonding orbital formed by the C-C bond of interest (as well as all the other orbitals in the molecule) in units of a.u. The units were somewhat ambiguous (at least to me), but what little information that exists online suggests the conversion is 1 a.u = 672.5 kcal/mol.

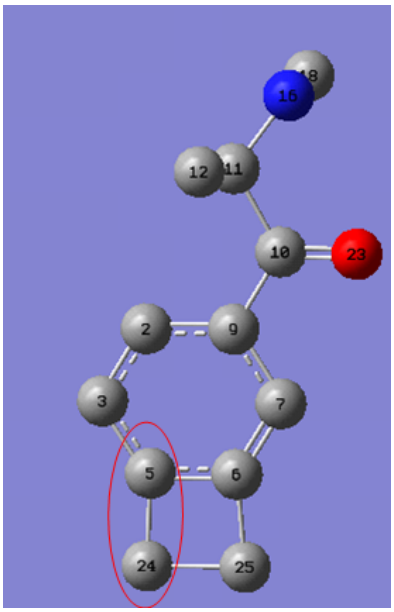
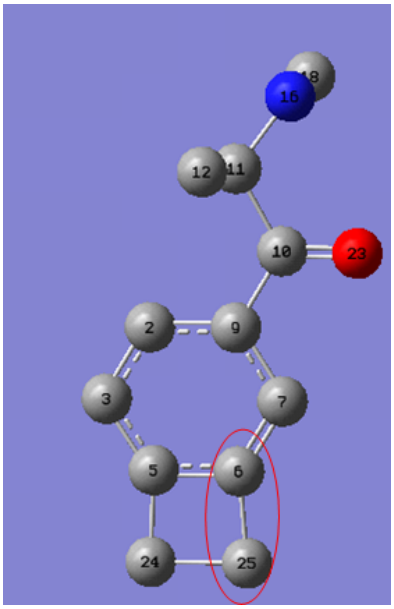
Some notable corner-cutting: the overall geometry optimized for 3,4-boxmmc in Avogadro is not planar whatsoever. The benzene ring and the area of interest remains planar, and Gaussian did not complain so the effect this has on overall results should be negligible.

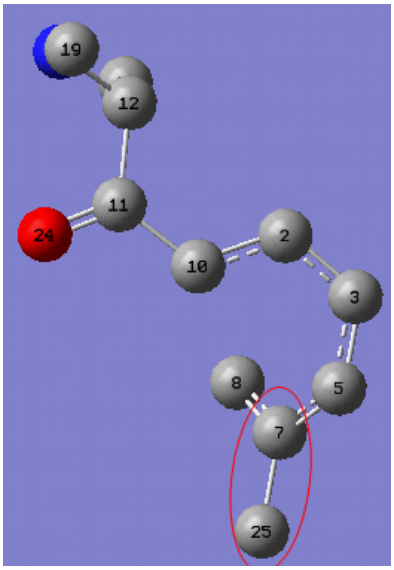
The Gaussian-optimized geometry for 3-mmc yielded some interesting bends in the benzene ring (though it is properly planar), which may have a more notable impact on final results, but alas, this isn't being graded so such is life.

Results

As expected, the bond orbitals in the box structure of the novel analog have a notably lower energy than that of the 3-methyl bond orbital in 3-mmc. The outermost bond between carbon 24 and 25 has a significantly lower energy than that of the carbon 24 and 5 bond, and carbon 25 and 6 bond. The data are summarized in the table below with visual aids.

Molecule	Energy (a.u)	Carbons Involved
3,4-boxmmc	-0.53882	

3,4-boxmmc	-0.59009	
3,4-boxmmc	-0.58571	

3-mmc	-0.63156	 *Carbon 8 should be in the plane of the benzene ring, and have a bond between it and carbon 10. This is the issue discussed at the end of the Methods section.

Conclusions

All evidence collected supports the hypothesis. It is interesting to note the difference in energy (which can basically be thought of as bond strength) between the outermost 3,4-boxmmc C-C bond (between carbons 24 and 25) and the other two bonds to the benzene ring. To me, this would indicate the most likely scenario, if this novel cathinone analog is a prodrug, is that the C24-C25 bond would be the first to break, producing 3,4-dmmc. Though the other bonds are still weaker than that of the 3-methyl C-C bond in 3-mmc, I would bet 3,4-dmmc is the major product of any prodrug reaction and the ethylmethcathinones discussed in the Hypothesis and Background Theory section would be minor products and occur infrequently.

It is worth noting that although there is a significant difference in the C24-C25 bond strength when compared to 3-mmc's 3-methyl bond, it is not so astronomically low as to break spontaneously. It is possible that this novel cathinone analog is stable enough to persist in the human body as a new psychoactive substance on its own.

Link to supporting information: https://github.com/bigmacked4/Novel-Cathinone-Analog-Analysis.git

Includes: Avogadro files, unoptimized z-matrices, optimized z-matrices for NBO calculations, and all output files. (use any text editor to read .gjf and .out files. You will need to install Avogadro to view the .cml files)