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Concept Articles

Practical Segregation of Incompatible Reagents in the Organic Chemistry Laboratory

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Abstract:

A new protocol of incompatible chemical reagent segregation has been developed. Serving as a second-level segregation beyond typical first-level separation of explosives/nonexplosives, flammables/nonflammables, corrosives/noncorrosives, and caustics/noncaustics, this method involves assigning the reactive functional groups constituting a given reagent to one of seven classes based on reactivity and then storing that reagent according to which of those functional groups is of the highest priority, based on defined rankings. This scheme, requiring a small number of segregation groups, differs from previously reported segregation methods by accounting for the fact that organic reagents typically contain multiple sites of varying reactivity.

Introduction

Scientists working in both industrial and academic settings who must use reactive chemicals, as well as the Environmental Health and Safety professionals of those organizations, face the hazards of not only the expected reactivity of those chemicals but also the unexpected reactivity deriving from the accidental mixing of those chemicals, as may happen given an ineffective method of incompatible chemical reagent segregation.[1] Ever-increasing regulatory demands placed on scientific organizations only exacerbate the need for a workable means of segregating incompatible chemicals.[2,3] Within the constructs of a safe segregation system, though, is the necessity to require a minimal number of storage classes, such that all of a scientist's reagents can be stored within the confines of his or her own workspace. Proper chemical segregation also allows for more organized tracking of chemical inventory, which can significantly affect operating costs.[4]

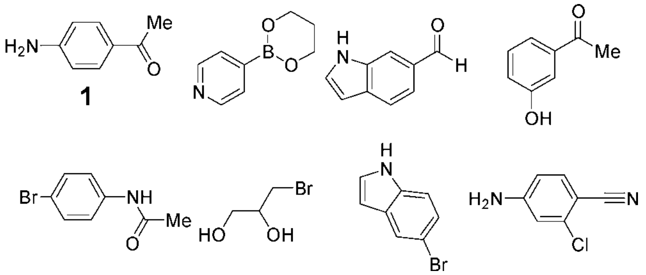

Figure 1. **Reagents ambiguously assigned during the electrophile vs nucleophile segregation.**

Synthetic organic chemistry laboratories contain a variety of commercially available reagents that often contain two or more reactive functional groups ("polyfunctional" reagents). Whereas agreement exists that chemicals should be separated according to reactivity (e.g., the typical acid vs base, electrophile vs nucleophile, or oxidant vs reductant distinctions), the polyfunctional nature of most reagents renders the process of segregation more difficult, as, for example, one part of a single molecule may be electrophilic while another part may be nucleophilic.

The deficiencies of such an electrophile vs nucleophile classification became clear during an initial attempt to classify and segregate our large chemical inventory onsite. Multiple chemists were asked to apply an "electrophile" or "nucleophile" designation to each of several hundred bottles. As an example of the problems evoked by this strategy, of 205 unique reagents to which the electrophile vs nucleophile approach was applied by multiple chemists, different categories were applied to 31 of these unique reagents (15% discrepancy rate). The reasons for these errors, as can be seen by examining selected examples of ambiguously assigned reagents in Figure 1, typically related to confusion about how to handle multiple functional groups within a single molecule. To our knowledge, no clear description of how to classify and separate polyfunctional reagents exists

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(1) (a) Hazard Investigation: Improving Reactive Hazard Management, Report No. 2001-01-H; U.S. Chemical Safety and Hazard Investigation Board: Washington, DC (accessed at http://www.csb.gov/assets/document/ReactiveHazardInvestigationReport.pdf on 6/3/09). (b) Use and Misuse of Chemical Reactivity Spreadsheets, U.S. Department of Energy Chemical Safety Topical Subcommittee: Washington, DC, 2005 (accessed at http://www.hss.energy.gov/HealthSafety/WSHP/chem_safety/Self_Assess/usepaperrevision.pdf on 8/22/08). (c) Recommendations for Addressing Recurring Chemical Incidents at the U.S. Department of Energy, U.S. Department of Energy Chemical Safety Topical Subcommittee: Washington, DC, 2005 (accessed at http://www.hss.energy.gov/HealthSafety/WSHP/chem_safety/cstcchem/safety/recommend.pdf on 8/22/08).

(2) A variety of publications, and references therein, concern chemical segregation and storage: (a) Simmons, F.; Quigley, D.; Whyte, H.; Robertson, J.; Freshwater, D.; Boada-Clista, L.; Laul, J. C. *J. Chem. Health Saf.* **2008**, *15*, 23. (b) Yohe, B.; Dunkelberger, G. *J. Chem. Educ.* **1985**, *62*, 876. (c) Williamson, J. R. *J. Chem. Educ.* **1983**, *60*, 668. (d) Pipitone, D. A.; Hedberg, D. D. *J. Chem. Educ.* **1982**, *59*, A159. (e) The Safety Committee of the New York Section of the American Chemical Society *J. Chem. Educ.* **1982**, *59*, A9.

(3) Winder, C.; Zarei, A. *J. Hazard. Mater.* **2000**, *A79*, 19.

(4) *Top Six Reasons Why Chemical Inventory Process Fail*; Chem SW Inc.: Fairfield, CA (accessed at http://www.chemsw.com/cn705abp.htm on 8/22/08).

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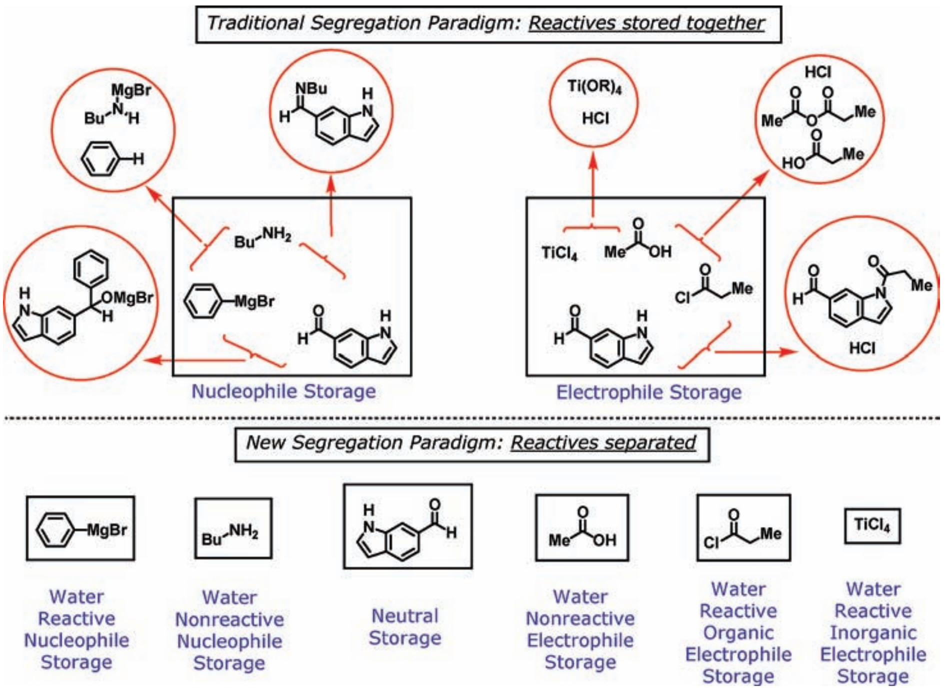

Figure 2. **Reactive incompatibles separated under the new segregation paradigm.**

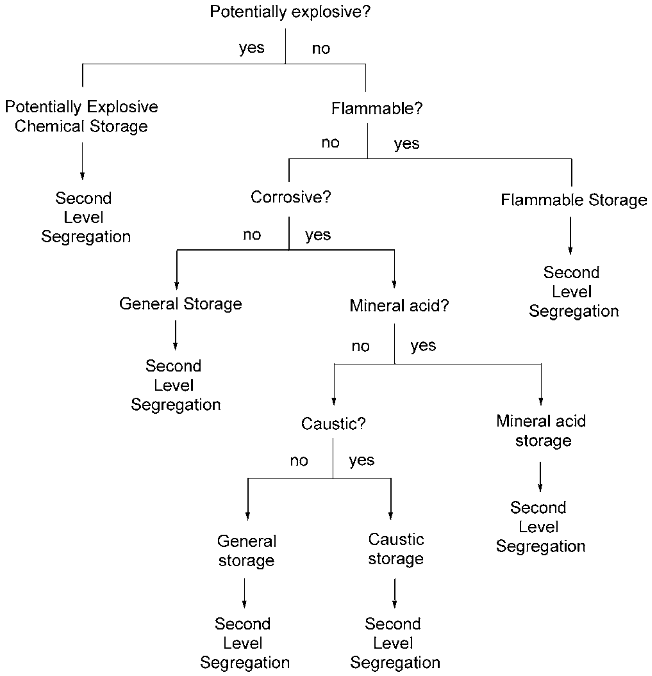

Figure 3. **First level segregation: general hazards.**

in the literature. Thus, we, as chemists working with these reagents on a daily basis, sought to develop a protocol that would preclude these discrepancies, both to render the classification of chemicals already onsite more straightforward and to make the classification of newly ordered reagents error-free and consistent. The chemical community as a whole would benefit from a consistent means of describing any given reagent (whether monofunctional or polyfunctional) as belonging to a certain reactivity group for the purpose of safe storage. Indeed, a practical segregation system must involve a set of clear guidelines delineating the placement of common reagent classes without requiring the scientist who is doing the actual separation to judge each individual case based on his or her own concept of that reagent's reactivity.

Only a small number of systems for incompatible chemical segregation have been reported. Chemical suppliers such as Fisher Scientific and J.T. Baker provide guidelines for chemical storage (the ChemAlert Storage plan and the SAF-T-DATA Labeling System, respectively), which employ color-coded labels to describe hazard classes of various reagents, including flammable, health, reactivity, and corrosive hazards. Similarly, the National Fire Protection Association (NFPA) and OSHA's Hazardous Material Identification System (HMIS) rely on color-coding to give information about these general hazards for specific chemicals. The U.S. Department of Transportation describes nine general hazard classes (flammable solids, flammable liquids, explosives, corrosives, poisons, oxidizers, gases, and miscellaneous).

The U.S. Coast Guard Chemical Hazards Response Information System (CHRIS)[5] was developed for ensuring safe maritime transport but establishes rules of segregation that can apply more generally. CHRIS lists 36 categories of different chemical reactivity classes and provides a matrix for determining which of these categories are incompatible with each other; these categories each describe reagents with a single reactive functional group. The United Nations Dangerous Goods system[6] involves categories covering chemical reactivity and physical properties (toxic, poisonous, etc.). The U.S. Environmental Protection Agency has developed an incompatibility system

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(5) Chemical Hazards Response Information System (CHRIS); U.S. Coast Guard: Washington, DC (accessed at http://www.chrismanual.com on 5/14/08).

(6) *United Nations Recommendations on the Transport of Dangerous Goods*, 15th ed.; United Nations Economic Commission for Europe, Committee of Experts on the Transport of Dangerous Goods: New York, NY, 2007 (accessed at http://www.unece.org/trans/danger/publi/unrec/rev15/15files_e.html on 8/22/08).

Oxidizing (OX)

$KMnO_4$, MnO_2
$NaIO_4$
OsO_4
I_2 & Br_2
Chloramine B & T
Bromates
Peroxide & peracids
Oxones
Nitrates & nitrites
Chlorates & chlorites
N-halosuccinimides
Hypervalent iodine (IBX)
Dess-Martin periodinane
TPAP
Sulfur trioxide (SO_3) and complexes

Neutral (NEUT)

Alkyl, aryl nitriles (RCN, ArCN)
Amides & imides
Acetals & ketals
Carbamates
Esters
Ethers & sulfides
Halo-, NO_2-, CF_3-sub'd phenyl & vinyl
NO_2-, CF_3-sub'd alkyl
Hydrocarbons
N-alkyl succinimides
Orthoformates
Phosphonium bromides
Phthalimides, ureas, thioureas
R_4Si, R_4Sn & R_3SnCl
Siloxanes
Silyl ethers
Sulfonamides, sulfonates
Sulfur (elemental)

Water-nonreactive Nucleophilic, Weak Base, and Salt (WNR NUC)

Alcohols, phenols & thiols
Amidines & oximes
Amines, amino acids, anilines & salts thereof
Aromatic heterocycles
  (excluding 2-halo heterocycles)
Guanidines
Hydrazines and salts & hydrazones
Lawesson's reagent
Non-halo phosphines
Phosphinates & phosphonates
Phosporic amides
Phosphorous ylides (bound to EWG)
Tetrabutyl ammonium halides
Pd(0) & Ni(0) species
Rh(I), Rh(II), Pd(II), Ni(II) & Bi complexes
ZnO_2, PtO_2

- -

Metals (Cu, Zn, Hg, Ag, Na, K, Li, Mg, Ru, Rh, Pd, Ir, Co, Ni, Fe, Cr, Ca, Sm, Bi, Ce, In) bound to: { carbonates, bicarbonates, acetates, phosphates, cyanides, sulfates, dithionates, etc.

Water-reactive Nucleophilic (WR NUC)

Alkyl lithiums, cuprates & zincs
Alkyl ylides
Grignards
Hydrides
Metal(0) species: Na, K, Li, Mg, Zn, Cu, etc.
Metal-alkoxides
Silanolates
Metal-bis(trimethylsiyl)amides

Water-nonreactive Electrophilic (WNR ELEC)

Aldehydes & ketones
Alkyl halides, mesylates & tosylates
Aziridines & oxaziridines
Boronic acids/esters
Carboxylic acids
Dialkyl carbonates
Enones & ynones
Epoxides & episulfides
2-Halo aromatic heterocycles
Halophosphines
Imines & imidates
Lactones & lactams
Nitroalkenes & nitroarenes
Organic azides
Oxalates
Oxonium species
Phosphorus (elemental)
Sulfonic acids
TOSMIC
1 to 4 M HCl in organic solvents

Water-reactive Organic Electrophilic (WR ORG ELEC)

Acid chlorides
Anhydrides
Chloroformates
Coupling reagents
  CDI, DCC, EDCI, etc.
Cyanoformates
Isocyanates & isothiocyanates
Mitsunobu reagents
  DEAD, DIAD, etc.
Silyl chlorides, triflates & amines
Silyl cyanides & azides
Sulfonyl, thionyl, phosphoryl halides
$PhNTf_2$
DPPA

Water-reactive Inorganic Electrophilic (WR INORG ELEC)

Inorganic Lewis Acids, including metals bound to halides
  AlR_3, $TiCl_4$, $SiCl_4$, $SnCl_4$, BF_3, SmI_2, $MgBr_2$, etc.
Metal trifluoromethanesulfonates
Hexafluoroantimonates
Tetrafluoroborates
Metal carbonyls (Co, Fe, W, Mo)
Trialkyl borane
Phosphorus pentahalides
HBr in organic solvents

Figure 4. **Commonly encountered functional groups, by class.**

covering hazardous wastes[7] that combines chemical reactivity concerns with environmental properties. In an effort to develop a comprehensive system, Winder[2] merges these three aforementioned protocols into one overarching scheme containing 100 different segregation categories; each category represents reagents with a single reactive functional group.

As an illustrative example of a reagent that demonstrates not only the need to consider polyfunctionality but also the need for more than simply two storage areas, consider the ambiguous reagent 4-aminoacetophenone (compound **1**, Figure 1). In the absence of other chemicals, this reagent could reasonably be viewed as either an electrophile or a nucleophile. Yet, when choosing between one of only two categories (nucleophile vs electrophile), each of which contains many other reagents, the decision of where to place 4-aminoacetophenone is in fact much more complicated. On one hand, if that reagent were stored as an electrophile, then the anilinic portion of the molecule could react with aldehydes or, more likely, with the much more reactive acid chlorides, all of which would be stored as electrophiles as well. Similarly, if 4-aminoacetophenone were stored as a nucleophile, the ketone portion of the molecule could potentially react with amines and, more violently, with the much more reactive Grignard reagents, all of which would also be stored as nucleophiles. Thus, not only must the polyfunctional nature of organic molecules be taken into account in a consistent and scientifically sound manner based on reactivity, but also the electrophile vs nucleophile distinction alone is insufficient to describe the wealth of incompatible organic reagents, given the vast reactivity differences within the various types of electrophiles and the various types of nucleophiles.

I. OX > WR NUC > WNR NUC > NEUTRAL

II. OX > WR ORG ELEC = WR INORG ELEC > WNR ELEC > NEUTRAL

III. WNR NUC = WNR ELEC
(one of each → cancellation = NEUTRAL)

IV. WR NUC = WR ELEC
(one of each → cancellation = NEUTRAL)

Figure 5. **Functional group prioritization rules.**

Three key questions remain, then, when comparing the approaches to chemical segregation that have been reported to the needs of the practicing synthetic laboratory: What is the optimal method for separating chemicals into a manageable number of reactivity classes? How is a reagent that possesses multiple functional groups, and so can be viewed as one of at least two different reactivity classes, to be stored? How can different people consistently decide on the same reactivity storage class for a given reagent?

The approach outlined herein seeks to answer these questions in a practical manner by creating a system with a small number of total storage areas that uses rules-driven functional group prioritization to specify the reactive class of any reagent, whether mono- or polyfunctional. Importantly, this new system results in separate storage for reagents that can react with one another but that would be stored together within a typical electrophile vs nucleophile system. As can be seen in Figure 2, using the tendency of different reagents to react when exposed to water as a guide for how they will react with one another has enabled a reasonable separation of differently reactive nucleophiles and electrophiles.

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(7) A Method for Determining the Compatibility of Hazardous Wastes. Environmental Protection Agency: Cincinnati, OH; EPA-600/2-80-076, April 1980 (accessed at http://www.sefsc.noaa.gov/HTMLdocs/appendix-H.htm on 8/22/08).

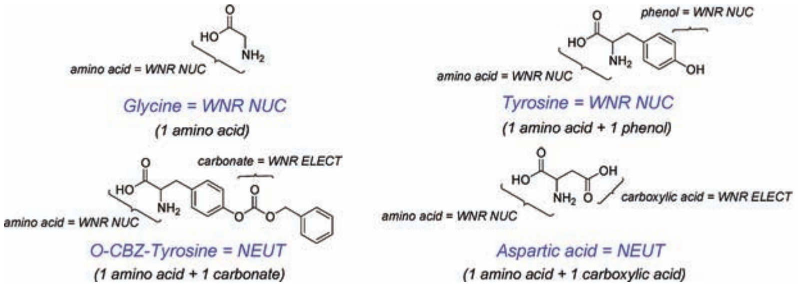

Figure 6. **Categorization of reagents containing amino acid functional groups.**

Notably, this type of classification marks a second layer of segregation below the typical first-pass separation of potentially explosive chemicals apart from nonpotentially explosive chemicals, flammables apart from nonflammable, and corrosives and caustics apart from noncorrosives and noncaustics (Figure 3). Once this first level of segregation has been performed, separating the reactive types within each of these classes can be accomplished, and it is the purpose of the following discussion to detail that second-level process.

Design and Implementation of Segregation System. To design and implement a new incompatible chemical segregation system meeting the criteria detailed above, a large, representative chemical inventory was examined. Seven classes of functional groups were identified, one or more of which are present in any chemical reagent (detailed below). Notably, within these seven groups, both the electrophile class and the nucleophile class are each broken down into two further classes based on reactivity (the so-called "water-reactive" and "water-nonreactive" types). Such a distinction allows nucleophiles that would react with each other to be stored separately (for example, diethylamine and *n*-butyllithium), and it similarly allows electrophiles that would react with each other to be stored separately (for example, a carboxylic acid and a carboxylic acid chloride). A further distinction is made between inorganic and organic electrophiles of the water-reactive type, in order to separate reagents such as Lewis acids from acid chlorides, which would react with one another.

1. **Oxidizing (OX)** groups (e.g., peracids).
2. **Neutral (NEUT)** groups (e.g., amides, hydrocarbons, ethers).
3. **Water-reactive nucleophilic (WR NUC)** groups (nucleophiles or bases which create a hazard when exposed to water, e.g. alkyllithiums).
4. **Water-nonreactive nucleophilic (WNR NUC)** groups (e.g., amines).
5. **Water-reactive organic electrophilic (WR ORG ELEC)** groups (organic electrophiles or acids which create a hazard when exposed to water, e.g. acid chlorides).
6. **Water-reactive inorganic electrophilic (WR INORG ELEC)** groups (inorganic electrophiles or acids which create a hazard when exposed to water, e.g. Lewis acids).
7. **Water-nonreactive electrophilic (WNR ELEC)** groups (e.g., ketones and aldehydes).

Commonly encountered functional groups for each of these classes are listed in Figure 4. As examples from these classes, groups such as ketones and aldehydes are classified as water-nonreactive electrophiles (WNR ELEC); amines, amine salts, and hydroxyl groups are classified as water-nonreactive nucleophiles (WNR NUC). Although the decision of how to define these and many other functional groups is straightforward, the classification of several other functional groups is less obvious and requires decisions to be made as follows. As one example, metal halides are defined as water-reactive inorganic electrophilic groups (WR INORG ELEC). Some of these entities (e.g., $TiCl_4$) are quite water reactive, but others (e.g., $CuCl_2$) are far less so; to establish a consistent rule that would be easy to implement without compromising safe storage, all such metal halides are defined as WR INORG ELEC. As a second example, aromatic heterocyclic functionality is broken into two groups: heterocycles in which a halogen is attached to a carbon that neighbors a heteroatom (as in a 2-chloropyridine functional group) are water-nonreactive electrophilic groups (WNR ELEC). All other heterocyclic moieties (such as a pyridine functional group) are water-nonreactive nucleophilic groups (WNR NUC).

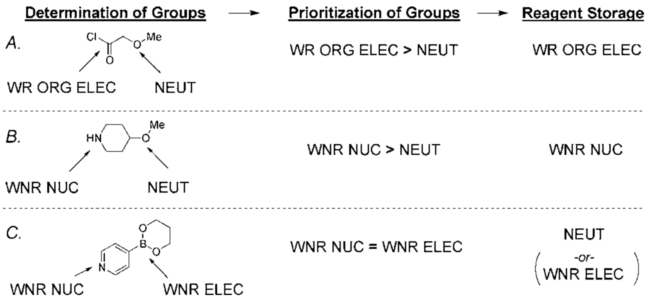

Figure 7. **Determining storage locations for example reagents.**

Having defined the functional group classes and detailed the most commonly encountered contents of each, it is next necessary to prioritize these classes, as outlined in Figure 5. Importantly, this rules-driven prioritization distinguishes the described system from the other reported methods of segregating incompatible chemicals.

Oxidizing groups take the highest priority. Water-reactives are higher in priority than water-nonreactives, with neutral functional groups having the lowest priority. Reagents that contain both water-nonreactive electrophilic and water-nonreactive nucleophilic functionalities are, by their nature, neutral in terms of reactivity, and the prioritization rules predict this fact: when each of these groups is present within a given reagent, the rules call for a cancellation and the application of the neutral (NEUT) code.

Because of this cancellation rule, the classification of the amino acid functionality in Figure 4 requires extra consideration. An amino acid, a molecule comprising one basic amine and one carboxylic acid, behaves generally as a zwitterionic amine salt (an ammonium cation and a carboxylate anion) and thus

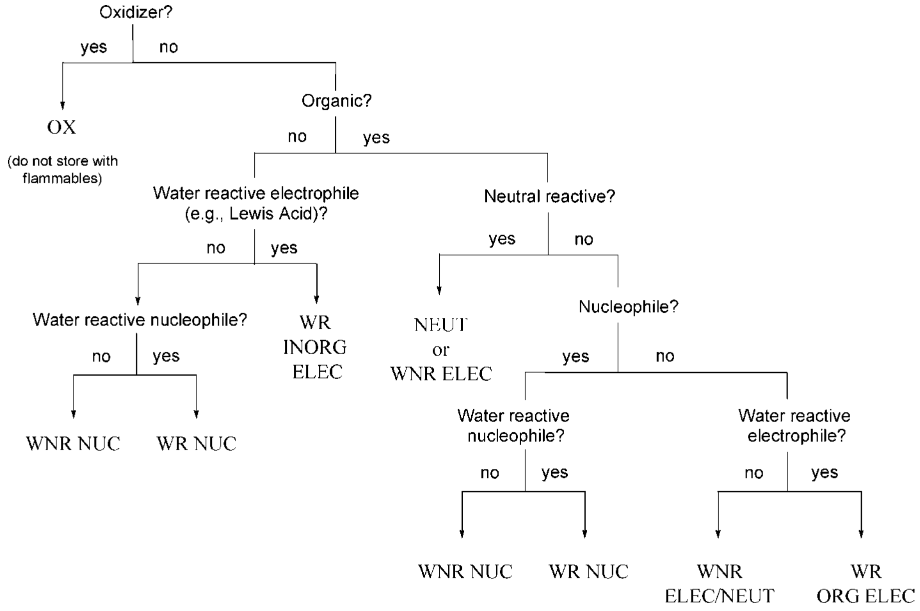

Figure 8. **Second level segregation: reactivity classes.**

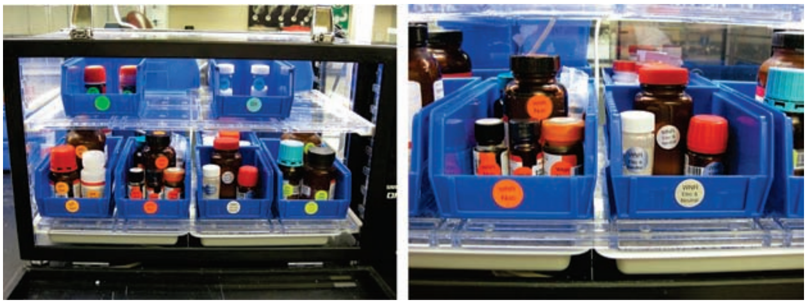

Figure 9. **Segregated reagents in secondary storage.**

warrants treatment as a water-nonreactive nucleophile (WNR NUC), akin to other amine salts. The prioritization rules would, on the other hand, prescribe that an amine (WNR NUC) and a carboxylic acid (WNR ELEC) must cancel to leave a neutral species (NEUT). Were such amine salts to be stored as NEUT, then they would be potentially stored alongside, for example, ketone-containing molecules such as 4-aminoacetophenone (compound **1**, Figure 1); the combination of amine salts with ketones is to be avoided. To prevent such incompatible situations from arising, the ubiquitous amino acid functional group is defined as a single entity and explicitly classified as a water-nonreactive nucleophilic functional group (WNR NUC) in Figure 4, just as are other amine salts. Because any *reagent* containing one basic amine functional group and one carboxylic acid functional group must be viewed as having one single functional group termed an "amino acid" group (WNR NUC; see glycine in Figure 6), such a chemical is stored as a WNR NUC *reagent*. Tyrosine (Figure 6) contains an amino acid functional group (one amine and one carboxylic acid = WNR NUC), and it also contains one hydroxyl functional group (WNR NUC), so this *reagent* is a WNR NUC. In contrast, a *reagent* that contains one basic amine, one carboxylic acid, and for example, one carbonate (as in the case of O-CBZ-Tyrosine, Figure 6), possesses one WNR NUC functional group (the amino acid) and one WNR ELEC functional group (the carbonate); it follows from the prioritization rules (Figure 5) that this *reagent* is neutral (NEUT). Indeed, were this reagent simply to be stored with other amino acids in the WNR NUC area, incompatibilities between the carbonate functionality and various nucleophilic amines would arise. Similarly, aspartic acid (Figure 6) contains an amino acid functional group (one amine and one carboxylic acid = WNR NUC) plus an additional carboxylic acid (WNR ELECT), so this *reagent* is neutral (NEUT). Were aspartic acid instead to be stored with other amino acids as a WNR NUC, then the presence of a discrete carboxylic acid functional group in the presence of basic amine functional groups would represent an undesirable incompatibility.

Finally, the process for storing a reagent must be described. Once the reagent's constituent functional groups are identified and ranked, the highest-ranking group takes precedence, and the reagent is simply stored according to that code. Any reagents for which the final determination of neutral (NEUT) is reached are best stored either in their own NEUT storage area (making the total number of second-level storage areas seven) or with the water-nonreactive electrophiles (WNR ELEC), with which no incompatibility issues exist, making the number of second-level storage areas as small as six, if desired.[8]

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(8) In contrast, neutrals (NEUT) should not be stored with the water-nonreactive nucleophiles (WNR NUC), as potential incompatibilities may arise, e.g. the neutral compound indole-6-carboxaldehyde (containing an aldehyde) would be stored alongside nucleophilic amine-containing molecules (such as benzylamine) with which it could react.

The examples in Figure 7 demonstrate the application of this approach, and the overall sequence is depicted in Figure 8.

To assess the consistency of this system, a number of chemists *who had not previously been exposed to this protocol* were asked to apply the system to a total of 1347 reagent bottles. After analyzing the results of this trial, only 81 of these bottles were identified for which the rules were applied incorrectly (a success rate of 94%), demonstrating this system to be suitable for use with large chemical inventories such as those found in pharmaceutical R&D organizations, academic institutions, etc.

Implementation of this system can be assisted through visual aids, allowing reagents to be stored easily and safely in appropriate secondary containment alongside reagents with the same colored sticker, as seen in Figure 9. A number of other safeguards can be incorporated to allow for the identification and resolution of miscategorized reagents, as follows. First, multiple bottles of a given reagent are commonly found at any R&D facility, distributed among different storage areas− checking for consistent labeling across all instances of each given reagent is one means by which miscategorized reagents can be identified and then reconciled. Second, each time a reagent is handled, that person (whether chemist or inventory technician) can be charged with the responsibility of ensuring that the warning label is appropriate; in this way, each reagent can be checked multiple times by various individuals, all of whom will have been trained in application of the chemical segregation rules.

This protocol, then, focuses on safe, practical segregation and a consistent means of applying the chemical segregation rules, while also allowing for easy identification of incorrectly stored chemicals.

Conclusions

A new method for the practical segregation of incompatible reagents commonly found in synthetic organic laboratories has been described. This rules-driven system, designed by chemists who use these reagents in the course of their daily work, is applied after common first-level separations and relies upon ascribing the functional groups constituting a given reagent to one of seven classes and then storing that reagent according to which of those functional groups is of the highest priority. Implementation of this system has allowed for a manageable number of segregation groups while accounting for the polyfunctional nature of many synthetic reagents and has eliminated reliance upon the judgment of different (though well-intentioned) people who may make irreproducible or inconsistent decisions about storage of complicated reagents. To our knowledge, this system is the first in the chemical literature to present a practical and safe segregation and storage protocol, in terms of the variables and classification criteria described here, for the polyfunctional molecules typically found in a synthetic organic chemistry laboratory.

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