

Two Isostructural Explosive Cocrystals with Significantly Different Thermodynamic Stabilities**

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Cocrystallization is currently having a tremendous impact on pharmaceuticals^[1] and energetic materials (energetics)^[2] and is poised to make a significant mark on other fields such as non-linear optics,^[3] ferroelectrics,^[4] and organic electronics.^[5] In the energetics field the ability of cocrystallization to combine two known explosive compounds into a novel material with distinct properties presents an elegant means of generating improved explosives from existing compounds, and several such cocrystals have recently been reported.^[6] Unfortunately, with the chemistries of energetic compounds being defined primarily by weakly interacting nitro groups, energetic cocrystals have proven difficult to design; this contrasts with their hydrogen-bonded counterparts in the pharmaceutical cocrystal field. As such, many reported energetic cocrystals were discovered through screening different stoichiometries of existing compounds. Needed in the field are reliable design strategies for generating novel energetic–energetic cocrystals.

One supramolecular synthon that has proven reliable in previous energetic cocrystal work involves interactions of the electron-deficient aromatic ring common to energetic compounds such as 2,4,6-trinitrotoluene (TNT) and 1,3,5-triamino-2,4,6-trinitrobenzene (TATB). Such molecules have been observed to π -stack with the electron-rich rings of many aromatic compounds such as naphthalenes, anthracenes, and perylene.^[2a] Unfortunately, electron-rich rings are rare among energetic compounds, which often feature significant electron-withdrawing nitro substitution. Thus, in order for this synthon to be used to design energetic–energetic cocrystals, an electron-rich energetic compound with favorable geometry for interacting with electron-deficient rings must be found.

Diacetone diperoxide (DADP) is a member of the acetone peroxide family of energetic compounds and features a conformation and electrostatic potential that make it ideal for cocrystallizing with electron-deficient aromatic compounds (Figure 1a). Acetone peroxides are the cyclic products of the acid-catalyzed nucleophilic addition of hydrogen peroxide to acetone. The dimer product, DADP, and the

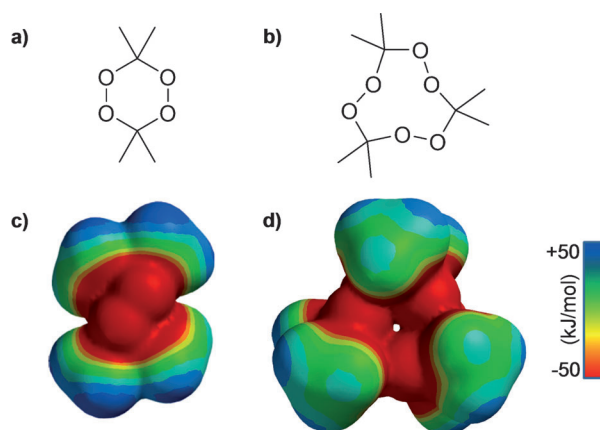


Figure 1. Chemical structures of a) diacetone diperoxide (DADP) and b) triacetone triperoxide (TATP). Electrostatic potential maps of c) DADP and d) TATP by AM1 semi-empirical calculation.

trimer product, triacetone triperoxide (TATP, Figure 1b), are the two most common of these compounds, and their formation can be dictated by the strength of the acid used in the reaction.^[7] Though TATP is the more common of the two, DADP has an important feature that makes it more useful for energetic cocrystal design: the peroxide oxygen atoms of DADP are accessible (Figure 1c) while those of TATP are largely shielded by methyl groups (Figure 1d). Thus, DADP is better positioned to interact with electro-positive moieties in the solid state. With this in mind, DADP was expected to cocrystallize with some common energetic compounds that feature electron-deficient nitro-substituted rings such as TNT, TATB, and the TATB precursor 1,3,5-trichloro-2,4,6-trinitrobenzene (TCTNB, Figure 2).^[8] The last of those compounds also features halogens, which make it especially well-suited for cocrystallization as halogens are reported to participate with nitro groups in supramolecular synthons.^[9] Noting these potential interactions, DADP and

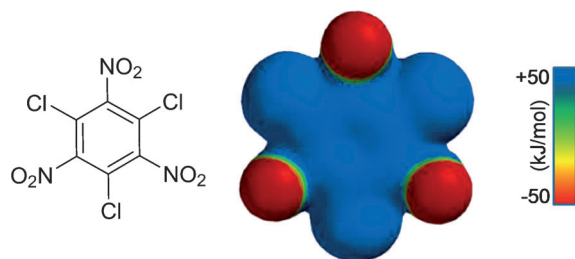


Figure 2. Chemical structure of 1,3,5-trichloro-2,4,6-trinitrobenzene (TCTNB) and its electrostatic potential map.

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[**] This work was supported by the Defense Threat Reduction Agency (HDTRA1-09-1-0033). We acknowledge funding from NSF Grant CHE-0840456 for the Rigaku AFC10K Saturn 944 + CCD-based X-ray diffractometer.



Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.201302814>.

TCTNB were combined and, indeed, a 1:1 DADP/TCTNB cocrystal (DADP/TCTNB) was synthesized (see Supporting Information).

DADP/TCTNB forms readily as colorless prisms that are easily isolated for characterization by single-crystal X-ray diffraction.^[10] The cocrystal structure features the expected interaction between the peroxide oxygen atoms of DADP and the electron-deficient ring of TCTNB (Figure 3a). These

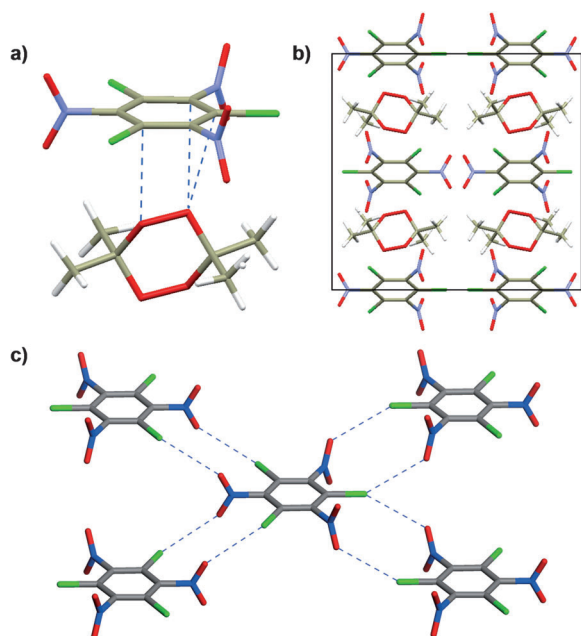


Figure 3. The DADP/TCTNB cocrystal. a) Peroxide-ring interactions. b) Unit cell viewing down the *c*-axis. c) Infinitely propagating chlorine–nitro interactions in DADP/TCTNB.

interactions generate alternating stacks of TCTNB and DADP (Figure 3b). In addition, the DADP/TCTNB cocrystal exhibits intermolecular chlorine–nitro interactions that propagate through the cocrystal structure to form infinite sheets of TCTNB (Figure 3c). These sheets constitute layers that stack with layers of DADP through the aforementioned ring–peroxide interaction. Similar chlorine–nitro interactions of the same length, 3.2 Å, exist in the crystal structure of pure TCTNB;^[11] however, unlike in the cocrystal, those form between dimers and do not propagate throughout the crystal.

Following the success of the DADP/TCTNB cocrystal design, we attempted cocrystallizing DADP with the brominated analogue of TCTNB, 1,3,5-tribromo-2,4,6-trinitrobenzene (TBTNB, Figure 4a). Our hypothesis was that the brominated compound would bring enhanced density and improved oxygen balance without disrupting the peroxide–ring interaction principle. TBTNB was synthesized by reported methods^[8] and co-dissolved at a 1:1 ratio with DADP in acetonitrile. As the acetonitrile evaporated the DADP/TBTNB cocrystal emerged as colorless needles, but in extremely low yield and amidst the concomitant growth of much pure DADP and TBTNB.

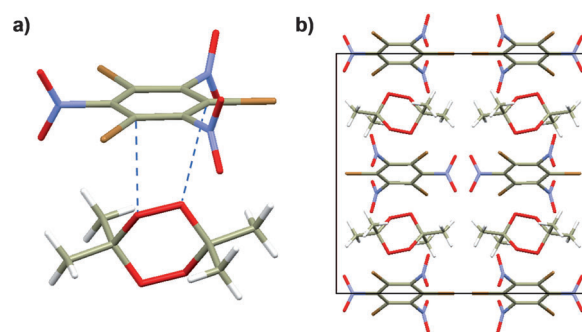


Figure 4. The DADP/TBTNB cocrystal. a) Peroxide-ring interactions. b) Unit cell viewing down the *c*-axis. This cocrystal is isostructural with DADP/TCTNB.

A single needle of DADP/TBTNB was carefully collected from the original batch and characterized by single-crystal X-ray diffraction.^[12] The crystal structure of DADP/TBTNB is isostructural with that of DADP/TCTNB and exhibits identical solid-state interactions: short contact between the peroxide oxygen atoms of DADP and the TBTNB π -ring with halogen–nitro interactions that form infinite sheets of TBTNB alternating with sheets of DADP (Figure 4b). Furthermore, the unit cell of DADP/TBTNB is nearly identical to that of DADP/TCTNB with lengths and angles that are within 0.2 Å and 1.07° of each other. With the unit cells and stoichiometries being essentially identical, the density and oxygen balance are, as expected by design, both higher for DADP/TBTNB relative to DADP/TCTNB: 1.94 g cm⁻³ vs. 1.55 g cm⁻³ and –49.5% vs. –63.7%, respectively.

In attempts to scale up the cocrystal for further analysis, it was observed that DADP/TBTNB did not form as easily as DADP/TCTNB, despite the structural similarities of the two cocrystals. Furthermore, DADP/TBTNB failed to form reliably via many commonly employed crystallization methods, such as solvent-mediated transformation (slurries). Even when seeded, slurries failed to produce the cocrystal and seeds were seen to completely disappear, even in the presence of solutions saturated with DADP and TBTNB. Though incongruently saturating systems can complicate the behavior of cocrystals in slurry,^[13] the behavior of DADP/TBTNB is distinct in that the cocrystal disappeared completely in the slurry and both pure components emerged; this indicates that there is no region of cocrystal stability on the DADP–solvent–TBTNB phase diagram at room temperature.^[14] The most reliable and efficient method of producing this cocrystal was found to be rapidly cooling solutions supersaturated with both DADP and TBTNB in a mutually poor solvent, such as cyclohexane. If removed and stored properly these cocrystals were stable indefinitely; however, if left in the mother liquor for over 1 h (in the case of cyclohexane), it was observed that the cocrystal disappeared while solid DADP and TBTNB remained. These difficulties in scale-up and the unusual behavior of this cocrystal suggested the possibility that the DADP/TBTNB cocrystal exists in an unfavorable equilibrium with its pure components.

Kinetic forms are a well-known phenomenon in single-component crystals but the possibility of kinetic forms has not been sufficiently explored for multi-component systems such as cocrystals. In cases where one crystal structure of a compound is metastable relative to another, the former is referred to as a kinetic form; thermodynamically less favored than other forms but nevertheless metastable on its own and potentially desirable for application. The same situation can exist for cocrystals, though the relationship among forms is more complex because there are more compounds, and thus more possible solid forms to consider. To our knowledge no cocrystal has been reported previously that is unstable relative to the pure solid forms of its components.^[15]

The behavior of DADP/TBTNB demonstrates it to be unstable relative to its pure components under equilibrium conditions at room temperature. DADP, TBTNB, and seeds of DADP/TBTNB were each added to vials and sealed beneath solutions co-saturated with both DADP and TBTNB in various solvents (see Supporting Information). This method is commonly used not only in establishing relative thermodynamic stabilities of solid forms^[16] but also for discovering cocrystals.^[17] In all cases the seeds dissolved, usually in seconds, while the pure solids remained, indicating that the cocrystal is more soluble than the pure forms. From these results, the DADP/TBTNB cocrystal was shown to be less thermodynamically stable than saturated solutions of DADP and TBTNB at room temperature, thus validating our hypothesis that DADP/TBTNB is thermodynamically unstable relative to its pure components. Though establishing definitions is admittedly challenging in this field, we propose that such a condition be termed a schizophylic^[18] cocrystal: a cocrystal that is unstable relative to the pure forms of its constituents.

Polymorphs are known to exhibit either monotropic or enantiotropic behavior, depending on how their relative thermodynamic stabilities vary as a function of temperature. While these relationships may not be directly appropriate to the cocrystal systems here, the possibility of analogous temperature-dependent stability changes were considered. Experiments aimed at growing DADP/TBTNB at different temperatures were conducted to assess whether a similar relationship exists between the cocrystal and its pure components. DADP, TBTNB, and DADP/TBTNB were combined and slurried at various temperatures in solutions co-saturated with both DADP and TBTNB. For samples held at temperatures between 4 and 40 °C, no transformation to the cocrystal was observed and cocrystal seeds disappeared. However, at temperatures between 40 and 60 °C the cocrystal was seen to persist and grow, indicating that there is a crossing point in the Gibbs free energy of these solid forms within this temperature range and that the cocrystal exhibits a relationship with its pure components that is analogous to an enantiotropic relationship between polymorphs.

The existence of the DADP/TBTNB as a schizophylic cocrystal holds significant importance for the cocrystal field, especially with regards to cocrystal discovery. Traditional cocrystal discovery methods assume that the cocrystal is the thermodynamic product and these would not have revealed DADP/TBTNB. Thus, had it not been for the existence of the

DADP/TCTNB cocrystal and the demonstrated success of the peroxide-ring interaction used to design it, it is unlikely that DADP/TBTNB would have ever been prepared. This brings to light the fact that kinetic growth methods must be considered in order to more fully access possible forms in cocrystal discovery. Furthermore, the timing of observation during kinetic growth methods must also be considered. As described, DADP/TBTNB forms during temperature-driven precipitation in poor solvents but the cocrystals dissociate to pure components if left in the mother liquor for too long. Therefore, great care should be exercised during cocrystal screens to both consider the possibility of kinetic forms and isolate them in a timely manner. As in the case of DADP/TBTNB, kinetic forms can be metastable and may be stored if properly isolated from conditions that would allow for their transformation.

In summary, two cocrystals containing DADP were synthesized in order to demonstrate energetic cocrystal design based on the interaction between the exposed electron-rich peroxide oxygen atoms of DADP and the electron-deficient rings of nitro-substituted aromatics. These cocrystals pair DADP with either TCTNB or TBTNB, electron-deficient aromatic energetic compounds that also feature halogens suitable for halogen–nitro interactions. Both the DADP/TCTNB and DADP/TBTNB cocrystals feature the intended solid-state interactions and are isostructural. However, the DADP/TBTNB cocrystal is demonstrated to be unstable relative to the pure forms of its components, a condition we term “schizophylic”. Thus, the DADP/TBTNB cocrystal is only formed through kinetic growth methods and must be carefully isolated in order to prevent spontaneous transformation. The existence of such a cocrystal carries significant implications for cocrystal discovery. The kinetic discovery conditions of such cocrystals suggest that traditional screening techniques need to be expanded to consider the formation of cocrystals with such stability.

Received: April 5, 2013

Published online: May 6, 2013

Keywords: cocrystallization · crystal design · explosives · peroxides · supramolecular synthons

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