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SPECIAL FEATURE SECTION: SAFETY OF CHEMICAL PROCESSES

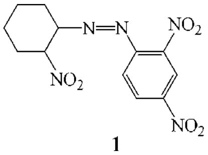
Safety Highlights

Safety Notables: Information from the Literature

This is the fourth annual literature overview on safety issues which are of interest to process chemists and engineers to appear in *Org. Process Res. Dev.* As in the previous years, this review will cover recent articles from the literature which address safety issues, common safety mistakes which seem to be repeated all too often, and major industrial accidents. This paper is not intended to be all inclusive of the safety literature, nor should the information presented be used to make decisions regarding safety without reading the full text of the appropriate article. The intent is to give a flavor of the issues facing other chemists and engineers and how they are solving these problems.

Thermal Decomposition Behaviors

Many readers of this review are looking for ways to lessen, or avoid altogether, working with molecules that have hazardous thermal properties. However, scientists working to prepare propellants, explosives, and thermal, free radical initiators deal with the dangers and rigors of working with thermally unstable compounds on a daily basis. The preparation and thermal characterization of compounds such as **1** (*J. Mol. Struct.* **2005**, *779,* 49) and **2** (*Thermochim. Acta* **2006**, *437*, 168) are outlined in very good detail in their respective articles.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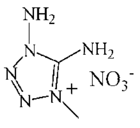
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Reading these types of papers gives one a solid background on the preparation of thermally energetic compounds. Hopefully it will lead to insights into the proper amount of data required prior to synthesizing other potentially unstable targets.

Implementation of Lessons Learned in Newly Acquired Facilities

The number of acquisitions, down-sizings, early retirements, and layoffs in the chemical industries has led to a tremendous amount of lost knowledge. Couple this knowledge loss with the unwillingness of many chemical companies to publicize accidents and their causes, and there is a growing gap in the institutional memory required to prevent repeat incidents. In an article by Brian Dunbobbin et al. (*Process Saf. Prog.* **2006**, *25*, 64) a tiered approach to ensure that acquiring companies identify as quickly as possible the key process safety risks so that employee, community, and company interests are adequately protected is given. The authors walk through the process and offer recommendations on how to achieve the transition with as minimal a loss of information as possible.

Materials of Construction

The choice of the proper materials of construction for a build-out of a new reactor train or other process equipment is a critical decision for process engineers (*Chem. Eng.* **2005**, *September*, 60). The classical choices of carbon and stainless steel can suffer from chemical incompatibility which leads to selecting lined equipment or more exotic metals. The lined equipment choices range from glass, fluoropolymers, graphite, or modified polymers. The exotic metals include zirconium, tantalum, titanium, Hastelloy, and Inconels. The author walks the reader through key properties of the new equipment such as chemical compatibility, metallurgy, heat transfer properties, static electricity, process conditions, and maintenance factors that should be considered prior to selecting materials of construction. Also provided in the article is a thorough table on the thermal conductivity of various materials of construction that is handy to have around.

Effect of Iron or Stainless Steel on Decomposition Characteristics

The lowering of the onset temperature for thermal decomposition of compounds by impurities or contamination is an area of growing concern for process safety professionals. Accidental introduction of iron or stainless steel into chemicals or reaction mixtures is not uncommon during chemical processing. High-energy chemicals such as hydrogen peroxide and hydroxylamine are known to be sensitive to metals such as iron, but the sensitivity of many processes are not known. A group at Eastman Kodak Company has performed a systematic DSC study on the effect of iron or stainless steel contamination on the decomposition characteristics of nitrobenzenes, tetrazoles, hydrazines, hydroxylamines/oximes, and sulfonic acid derivatives (*J. Hazard. Mater.* **2006**, *130*, 48). In addition, several low-energy functional groups were studied for contributing effects. Differences in decomposition onset temperatures and peak

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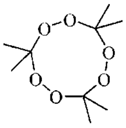
temperatures were used to assess sensitivity. A ratio of the maximum heat flow rates was used to determine the relative severity of decomposition. Hydrazine and hydroxylamine/oxime derivatives were found to have significantly lower decomposition temperatures and increased severity of decomposition when contaminated with iron or stainless steel. Nitrobenzenes were found to be sensitive only if they possessed acid chloride or chlorine substituents. Decomposition of tetrazoles and sulfonic acid derivatives did not change with contamination.

Decomposition of Triacetone Triperoxide and Other Organic Peroxides

In last year's review, a discussion of triacetone triperoxide (TATP) and its link to several terrorist bombings in the past years was presented. TATP is a very sensitive explosive with power close to that of TNT and without the commonly used nitro groups or metallic elements present in commonly used explosives; thus, the detection of TATP is very difficult.



TATP

The lab of Professor Cooks, from Purdue University, has published a simple on-site mass spectrometry method to quickly detect trace quantities of TATP and other explosive organic peroxides (*Chem. Commun.* **2006**, 953) and (*Chem. Eng. News* **2006**, *January 23,* 32). The key breakthrough is the ability to use a recently developed desorption electrospray ionization (DESI) technique without the need for sample preparation.

Two additional articles have been published recently which discuss the thermal decomposition hazards of organic peroxides. In the first article, by Drs. Li and Koseki, the kinetics of the thermal decomposition of liquid organic peroxides was investigated (*J. Loss Prev. Process Ind.* **2005**, *18*, 460). A key to the safe handling of liquid organic peroxide is to determine which molecules decompose via an autocatalytic mechanism and thus have the potential for a runaway scenario. This paper gives experimental kinetic data on several commonly used organic peroxides and determines the self-accelerating decomposition temperature to help in the safe handling of such compounds. In the second article, the mixing hazards of seven common organic peroxides with other chemicals are presented (*J. Loss Prev. Process Ind.* **2005**, *18*, 380). The data generated in this study led to the classification of the mixtures into four separate categories due to hazard criteria.

Rationale for Changing the Synthetic Route

A review article on identifying and characterizing the criteria needed for rejecting a potential synthetic route to an active pharmaceutical ingredient was written by a group of process chemists from AstraZeneca, Pfizer, and GSK (*Chem. Rev.* **2006**, *106*, 3002). The review provides a uniform set of criteria (SELECT) which represent the different drivers for changing a synthetic route. The acronym SELECT stands for:

- Safety
- Environment
- Legal
- Economics
- Control
- Throughput

The authors state that safety is the most important of the SELECT criteria. If a route cannot be scaled up safely, it should not be scaled up at all. The safety criterion is then broken down into the subcategories of thermal or reactive hazards and toxic hazards. The ensuing paragraphs outline a step-by-step approach to determine the safety hazards of the selected route and describe the equipment needed at each step. The path from Desk Screening, to Thermal Screening, to Characterizing the Desired Reaction, and on to Determining and Characterizing Undesired Reactions is given in order to define the basis of safety. Several case studies are then given. The subjects of these case studies include how to safely scale up an ozonolysis reaction, how to engineer a safer process toward idoxifene, the removal of a potential explosion hazard, and the removal of a genotoxicity hazard make the theory come to life for the reader. This article is an excellent review of process chemistry in general as well as a solid starting point on how to safely scale up chemical processes.

Online Monitoring of Hydrazoic Acid

Hydrazoic acid is a volatile, toxic compound that is formed in many azide processes due to the presence of small amounts of protic species. In addition to the handling issues related to its toxicity, hydrazoic acid has been reported to decompose violently when mixed with air or nitrogen above a concentration of 8−15%. Therefore, it is prudent to monitor the concentration of hydrazoic acid in the gas phase to ensure a proper level of safety. Analytical methods that require sample handling and preparation increase the risk of exposure. Researchers from Novartis Pharma AG have developed an online IR method to determine levels of hydrazoic acid in the headspace (*Org. Process Res. Dev.* **2006**, *10*, 349). The group found that both mid-IR and NIR can be used, but they chose to demonstrate the NIR technology on-scale in a 4000-L glass-lined steel reactor due to convenience and cost considerations. The IR results were found to be consistent with the results from a traditional off-line UV method run in parallel during the scale-up. The authors make recommendations for corrective actions if high levels of hydrazoic acid are detected. They also mention that titanium was found to be compatible with hydrazoic acid through corrosion studies, and Hastelloy C276 showed no visible corrosion at the lab scale, but a formal corrosion study was not performed.

Thermal Hazards of Reactions Containing DMSO

Dimethyl sulfoxide (DMSO) undergoes a severe exothermic decomposition just above its atmospheric boiling point, and there are several reports in the literature that describe incidents associated with its use on laboratory and industrial scales. Researchers at Merck report that several processes using DMSO as solvent were found to have significantly lower onset temperatures of decomposition compared to neat DMSO (*J. Therm. Anal. Calorim.* **2006**, *85*, 25). Two case studies describing the hazards are presented, including a discussion of simple process modifications prior to scale-up in a pilot plant. The authors also mention that decompositions of mixtures containing DMSO tend to exhibit autocatalytic behavior; therefore, the effects of thermal history should be studied.

In the first case study, two bromo compounds are coupled using copper powder in DMSO at 50 °C. ARC analysis on the pre-reaction mixture showed two exotherms starting at 50 and 70 °C. The first exotherm was relatively mild, but the second exotherm generated heat and pressure at an extremely high rate. The authors suggest that the byproduct copper bromide may be responsible for the severe decomposition as bromides are known to catalyze the decomposition of DMSO. When DMF was used as the reaction solvent, the onset temperature by ARC was found to be 135 °C, and the maximum rates of heat and pressure were not significant.

In a second case study, a fluoro compound and a quinone were coupled with potassium *tert*-butoxide in DMSO at 150 °C for 20 h. A heat-wait-search ARC experiment of the pre-reaction mixture did not reveal an exotherm. However, an isothermal age ARC at 170 °C revealed a thermal runaway after 23 h. In addition, the postreaction mixture was also found to be thermally unstable at the operating temperature. A revised process using DMSO as solvent and 18-crown-6 additive at 100 °C for 70 h was judged to be acceptable for scale-up with the appropriate engineering controls in place.

DMF−DMA-Promoted Polymerization of 2,3-Butanedione

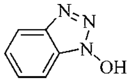
A research group at Pfizer reported a violent polymerization that occurred while attempting to make the condensation product of 2,3-butanedione with DMF−DMA (dimethylformamide dimethylacetal) (*Org. Process Res. Dev.* **2005**, *9*, 702). The analogous condensation with ethyl pyruvate was reported to occur without incident (*J. Heterocycl. Chem.* **2003**, *40*, 487). An NMR investigation confirmed that polymerization had occurred, presumably by initiation with DMF−DMA. Thermal analysis in an adiabatic calorimeter revealed a maximum self-heat rate of over 3000 °C/min and a maximum pressure rise of 1300 psi/min. Carbon dioxide and methanol vapors were detected by mass spectrometry at the end of the experiment.

An Industry-Wide Process Safety Incident Database

The Center for Chemical Process Safety (CCPS) started a project, called the process safety incident database (PSID), in 1995 to develop a database that tracks industrial incidents. The purpose is for sharing lessons learned among manufacturing companies who are willing to support the effort. Adrian Sepeda of the CCPS has reported on the goals, requirements, and benefits of process safety incident databases (*J. Hazard. Mater.* **2006**, *130*, 9). Attributes should include accessibility, user friendliness, accuracy, sufficient volume, standardization, confidentiality, and a comprehensive query system. The author reports that the CCPS's PSID is an example of a database that meets all of these requirements, except the "fuzzy query" criterion, a query that not only answers the question itself but also suggests other potential paths. Additional information on the CCPS PSID project can be found at http://www.psidnet.com.

Amide Bond Formations

The formation of amide bonds is a widely used reaction in organic chemistry. There are many combinations of carbonyl activating agents and additives which can increase the rate of the desired reaction and/or decrease unwanted side reactions in the process. One popular carbonyl activating agent is 1-hydroxybenzotriazole (HOBt).



1-hydroxybenzotriazole

There are drawbacks of using HOBt in the chemical industry of which users of this material should be aware. The compound is known to explode when heated beyond its melting point (156 °C), and it has a large energy of decomposition (−1715 J/g with an onset temperature of 159 °C) when measured by DSC at a heating ramp of 5 °C/min. The drying of the wet commercial material should be avoided. HOBt also is classified by the UN committee and the European Chemicals Bureau as a Category 1 explosive when in anhydrous form and as a Category 4.1 desensitized explosive, or "self-reactive" solid, when containing 10−20% water. Thus, HOBt is subject to transportation and storage restrictions because of this explosive potential. Two potential alternatives to HOBt have been published including 2-hydroxypyridine (*Org. Process Res. Dev.* **2004**, *8*, 1055) and 2-mercaptobenzothiazole (*Spec. Chem. Mag.* **2005**, *September*, 50). Please note that although comparison of thermal safety analysis was given for the use of 2-hydroxypyridine versus HOBt no such analysis was provided for the use of 2-mercaptobenzothiazole.

Screening Reactive Chemical Hazards

Many medium-sized and large companies have dedicated process safety professionals that specialize in quantifying reactivity hazards. Given the labor and material intensive nature of the work, quantification of all chemical reactivity is typically not a practical or efficient use of resources. The use of appropriate screening tools can help process safety professionals decide which reactive hazards should be quantified. In addition, the use of these screening tools can help chemists make informed decisions regarding the hazards associated with a particular chemistry during route selection and/or process development. Researchers at the Mary Kay O'Conner Process Safety Center have described the use of four such screening tools (*Chem. Eng. Prog.* **2006**, *102*, 41). Two of the tools are well-known by chemists and engineers: *Bretherick's Handbook of Reactive Chemical Hazards* and material safety data sheets (MSDS). Two less well-known tools are also discussed. One of these tools is The National Oceanic and Atmospheric Administration's (NOAA)

Chemical Reactivity Worksheet. The worksheet is a database (containing over 6000 substances) that is useful for identifying potential chemical incompatibilities. Free NOAA Chemical Reactivity Worksheet software for both Windows and Macintosh platforms is available for download at http://response.restoration.noaa.gov/chemaids/react.html.

The other little known tool is New Jersey's Toxic Catastrophe Prevention Act (TCPA, available at http://www.nj.gov/dep/rpp/download/conrulerev5a.pdf). Application of the TCPA involves the use of reactive hazard tables with reactive hazard substances and substance mixtures. The authors use the chemicals and functional groups listed in the tables as hazard indicators.

The authors go on to apply these screening tools to 167 reactive chemical incidents to determine how the tools perform when used sequentially. Due to limitations of the TCPA, 152 of the 167 incidents could be evaluated. When the other three screening tools were applied sequentially to the 152 incidents, six were not flagged as hazardous.

Reducing Risks with Hydrogen in Process Operations

Hydrogen is widely employed in chemical manufacturing and petroleum refining, and it also holds promise as a fuel. Hydrogen gas, however, is highly explosive, and special care must be taken when utilizing hydrogen on scale. In two separate articles, the handling of hydrogen as a raw material is discussed. In the first article, scientists from Pfizer describe the development of the *Hydrogen and Catalyst Handling Good Practices* guide which was implemented at all Pfizer manufacturing sites using hydrogen (*Proc. Saf. Prog.* **2005**, *24*, 244). The guide outlines the good practices not only for the design of newer contemporary facilities but also describes the minimum best practices required in older facilities for the use of hydrogen. A detailed review for handling hydrogen in process plants was also published (*Chem. Eng.* **2006**, *April*, 54). This article goes through the hazards associated with working with hydrogen and then describes the required supply and piping lines needed, the appropriate materials of construction to be used, the needed controls and monitoring for the facility, and the fire protection system required.

Inherently Safer Technology

Trevor Kletz in his book on plant design (*Plant Design for Safety*; Hemisphere Publishing Corporation: New York, 1991) stated, "The essence of inherently safer approach to plant design is the avoidance of hazards rather than their control by added-on protective equipment." This year, as usual, many articles were published which discussed the principles of inherently safer design of chemical processes and process plants. For an overview on this topic, please see the well-written full review of inherently safer design by Dennis Hendershot (*Process Saf. Prog.* **2006**, *25*, 98). Dennis Hendershot also penned a well-written opinion piece on some recent issues surrounding process safety, suggesting that the implementation of inherently safer technology should only occur in situations where it makes sense (*J. Chem. Health Saf.* **2006**, *13*, 36).

A comparison of the different indices to evaluate inherent design was published. This article (*J. Loss Prev. Process Ind.* **2005**, *18*, 327) concluded that the inherent safety methods available are fast and reasonably accurate for hazard evaluation in early process development.

An article on the evolution of inherently safer technology at Dow was written by Tim Overton and George King (*Process Saf. Prog.* **2006**, *25*, 116). This overview gives the reader insights into the lesson learned at Dow during the application of inherent safety technologies at various stages of the life cycle of a process.

In a paper written by Gunasekera and Edwards (*J. Loss Prev. Process Ind.* **2006**, *19*, 60) a method to estimate the inherent environmental friendliness of a chemical process by considering the potential toxicity impact on the aquatic, terrestrial, and atmospheric environments was proposed. By definition, an environmentally friendly plant does not give rise to situations that are hazardous to the environment. The usual course of action is to add on equipment to prevent catastrophic environmental pollution. In the inherently environmentally friendly model, the hazards are reduced or removed altogether from the process. Through the detailed examination of six different synthetic preparations of methyl methacrylate, the authors outline how to use this model to select the most inherently environmentally friendly process.

Safety Letters

Two reports of safety incidents appeared in *Chem. Eng. News* over the past several months. In one report, a violent explosion occurred during an attempt to recrystallize 3-iodotoluene from boiling water with vigorous stirring (*Chem. Eng. News* **2006**, *January 23*, 4). The cause was believed to be from heavy crystals of $ArIO_2$ settling out of the mixture due to ineffective stirring. A potential hazard for the synthetic procedure used for preparing hydride surface-terminated silicon nanoparticles was described (*Chem. Eng. News* **2005**, *December 19*, 4). In this procedure, which involves the reduction of $SiCl_4$ with $LiAlH_4$, the authors of the letter observed a "controlled burn" of a bright, orange flame from the oil bubbler on the reaction manifold. The authors state that no pyrophoric byproducts are mentioned in the literature citation on this preparation (*Phys. Rev. B* **1999**, *60*, 2704).

Mining the Web for Safety Information

The following is a list of web sites which we find useful for finding information on process safety and hazard analysis. If any readers have additions to this list, we would be most interested in seeing them and perhaps including them in next year's review.

1. http://www.fmclithium.com. FMC Lithium has created, and made available, two safe handling guides, *The Butyllithium Safe Handling Guide* and *The Organometallics and Reactive Specialty Organics Safe Handling Guide*. According to FMC Lithium, these guides cover recommended procedures for the safe transport, transfer, and use of butyllithium, organometallics, and reactive specialty organics.

2. http://www.dechema.de/. This site maintains several databases on the thermophysical and mixture properties of solvents as well as safety information on flammability and explosivity.

3. http://webbook.nist.gov/chemistry/. NIST Chemistry Webbook provides a wealth of thermodynamic data on compounds, including a tool to determine estimates of gas-phase thermodynamic properties based on a submitted structure.

4. http://www.aiche.org/ccps/publications/beacon/index.aspx: *Process Safety Beacon* is a free monthly electronic newsletter that covers a wide range of process safety issues.

5. http://www.chrismanual.com. The U.S. Coast Guard's Chemical Hazard Response Information System (CHRIS) database.

Gerald A. Weisenburger
Process Safety Laboratory, Pfizer, Inc.,
Groton, Connecticut 06340, U.S.A.
E-mail: gerald.a.weisenburger@pfizer.com
Paul F. Vogt
Chemical Development, Albany Molecular Research, Inc.,
Albany, New York 12212, U.S.A.
E-mail: paul.vogt@albmolecular.com

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