

Impact of Stereo- and Regiochemistry on Energetic Materials

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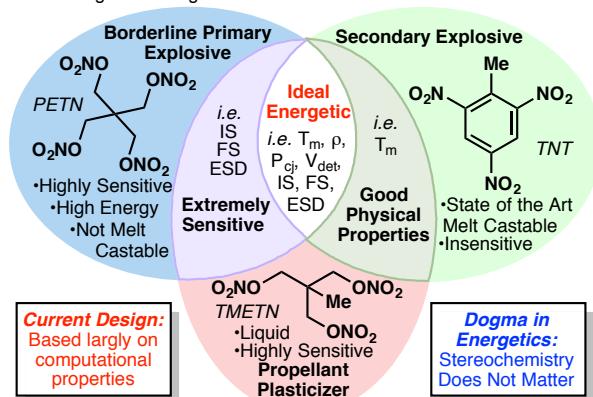
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Supporting Information Placeholder

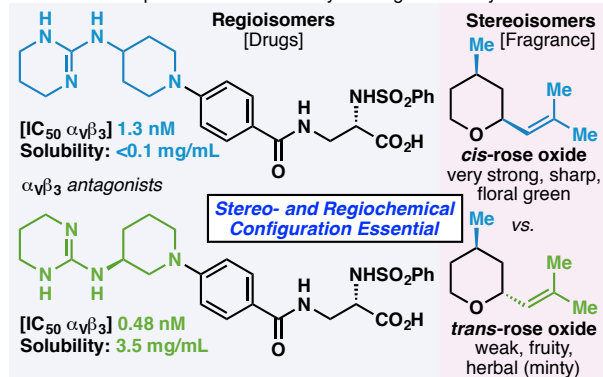
ABSTRACT: The synthesis, physical properties and calculated performances of six stereo- and regioisomeric cyclobutane nitric ester materials is described. While the calculated performances of these isomers, as expected, were similar, their physical properties were found to be extremely different. By altering the stereo- and regiochemistry, complete tunability in the form of low- or high-melting solids, standalone melt-castable explosives, melt-castable explosive eutectic compounds, and liquid propellant materials were obtained. This study demonstrates that theoretical calculations should not be the main factor in driving the design and synthesis of new materials, and that stereo- and regiochemistry offer a new dimension to consider when designing compounds of potential relevance to energetic formulators.

In pursuit of designing high-performing energetic materials,¹ the main criteria today is largely based on theoretically predicted performance properties.² While a given material's synthetic accessibility and the oxygen balance are factors in the design of new energetic materials, molecules in the energetics field have historically been prepared based largely on what a computer calculates with respect to their properties (density, heat of formation (ΔH), detonation pressure (P_{cj}), detonation velocity (V_{det}), and specific impulse (I_{sp})). Designing molecules based on these aforementioned calculated characteristics has largely formed the basis of energetic materials synthesis for the past several decades. Hence, many nitrated derivatives based on various nitrogen- and oxygen-rich heterocyclic systems, such as the furoxan,³ furazan,⁴ tetrazine,⁵ tetrazine-di-N-oxide,⁶ pentazole,⁷ tetrazole,⁸ triazole,⁹ and 1,2,4-oxadiazole,¹⁰ just to name a few, have been synthesized to-date. Unfortunately, while many of these legacy materials are high-performing based on computational calculations, they are plagued by issues such as very high sensitivity, thermal instability, moisture sensitivity, and in the case of nitrogen-rich energetic salts, an incompatibility with many common ingredients encountered in an explosive or propellant formulation mixture. For this reason, in the modern era of energetics research, classic energetics such as the highly sensitive borderline primary explosive pentaerythritol tetranitrate (PETN), the current state-of-the-art melt-castable

a Challenges in Energetics



b Functional impact of stereochemistry and regiochemistry



c Cyclobutane-based energetics as a probe

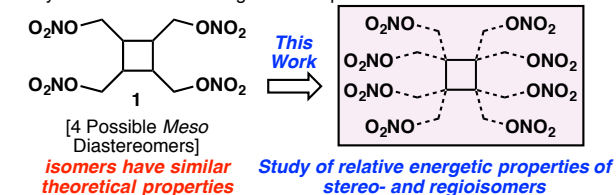


Figure 1. (A) An overview of challenges and variables in the design of modern energetics; (b) Canonical impacts of stereo- and regiochemistry in medicine and fragrances; (c) the design of a platform to interrogate stereo- and regiochemistry in energetics.

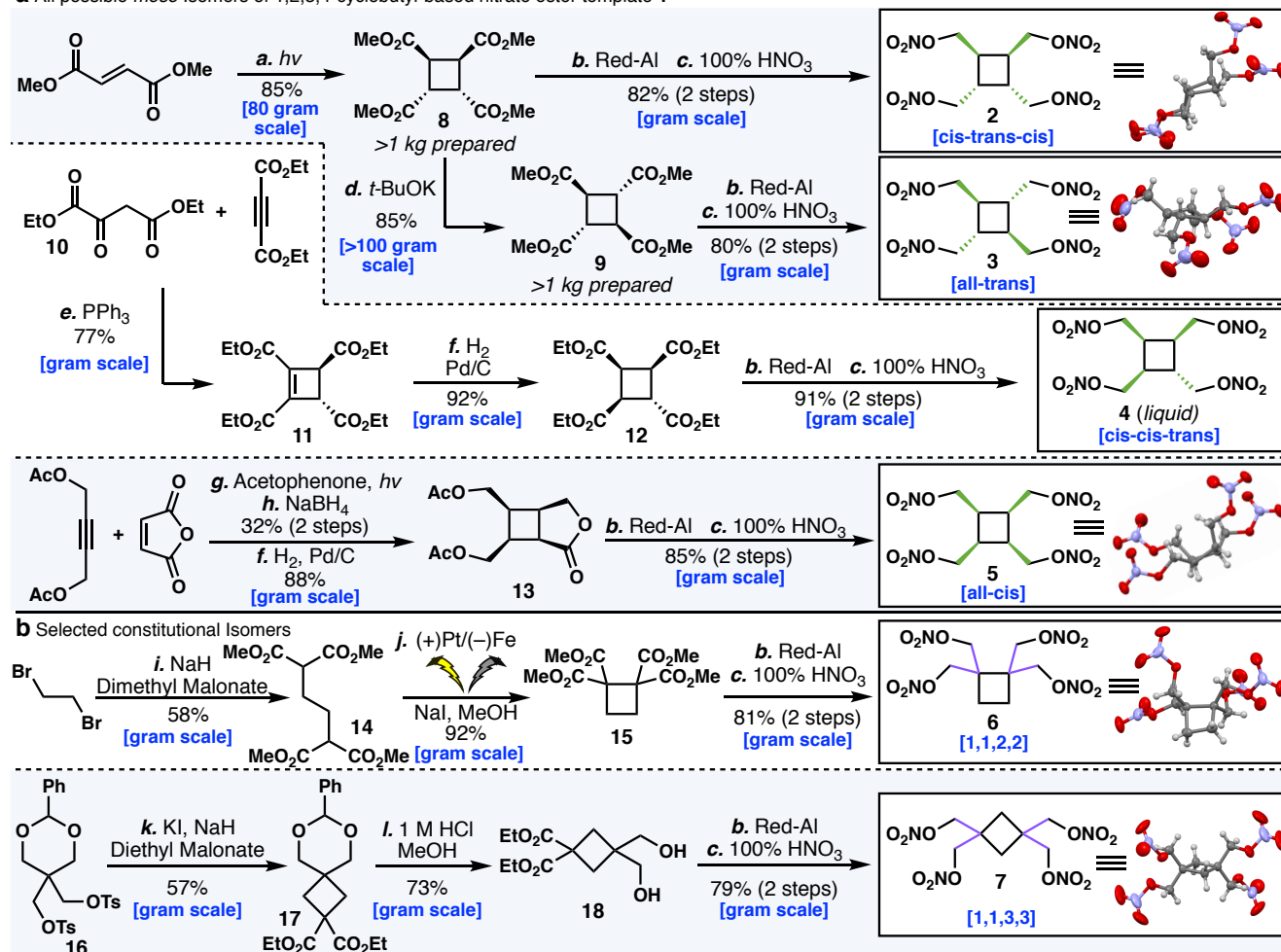
explosive trinitrotoluene (TNT), and the sensitive liquid plasticizer trimethylolethane trinitrate (TMETN) still find common use in explosive and propellant formulations (Figure 1A). In this Communication a long-overlooked strategy for the design of highly useful energetic materials is presented in an effort to develop highly energetic melt-castable and propellant plasticizing materials. In designing energetic materials of potential relevance, exploration of a class of materials based on systematic stereo- and regiochemical permutations is, to the best of our knowledge, without precedent. This has largely stemmed from the perception that stereo- or regioisomers of a given CHNO molecule are not advantageous to pursue since the predicted performance properties between the isomers will be minimal. Yet the critical role of stereo- and regiochemistry is documented in nearly all other areas of the chemical enterprise.¹¹ For example, as shown in Figure 1B, regioisomers can exhibit drastically different physical properties (such as $\alpha_V\beta_3$ antagonists) and when recognition events take place with

chiral receptors, the stereochemistry or shape of a small-molecule binder matters (such as rose-oxide).¹²⁻¹³

Herein, the long-held assumption that stereochemistry and regiochemistry are of little influence in the energetics field is challenged with a systematic analysis of a set of constitutionally isomeric cyclobutane-based nitric esters, differing only in stereo- and regiochemistry (Figure 1C). Despite having similar theoretical performance properties, this set of isomeric strained molecules exhibits remarkable differences in physical properties, tunable by virtue of these simple stereochemical and regiochemical changes. Such control is sure to garner the interests of the melt-castable explosives and propellants community.

Azetidines and cyclobutane moieties are known to tolerate various nitration conditions. Due to their ring strain, which provides further increases in performance by raising the heat of formation of the system, nitro group-bearing materials

a All possible *meso* Isomers of 1,2,3,4-cyclobutyl-based nitrate ester template 1



Scheme 1. *Reagents and Conditions: (a) *hν*, H₂O, rt. (b) 60% Red-Al (5 equiv.), Toluene, 0 to 80 °C, 16 h. (c) 100% HNO₃, 0 °C to rt (d) *t*-BuOK (0.3 equiv.), MeOH, 80 °C, 24 h. (e) 10 (1 equiv.), Diethyl acetylenedicarboxylate (1 equiv.), PPh₃ (1 equiv.), DCM, -15 °C to rt, 48 h. (f) Pd/C (5 mol%), H₂, EtOAc, rt, overnight. (g) Maleic anhydride (1 equiv.), 2-butyne-1,4-diol diacetate (1.2 equiv.), acetophenone (0.2 equiv.), *hν*, MeCN, rt, 9 days. (h) NaBH₄ (1.03 equiv.), THF, -65 °C to rt. (i) Dibromoethane (1 equiv.), Dimethyl malonate (5 equiv.), NaH (4 equiv.), DMF, 80 °C, 24 h. (j) NaI (0.67 equiv.), MeOH, Pt anode, Fe cathode, 100 mA, 6 F/mol. (k) Diethyl malonate (2.04 equiv.), NaH (2 equiv.), KI (0.1 equiv.), DMF, 70 to 140 °C, overnight. (l) 1 M HCl/MeOH (1:6), overnight.

containing these cores have been designed in the past. Two of the most energetic materials containing these strained rings are 1,1,3,3-tetranitro cyclobutane (TNCB)¹⁴ and the melt-castable explosive trinitroazetidine (TNAZ).¹⁵ TNCB was calculated to possess an explosive power in excess of HMX, but unfortunately decomposes significantly at 165 °C, and is hence of little practical value. Like TNCB, TNAZ was also calculated to possess an explosive performance in excess of HMX, possessing a melting point of 101-103 °C and a decomposition temperature of 216 °C. Materials that melt between 80-125 °C, while exhibiting a minimum temperature difference of 75 °C between the melting and decomposition temperatures are classified as potential melt-castable explosive materials. Despite successful efforts to scale TNAZ,¹⁶ its vapor pressure in the molten state was found to be significantly higher than that of the benchmark melt-castable explosive TNT, thus presenting a significant safety and processing hazard. The very high vapor pressure of TNAZ all but ended its potential applications as a melt-castable explosive material. It was noticed in searching the literature that tetra-(nitroxymethyl) cyclobutane, nor any of its isomers, had been made and thus the physical and energetic properties stemming from their stereo- and regiochemistries had not been studied. As a result, the tetrasubstituted cyclobutane nitric ester scaffold **1** was chosen based on its nitrated structure and its ring strain, coupled with its ability to introduce stereo- and regiochemistry into the structure.

Scheme 1A outlines the scalable synthesis of all four possible *meso* stereochemical isomers of compound **1** (**2-5**), as well as two constitutional isomers (**6-7**). To begin, both compounds **2** and **3** can be accessed by the photochemical dimerization of dimethyl fumarate,¹⁷ a widely available building block. This yields the head-to-head dimer **8**, in which the ester substituents around the central cyclobutane ring have a *cis-trans-cis* relationship to one another (prepared in >1 Kg quantities). Direct reduction of **8** gave the tetraol, which was immediately subjected to nitration to provide **2** (structure confirmed by X-ray crystallography). Conversely, **8** could be epimerized under basic conditions¹⁸ to afford its all-*trans* stereoisomer **9** (prepared in >1 Kg quantities). A similar sequence of reduction and nitration furnished the all-*trans* nitric ester **3** (structure confirmed by X-ray crystallography).

To obtain the *cis-cis-trans meso* stereoisomer, Claisen adduct **10**,¹⁹ was employed in a 1,4-addition/intramolecular Wittig cyclization²⁰ cascade to afford **11** as the sole diastereomer. Hydrogenation of the cyclobutene set the remaining two stereocenters, which after reduction and nitration yielded *cis-cis-trans* nitric ester **4**.

Synthesis of the all-*cis* stereoisomer **5** proved to be more challenging as the route needed to be both highly scalable and stereoselective for our purposes. Previous reports for the synthesis of the all-*cis* stereoisomer of **1** commenced from acenaphthylene²¹ (6% overall yield), cyclooctatetraene²² (5% overall yield), or 2(5H)-furanone²³ (3% overall yield, solid-state dimerization at -78 °C). It was reasoned that intercepting a cyclic intermediate of different oxidation state may eliminate some of the pitfalls that plagued previous syntheses. After much experimentation, acetate-protected 2-butyne-1,4-diol and maleic anhydride were found to undergo [2+2] cycloaddition. Direct reduction of the crude anhydride to the corresponding

cyclobutene-lactone to aid in isolation (the mass balance corresponds to maleic anhydride dimerization) and hydrogenation gave the all-*cis* product **13** as the sole diastereomer (convex approach of H₂). This sequence proved to be easily scalable due to the inexpensive nature of the starting materials. Lactone **13** was then directly subjected to reduction and exhaustive nitration to give the final *meso* stereoisomer **5** (structure confirmed by X-ray crystallography).

Two constitutional isomers of **1** were also targeted as a control to gauge the influence of regiochemistry on the physical and energetic properties within the same cyclobutane series (Scheme 1B). To that end, dimethyl malonate was alkylated with dibromoethane to give **14**, in which the major byproduct of this reaction arose from the intermediate mono-addition adduct intramolecularly cyclizing to give 1,1-diester cyclopropane. At this point, all initial attempts to cyclize **14** under reported bromination/thermal cyclization conditions²⁴ proved entirely irreproducible in our hands. Therefore, we instead turned to electrochemical methods. Gratifyingly, we found that a slight modification to the procedure reported by Elinson *et al.*²⁵ cleanly gave the desired **15** in excellent yield under anodic conditions in an undivided cell with a commercial potentiostat (see SI). Two additional steps then gave access to the 1,1,2,2-tetrasubstituted nitric ester **6**. Finally, the 1,1,3,3 constitutional isomer **7** could be accessed via the known compound **16**²⁶ after alkylation, acetonide deprotection, reduction of the diester, and nitration.

With multigram quantities of cyclobutane isomers **2-7** in hand, each isomer's physical properties and sensitivities to impact, friction and electrostatic discharge was determined. These values, along with the theoretical energetic properties, are given in Table 1. As expected, based off of the experimentally derived densities the calculated detonation velocities, detonation pressures, heats of formation and specific impulses of isomers **2-7** were in close agreement with one another. It is for exactly this reason that the pursuit of stereo- and regioisomeric structures in designing energetic materials has historically been dismissed. An examination of the physical properties of these isomers, however, tells a much different story. While melt-castable explosive candidates typically need to exhibit a minimum temperature difference of 75 °C between melting and decomposition temperatures and melt between 80-125 °C, the all-*trans* cyclobutane isomer **3** is a low-melting energetic solid. Thus, its 47.5 °C melting point is too low to be considered a melt-castable explosive. On the other hand, the all-*cis* and *cis-trans-cis* cyclobutane isomers **5** and **2** both possess melting and decomposition temperatures that allow them to find potential use in melt-castable explosive eutectic formulations. While **5** and **2** possess melting points slightly above 100 °C, these materials can be formulated with other high-energy energetic compounds to form a melting point between 80-95 °C. This melting point range is ideal for melt-castable explosive operations because it allows for steam heating to be employed at ambient pressure during a casting operation, thus reducing operating costs. In examining the cyclobutane regioisomers, 1,1,3,3-tetra-(nitroxymethyl) cyclobutane **7** possesses too high of a melting point to be of practical value in the melt-castable explosive arena. However, the 1,1,2,2-regioisomeric derivative **6** exhibits a melting point that fits well in the standalone melt-castable range. Like TNT, **6** does not need to

Table 1. Physical properties, sensitivities and theoretical performance of isomers 2-7, TNT and TMETN.

[Blue] = Desirable Melt Castable Properties [Purple] = Desirable Propellant Properties [Red] = Undesirable Properties

Data category	TNT	TMETN	2	3	4	5	6	7
T_m [°C] ^[a]	80.4	-3	106.0	47.5	<-40	100.8	85.9	146.9
T_{dec} [°C] ^[b]	295.0	182.0	198.5	199.7	186.8	194.3	192.8	196.2
Ω_{CO_2} [%] ^[c]	-74	-34.5	-44.9	-44.9	-44.9	-44.9	-44.9	-44.9
Ω_{CO} [%] ^[d]	-24.7	-3.1	-9.0	-9.0	-9.0	-9.0	-9.0	-9.0
ρ [gcm ⁻³] ^[e]	1.65	1.47	1.64	1.605	1.543	1.66	1.683	1.651
P_{cj} [GPa] ^[f]	19.3	23.7	24.5	22.9	24.5	24.5	24.6	24.4
V_{det} [ms ⁻¹] ^[g]	6950	7050	7438	7544	7577	7504	7604	7472
I_{sp} [s] ^[h]	-	247.0	240.5	238.7	240.4	242.5	243.6	240.6
$\Delta_f H^\circ$ [kJ mol ⁻¹] ^[i]	-59.3	-425.0	-510.1	-535.9	-512.0	-480.8	-465.5	-509.2
IS ^[j] [J]	15	0.20 ²⁷	6.2	6.2	9.0	6.2	4.7	6.2
FS ^[k] [N]	240	-	240	240	>360	240	>360	>360
ESD ^[l] [J]	0.25	-	0.125	0.125	0.125	0.125	>0.25	>0.25

[a] T_m = onset temperature of melting; [b] T_{dec} = onset temperature of decomposition; [c] Ω_{CO_2} = CO₂ oxygen balance; [d] Ω_{CO} = CO oxygen balance; [e] ρ = derived density from X-ray data; [f] P_{cj} = detonation pressure; [g] V_{det} = detonation velocity; [h] I_{sp} = specific impulse; [i] $\Delta_f H^\circ$ = molar enthalpy of formation; [j] IS = impact sensitivity; [k] FS = friction sensitivity; [l] ESD = electrostatic discharge sensitivity

be mixed with anything in order to further depress the melting point for casting operations to occur. It is worth noting that melt-castable candidates **2**, **5** and **6** possess detonation pressures that are ca. 25% more powerful than TNT, and thus exceed the explosive power of the state-of-the-art melt-castable ingredient by a wide margin.

Furthermore, **2**, **5** and **6** possess equivalent or lower friction sensitivities than TNT. Although these three tetranitric ester materials have higher impact sensitivities than TNT, **6** is still less sensitive to impact than the commonly manufactured PETN (3 J), while **2** and **5** possess identical impact sensitivities to the ubiquitous explosive RDX (6.2 J). The 0.125 J electrostatic discharge sensitivity of **2**, **5** and **6** is also equal to that of RDX. Thus, possessing sensitivities that are equal to or lower than commonly handled explosive materials demonstrates that these melt-castable tetranitric ester candidates are safe to handle.

Surprisingly, cis-cis-trans isomer **4** is distinct from the other cyclobutane tetranitric ester isomers in that it is a liquid, and can thus be classified as a potential energetic plasticizer ingredient for potential use in propellant formulations. As presented in Table 1, **4** was found to possess a significantly lower sensitivity to impact, yet possesses a higher density than the propellant plasticizer TMETN.²⁷ Although TMETN possesses a slightly higher specific impulse compared to **4**, it has a relatively high freezing point of -3 °C. Strikingly **4**, which differs from **2** (m.p. 106 °C) by a single stereocenter, did not freeze even at -40 °C. The low freezing point of **4** offers significant potential benefits with regard to propellant formulation capabilities, such as forming high-energy freezing point eutectic materials that are not currently possible with TMETN. It thus appears that by taking advantage of the stereo- and regiochemistry of a given CHNO molecule, it is possible to develop an entirely tunable energetic system that can potentially

serve energetics formulators in both the explosives and propellants field.

In summary, it has been demonstrated that stereochemistry and regiochemistry should play a significant role in the design of new energetic materials, and should not be dismissed on theoretical grounds. Depending on the stereochemistry and regiochemistry employed, tunable molecules were designed that gave rise to low-melting solids, standalone melt-castable explosives, melt-castable explosive eutectic compounds, high-melting solid materials, and extreme low-melting liquid materials. Such tunability has the potential to cater to both the explosives and propellants community. Yet had the stereo- and regiochemistries of cyclobutane isomers **2-7** not been explored to the fullest extent, their potential uses would have remained hidden, and likely dismissed on the grounds that they possessed similar calculated performance values. The physical properties exhibited across isomers **2-7** serves as a lesson that stereochemistry and regiochemistry in the pursuit of new energetic materials should not be ignored. It is hoped that other isomeric systems can be designed in the future, and that the energetic materials community will embrace the field of stereoisomerism much like many other chemical enterprises have already done.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Detailed experimental procedures and analytical data (PDF)

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NOTES

The authors declare no competing financial interest.

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