Sulfonate Esters - How Real is the Risk?

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Introduction – Description of the issue

- There have been growing concerns expressed by regulators in relation to the potential generation of genotoxic impurities as a result of interactions between strong acids and alcohols.
- This has centred primarily on sulfonate esters, theoretical impurities resulting from interaction between sulfonic acids and alcohols.

\[ R_S^+ + R'O^- \rightarrow R_S^+ R'O^- \]

This reaction produces esters which can be very difficult to control.

Design Space

Front of cube

- Understanding the (strongly) acidic system

Mid and rear of cube

- Understanding 'salt-like' systems

All reactions carried out in solution

Concentration of acid: 0.25M

Stoichiometry of added base: 1:1

These conditions are typical of standard process conditions

Reaction Systems

- Commonly used 1° and 2° alcohols in combination with the 2 most common sulfonic acids in terms of marketed salts
  - The methyl, ethyl and isopropyl esters of Methanesulfonic acid
  - The methyl, ethyl and isopropyl esters of Toluenesulfonic acid
- Initially study Ethanol-Methanesulfonic acid system
- Followed by focused studies on other systems

Reaction Mechanism

Reactions of (O18) labelled methanol with MSA were analysed by CG-MS:
- reaction occurs through nucleophilic attack of the sulfonate anion on the protonated alcohol
  - O18 label appears in the WATER.
  - Precludes mechanisms where the alcohol is the nucleophile
    - O18 label would have been found in the ester

NB Solvolysis is a significant additional mechanism consuming ester to form the ether and regenerate sulfonic acid
- This critical protonation dependence underpins all the observed results

Learning for Process Design

Minimise (avoid) sulfonate ester formation by
- Use an excess of the API base, or as near as possible to an exact stoichiometry.
- If an excess of sulfonic acid is needed, use the minimum excess possible and conduct the salt formation and isolation steps at the lowest practical temperature.
- Include water in the salt formation and isolation procedures where possible
  - Competition for proton.
  - Rapid hydrolysis rates relative to rates of ester formation.
- Avoid situations in which sulfonic acid and alcohol are mixed and stored before use.
- If this is unavoidable then any solutions should be prepared at as low a temperature as possible and hold times kept to a minimum.
- If low level formation likely ensure efficient washing of cake.

Conclusion

- Based on the thorough understanding of the reaction between sulfonic acids and alcohols developed through the PGRI studies it is entirely possible and straightforward to control process conditions such that levels of sulfonate esters can be controlled to such low levels as to present no appreciable risk

- Ultimately this shows that sulfonic acids can be used under the right conditions without fear of risk