Sulfonate Esters – How Real is the Risk?

Summary of Key Findings from PQRI Studies of the Reaction Between Sulfonic acids and Alcohols

A Teasdale

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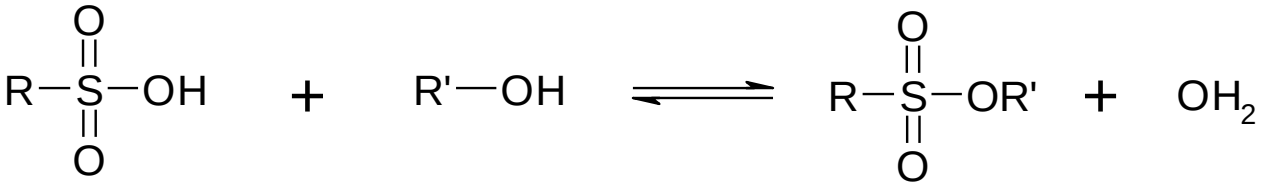
AstraZeneca
life inspiring ideas

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 - alkyl / aryl
R'- alkyl - methyl / ethyl / isopropyl etc.

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Introduction – Description of the Issue

- Issue was discussed at length at the DIA meeting on genotoxic impurities – November 2005
  - FDA expressed significant concerns over use of sulfonic acids as counterions.
- It was clear at the meeting that many companies had carried out in house studies
  - Showing some understanding of levels formed and how to control them.
- Clear challenge from this meeting going forward was for industry to build on these studies
  - To provide clear evidence of this understanding and to publish.
  - PQRI Initiative borne out of this need.

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What is PQRI (www.pqri.org)?

The Product Quality Research Institute www.pqri.org

- *"… (PQRI) is a collaborative process involving FDA's Center for Drug Evaluation and Research (CDER), Industry, and Academia."*
- *"The mission of PQRI is to conduct research to generate specific scientific information that should be submitted in a regulatory filing to CDER."*
- *"…PQRI tackles projects to ensure the quality, safety and performance of drug products."*

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Study Model

- Key aspect of the work was independent verification of data.
  - Specific challenge from FDA.
- Resource also a key factor.
  - Real issue for many PQRI activities.
- Also required the right skill set
  - Proven track record on trace analysis and of solving complex problems

Aims

- To provide a sound scientific understanding of the formation and decomposition of sulfonate esters,
  - under synthetically relevant conditions.

- To understand the absolute levels of such impurities that can form under process-related conditions.
  - Optimal process conditions to minimize the sulfonate ester formation.
  - Effective purge processes.

- To place reputable, peer-reviewed science-based knowledge into the public domain
  - Methodologies for analyses and kinetic studies
  - Teaching with regard process design to obviate/minimise ester formation

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Experimental Protocol

Step 1: <u>Investigation / Establishment of Analytical Methodology</u> + <u>Experimental Protocol</u>

1. Establishment of actual technique

- Wide dynamic range required (low to several thousand ppm)

2. Validation of analytical methodology

3. Study Methodology

- Establishment of a robust reaction study protocol
  - equipment and sampling (+ derivatisation) procedures
  - Definition of the numbers of samples and frequency of sampling required for kinetic modelling.

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Validation Data for analytical procedure

Key Data:

Linearity: Linear over the range 5 –500 ug/ml EMS (R^2 >0.999).

Precision:

RSD for EMS (as Et-TPFB derivative) measured relative to the internal standard 2 (d5-Et-TPFB) was:

- 3 % at 5 µg level and better than 1 % at the 50 µg level.

Limit of Detection: 0.5µg/ml

Limit of Quantification: 1 µg/mL, corresponding to 0.001 % conversion.

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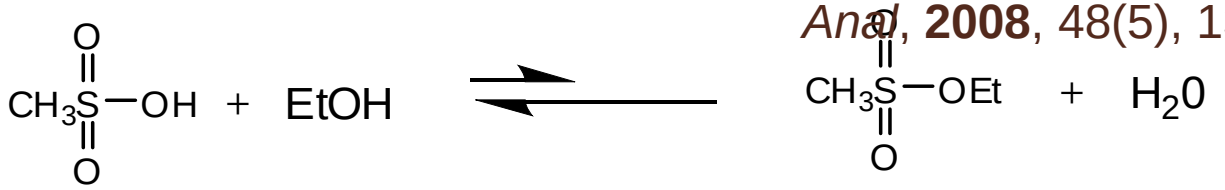
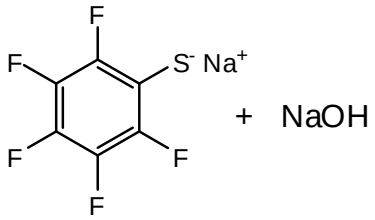
Analytical Procedure Based upon PFTP Derivatization

K. Jacq, et al *J.Pharm. Biomed. Anal*, **2008**, 48(5), 1339

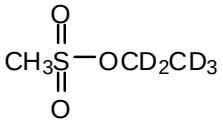


1) Samples withdrawn over time and treated with:



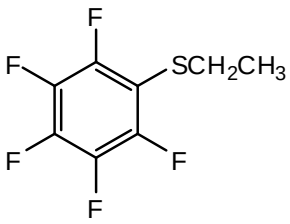
+ NaOH

2) Samples spiked with small amount of d5 EMS:

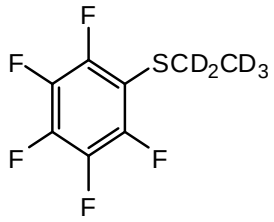


3) samples heated for period of time (15 min at 105 deg C in published method) to effect derivatization and insure equilibration within the Headspace prior to assay

4) Levels of Et PFTB and d5Et PFTB (internal standard) analyzed by GC/MS:



Et PFTB



d5Et PFTB

Concentration values vs time based upon ratio of Et PFTP to d5Et PFTP area counts

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Experimental Protocol

Step 2: Reaction Space Studies

1. Definition of Scope –Sulfonate Esters

- Commonly used 1° and 2° alcohols in combination 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

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Experimental Protocol

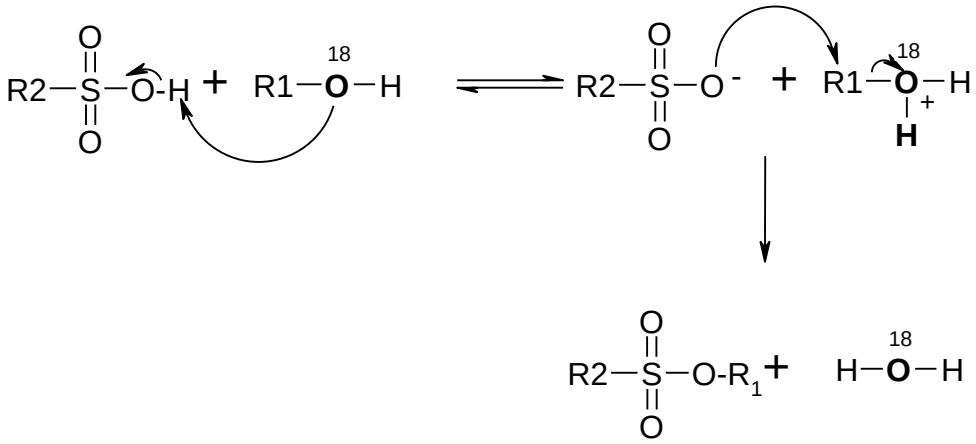
Step 2: Reaction Space Studies

2. Scope driven by common process conditions…

- Presence / absence of water
- Temperature
- Time
- Acidity
  - ‘parent system’ (no added base)
  - excesses and deficiencies of added base
    - Hunigs Base & Pyridines as models for API
      - 2,6-lutidine used, as sulfonate salts are highly soluble
      - weaker base than many pharmaceutical bases, therefore
      - protonated base is stronger acid than pharmaceutical salts…

Reaction mechanism – Ester Formation

- Reactions of (O^{18}) labelled methanol with MSA were analysed by CG-MS.



- Reaction occurs through nucleophilic attack of the sulfonate anion on the protonated alcohol – O^{18} label appears in the WATER.
  - Precludes mechanisms where the alcohol is the nucleophile - O18 label would have been found in the ester – it was instead restricted entirely to water
- NB Solvolysis is a significant additional mechanism consuming ester
  - to form the ether and regenerate sulfonic acid
- **This critical proton dependence underpins all the observed results**

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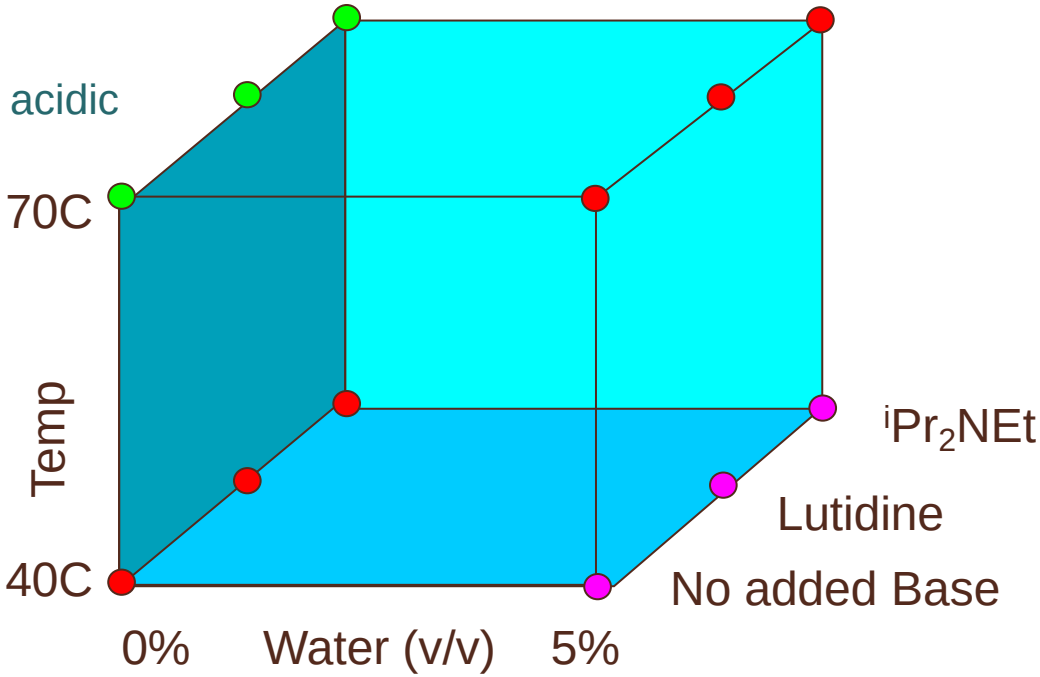
Original Design Space

- '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
Stoicheometry of added base: 1:1

- **Initial system : Ethyl Methanesulfonate (Ethyl mesylate, EMS)**

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Presentation of Results

- Results will be presented in graphical form:
  - ***conversion*** vs time
- Conversion means
  - Molar conversion of **sulfonate (anion)** to ester
  - Yields **in solution**
  - **Not** levels of ester in isolated yields of salts…
  - ***Does*** give teaching on upper limits which may be formed
    - And hence necessary purge efficiency for salt isolation

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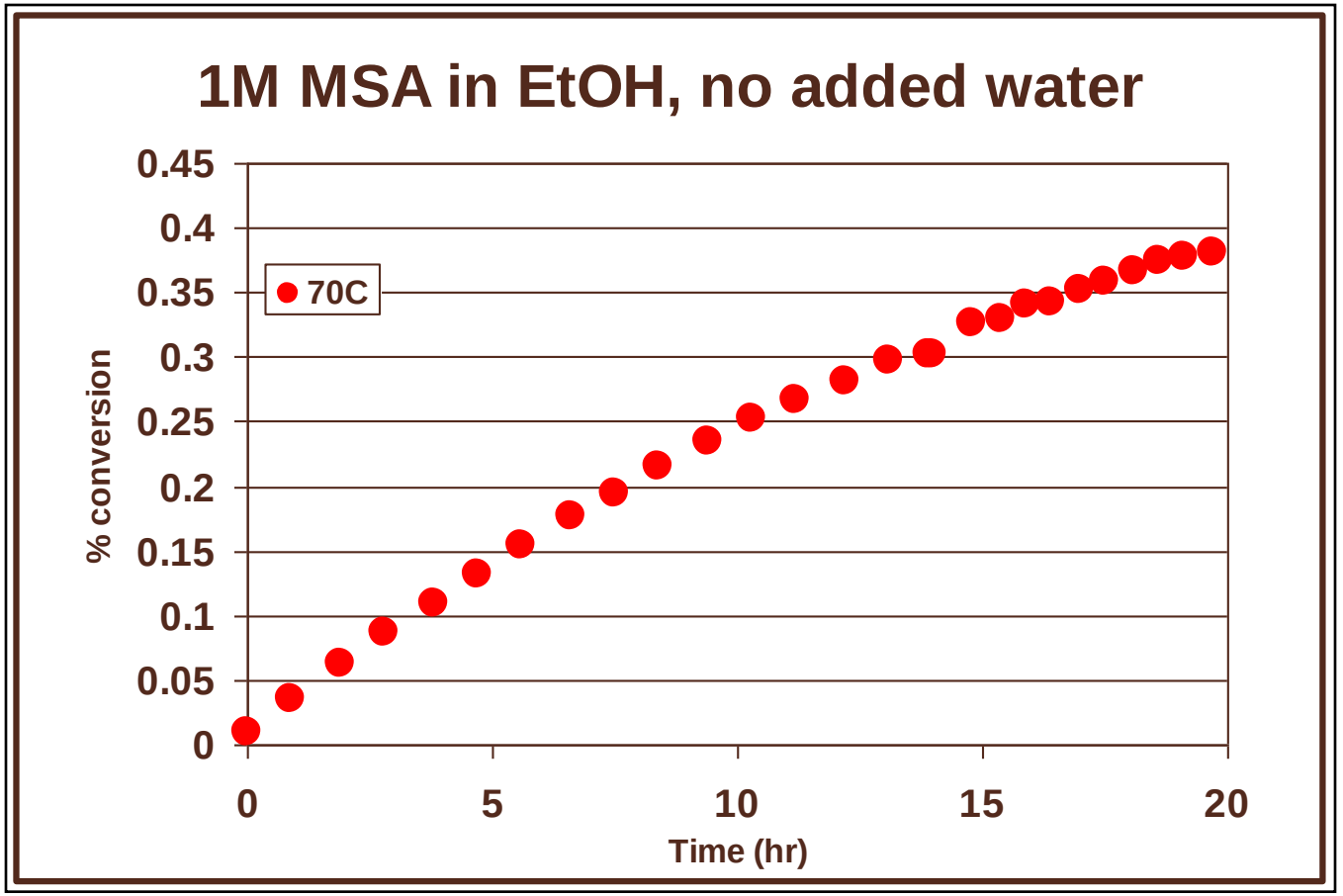
EMS Formation – Effect of Temperature



- Conversion to EMS depends on temperature and time.
  - As one would expect…

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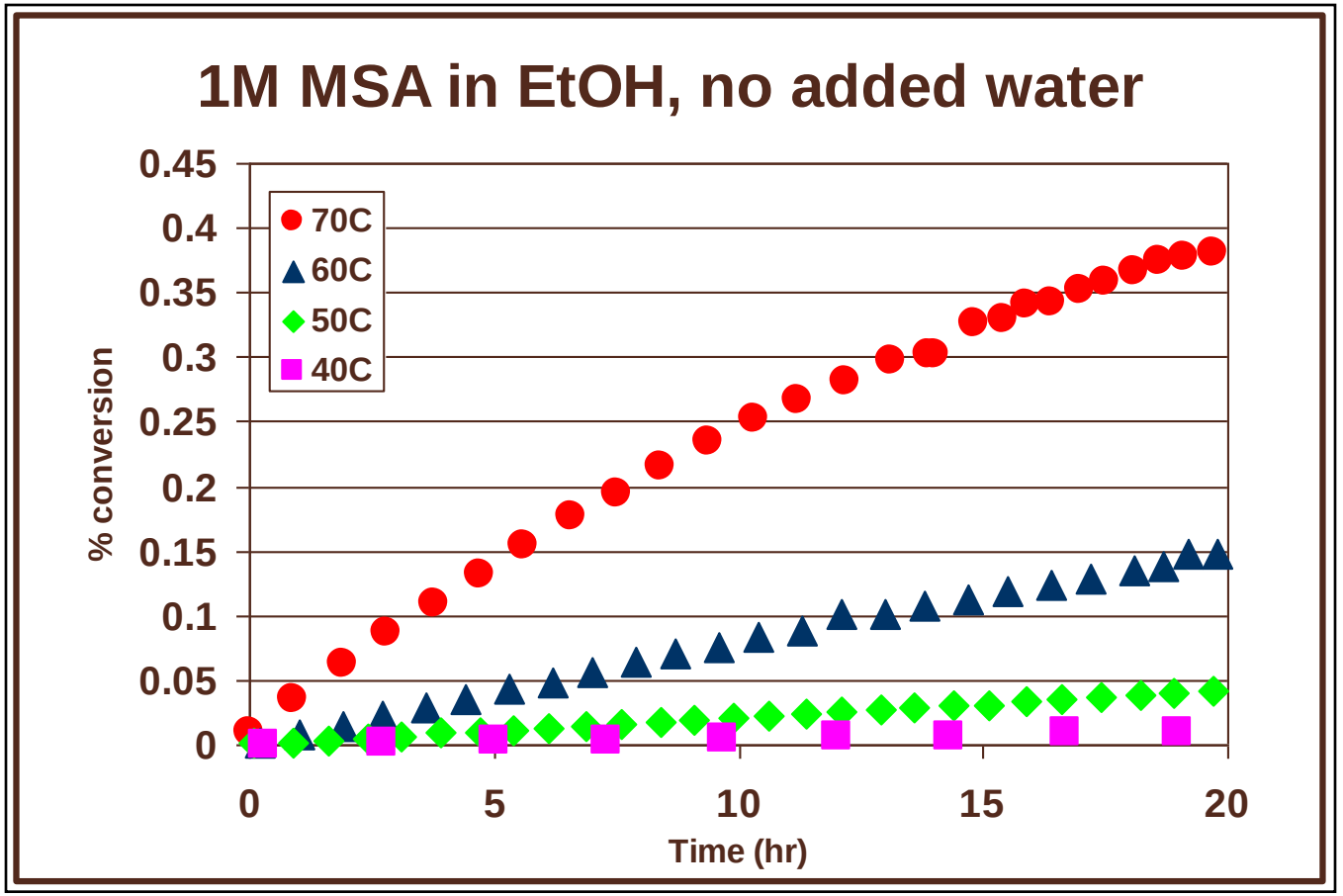
EMS Formation – Effect of Temperature



- Conversion to EMS depends on temperature and time.
  - As one would expect…

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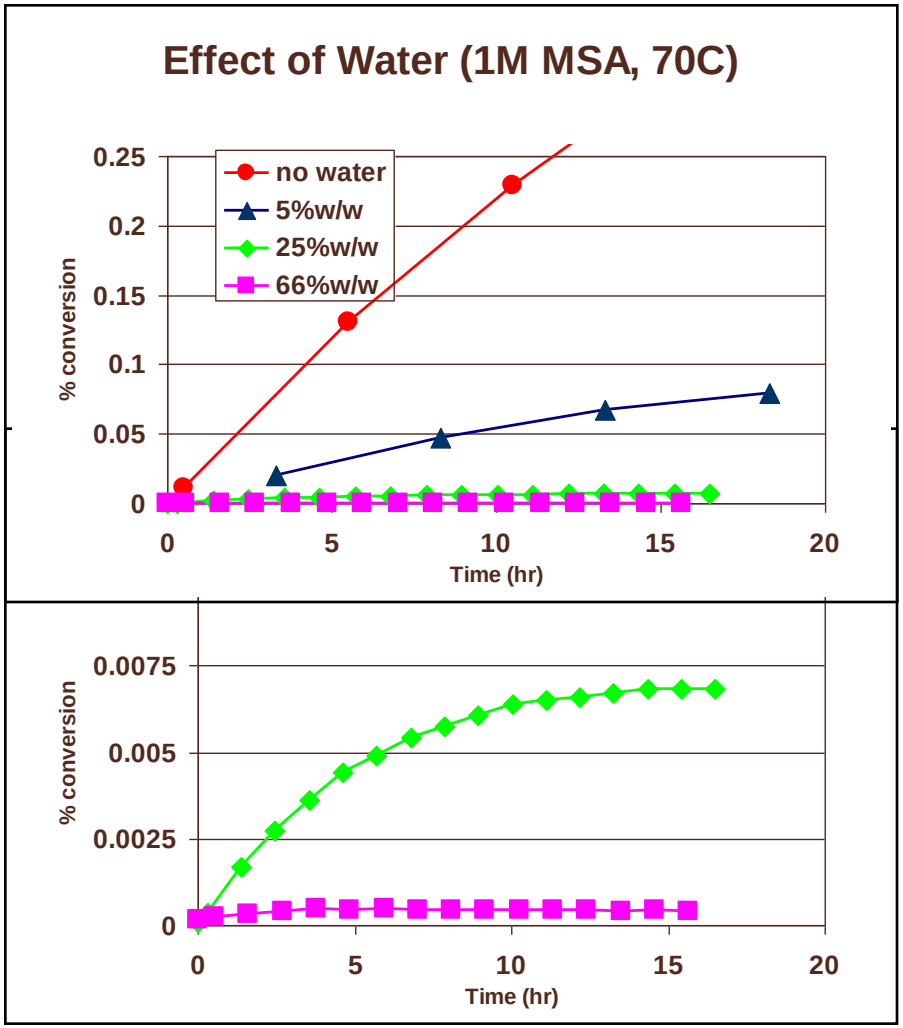
EMS Formation – Effect of Water

- Conversion to EMS is reduced in presence of water
- Even 5%w/w water has significant impact…
- 25%w/w water reduces conversion to <75ppm
  - after 15 hours at 70C



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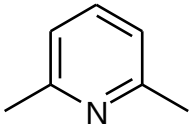
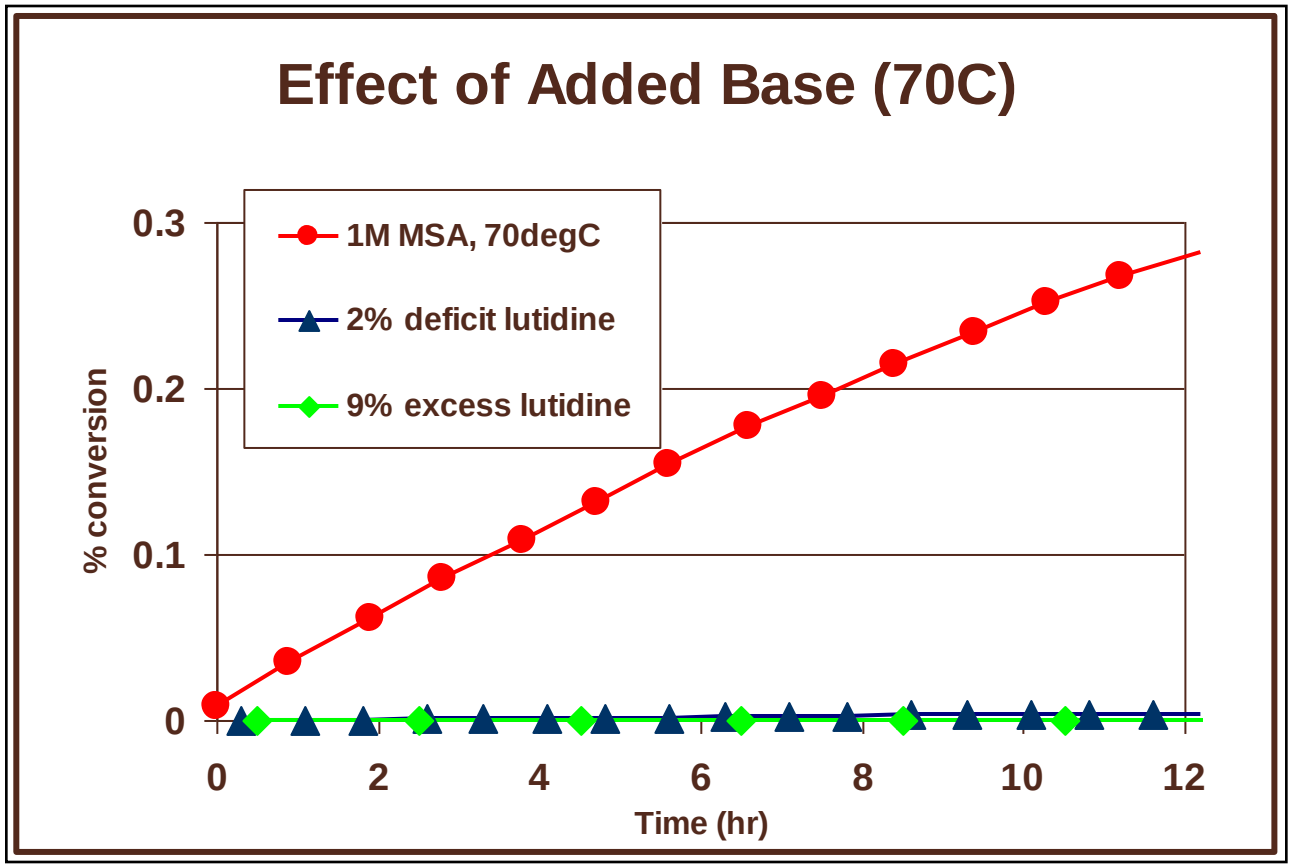
EMS Formation – Presence of 2,6-Lutidine





- Excess lutidine (green trace): Ester Undetectable over background…

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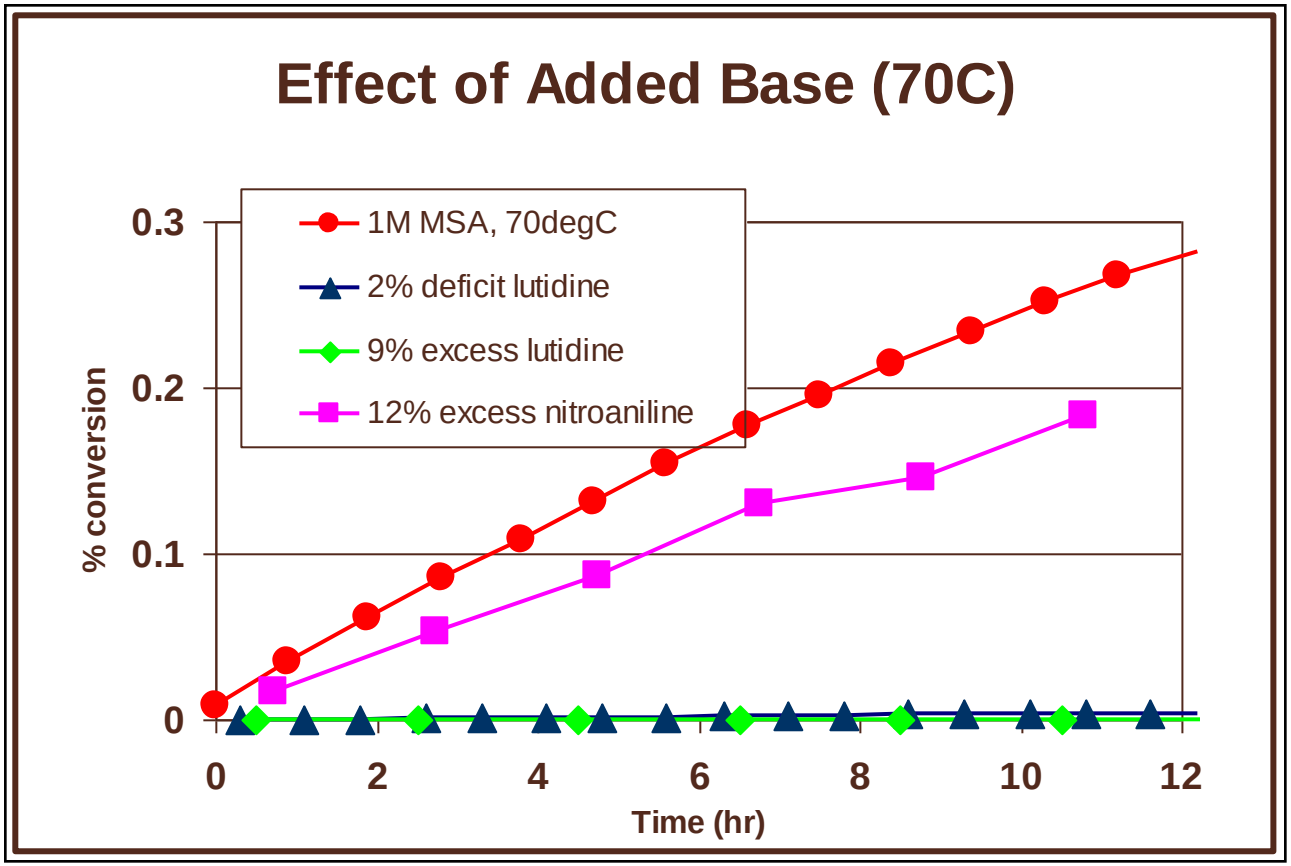
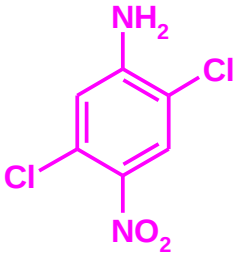
Acidity as a Driver of Forward Rate





Excess phosphoric acid afforded NO DETECTABLE EMS (lutidine:MSA:H_3PO_4 1:1:0.66)

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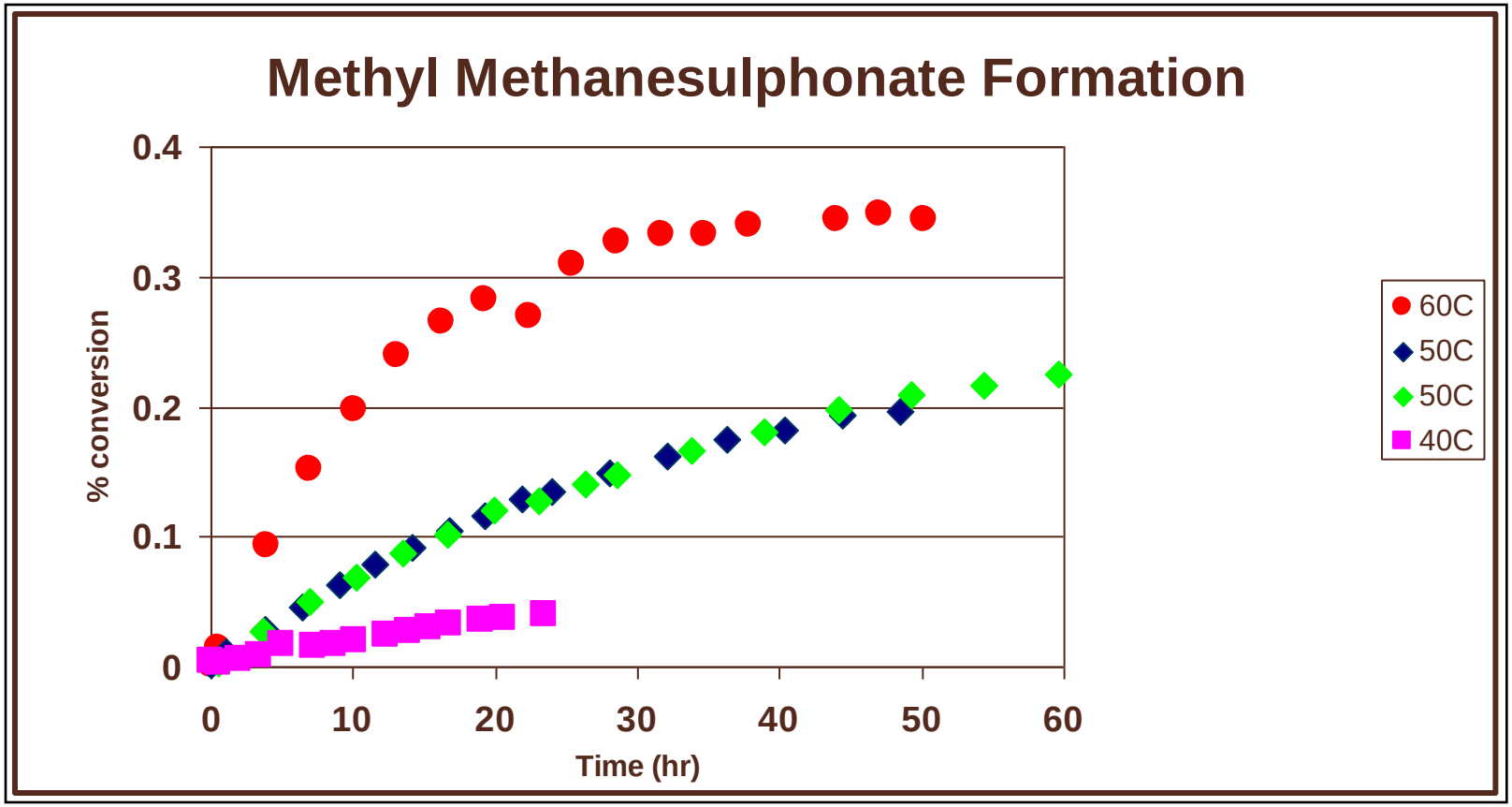
Other Systems - Methyl Mesylate



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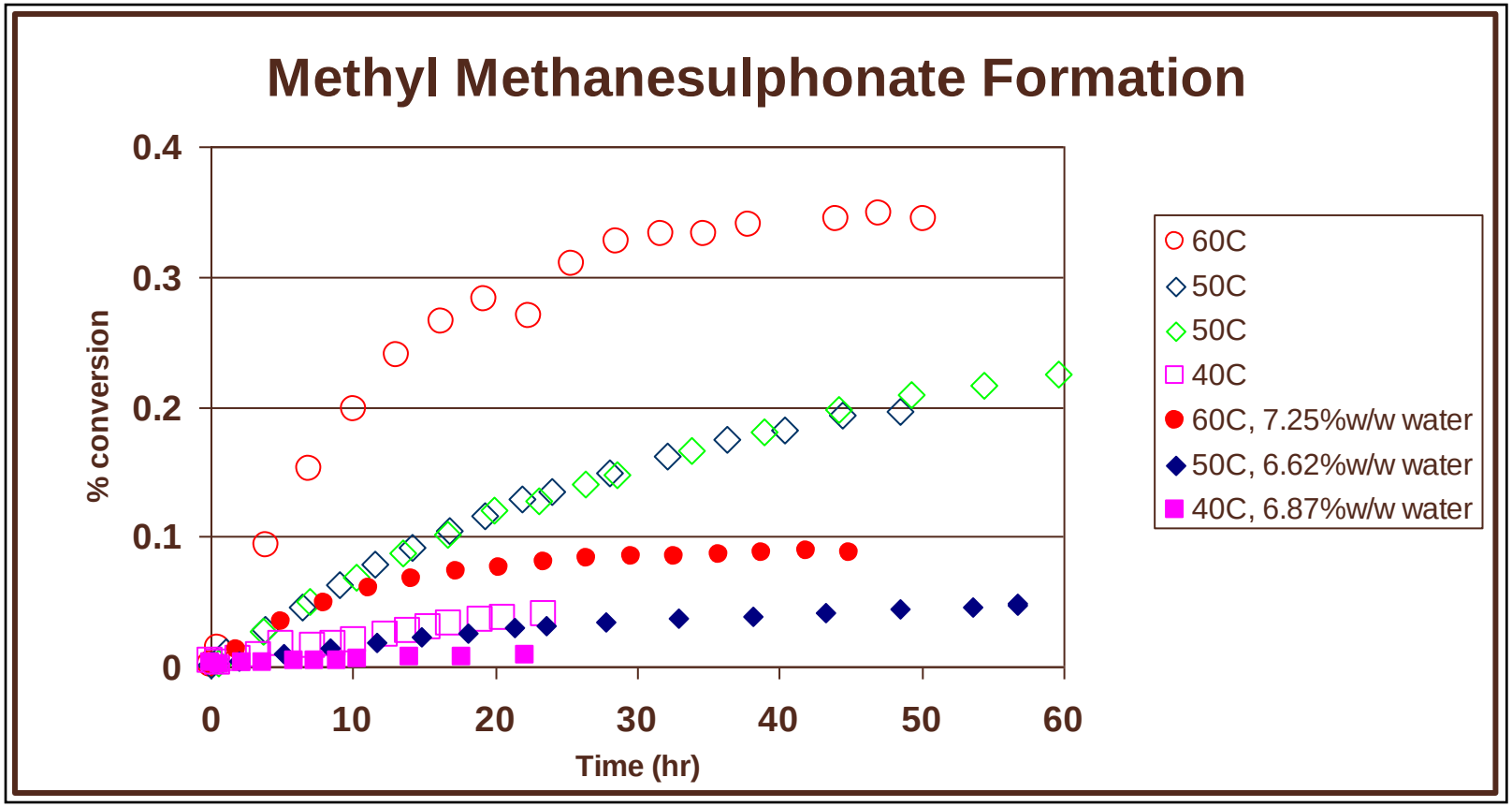
Other Systems – Methyl Mesylate



- As with EMS, no observable reaction seen in presence of lutidine

Teasdale, Eyley, Jacq, Delaney et al,
Org. Process Res. Dev. 2009, 13, 429

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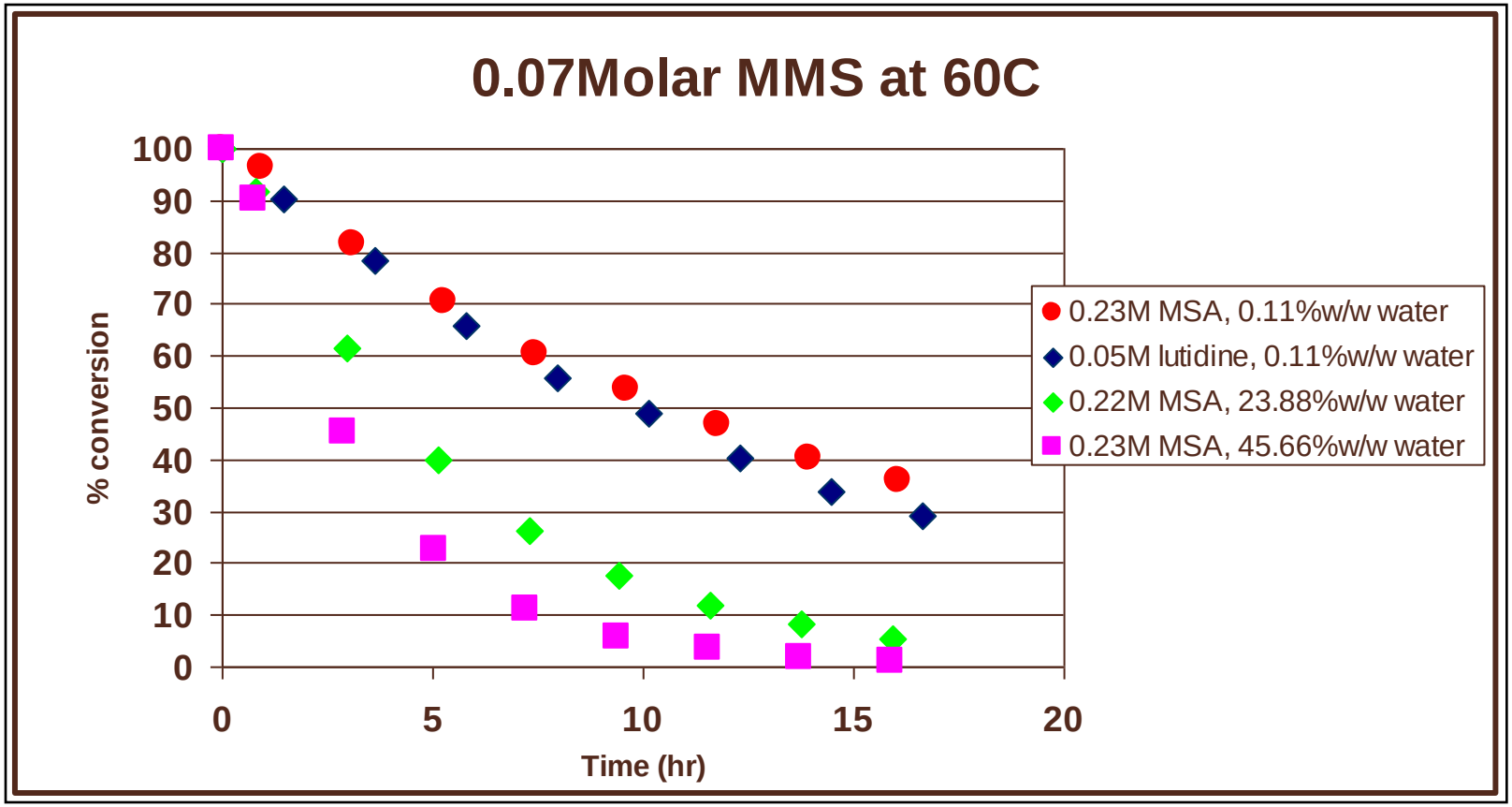
Solvolysis of Methyl Mesylate



- Strong influence of water on sulfonate ester stability
- Little influence of acid or base under these conditions

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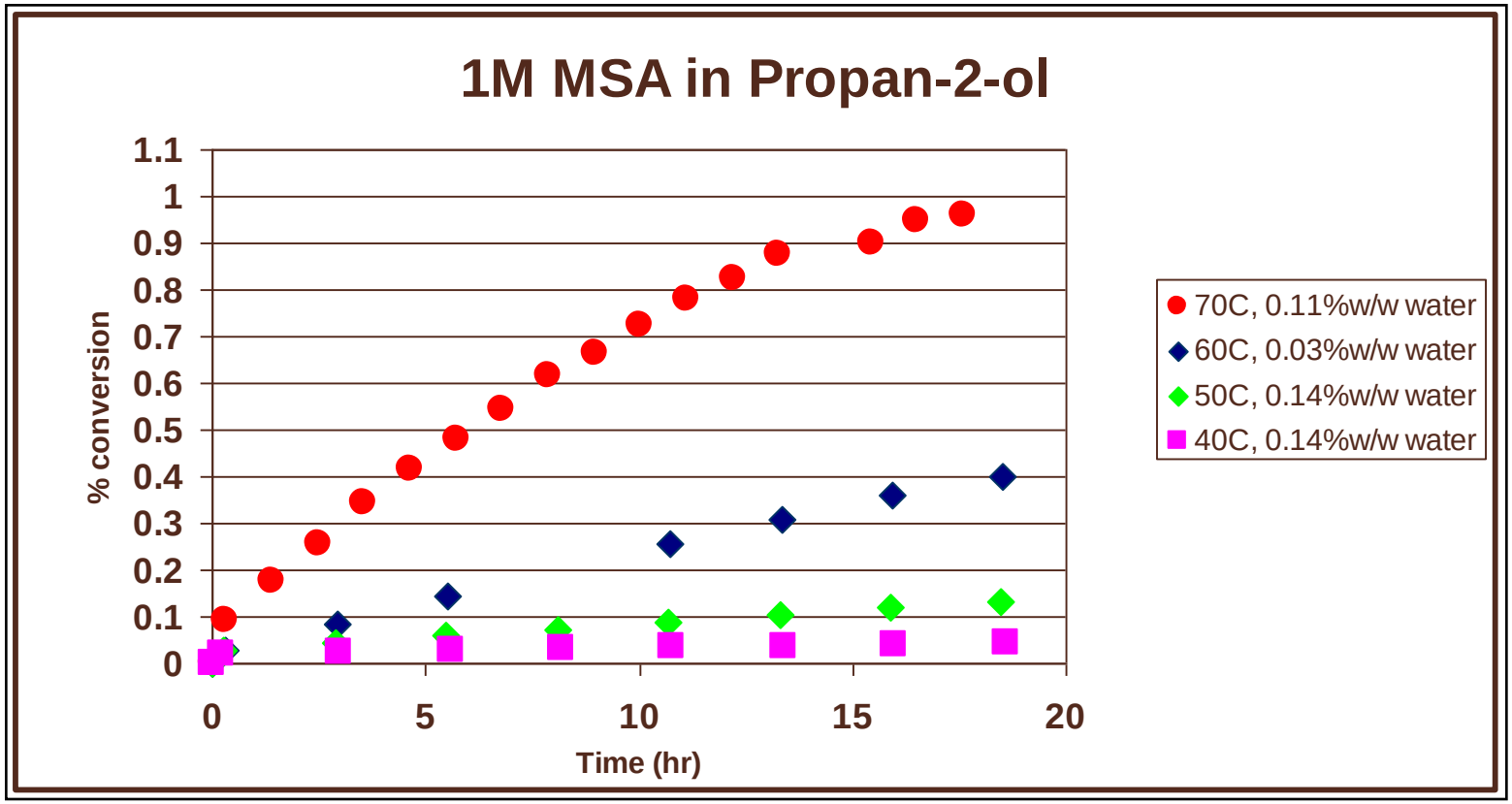
2-Propyl Mesylate Formation



- Profile similar to that of EMS, although levels of IMS formed are higher under anhydrous conditions.

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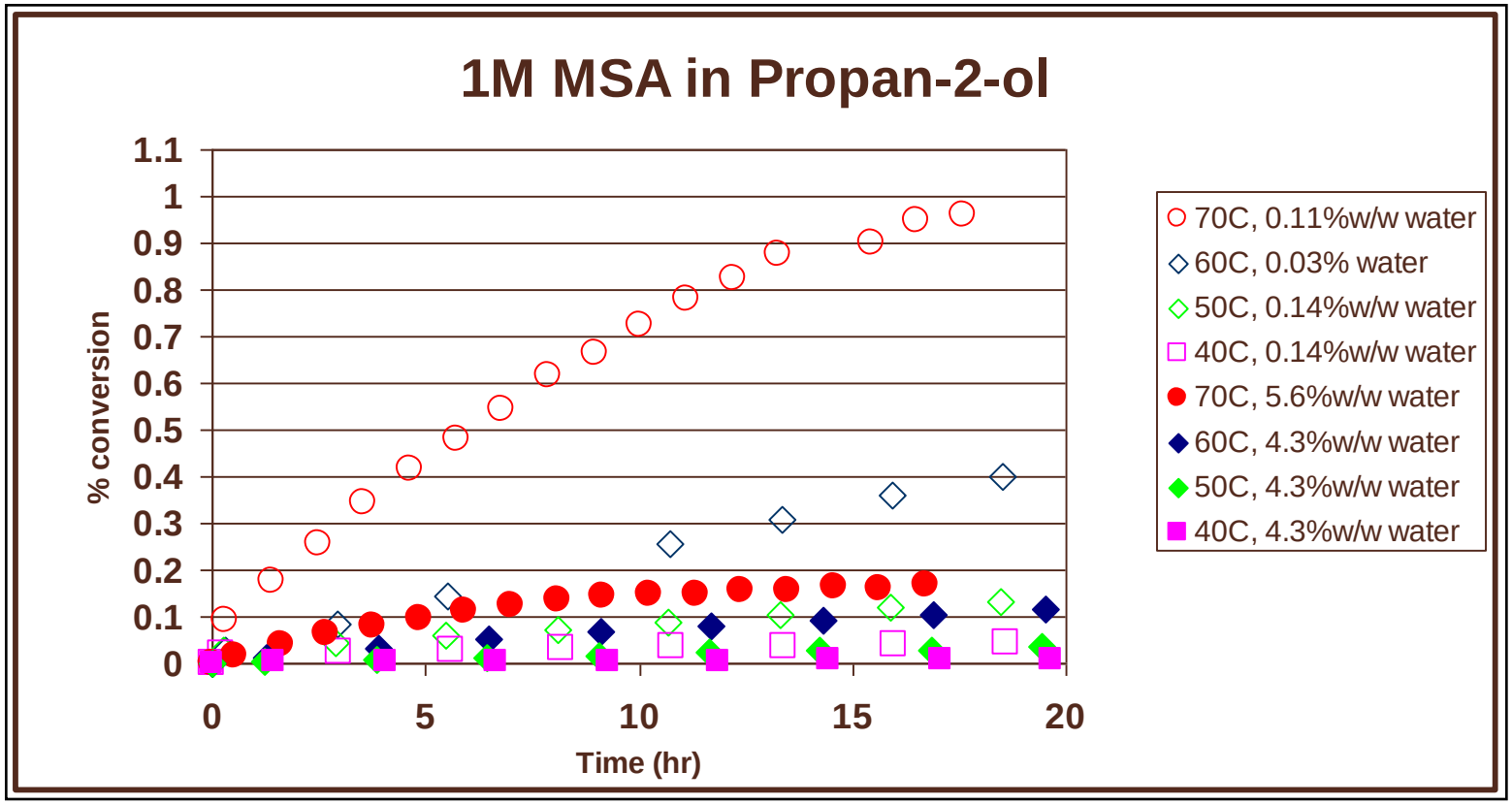
2-Propyl Mesylate Formation



- As with ethyl and methyl mesylate, no observable reaction seen in presence of lutidine

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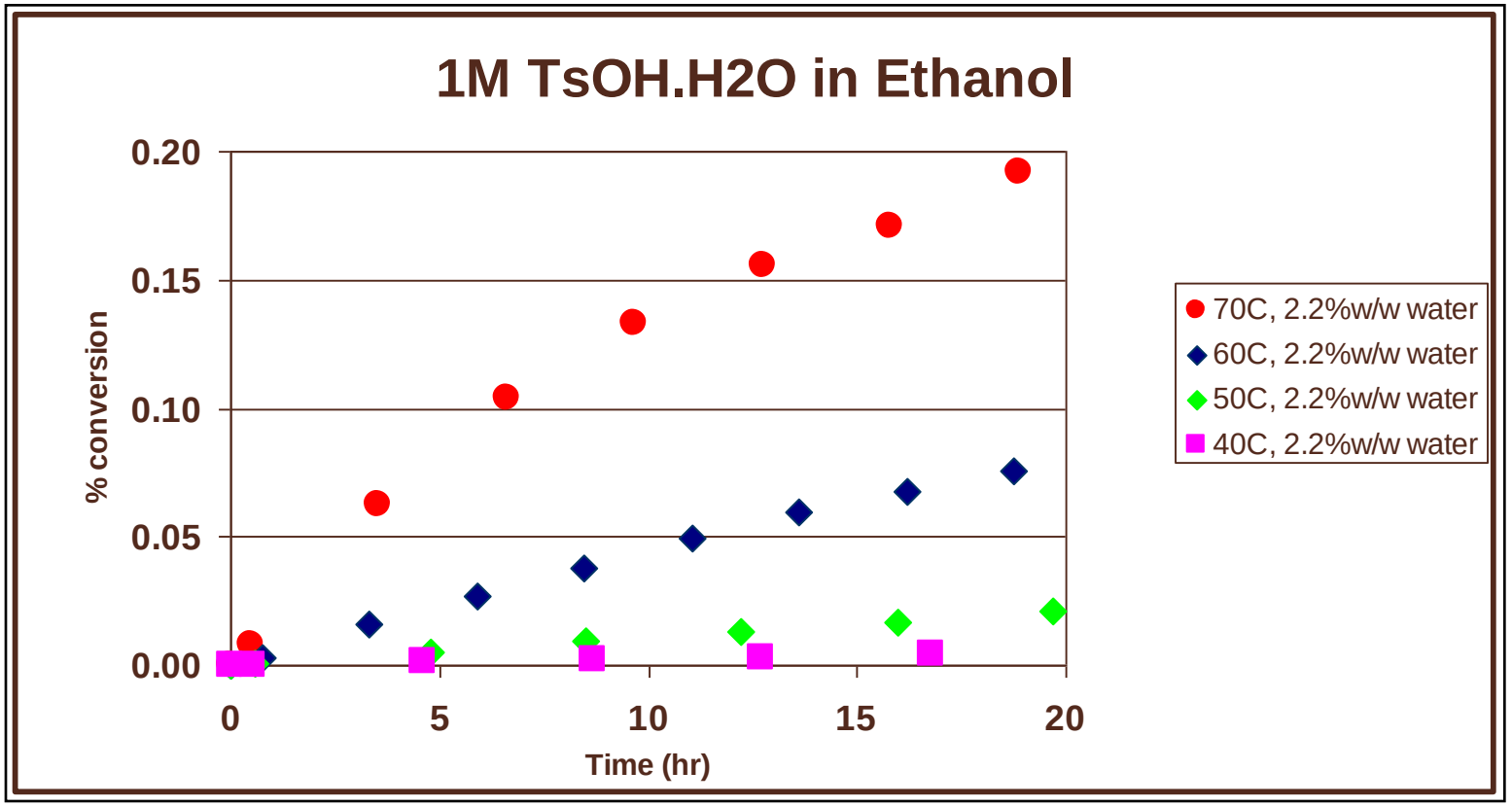
Ethyl Tosylate Formation



NB TsOH available commercially as the monohydrate

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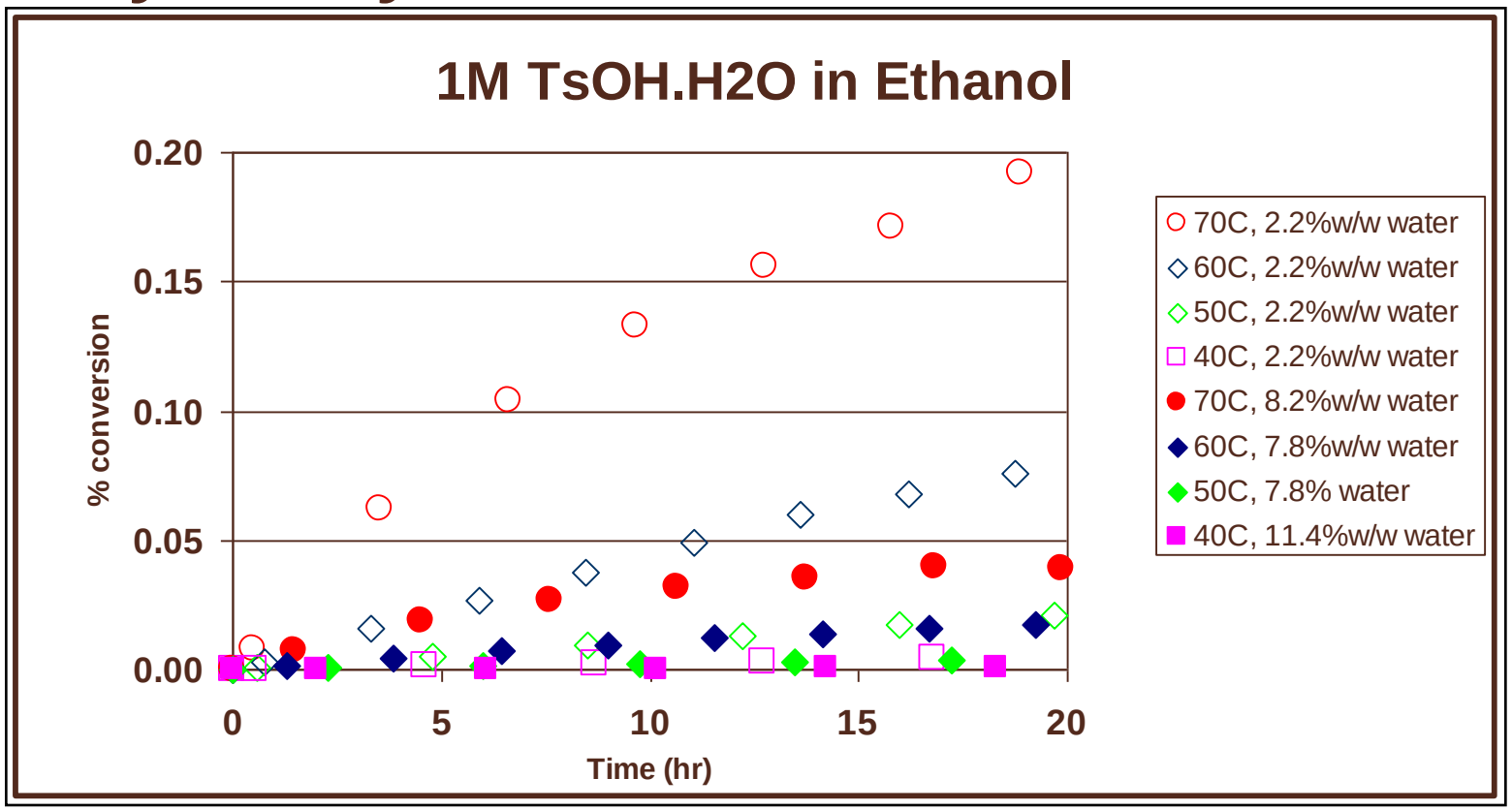
Ethyl Tosylate Formation



- Water reduces ester formation
- Excess 2,6-lutidine eliminates ester formation

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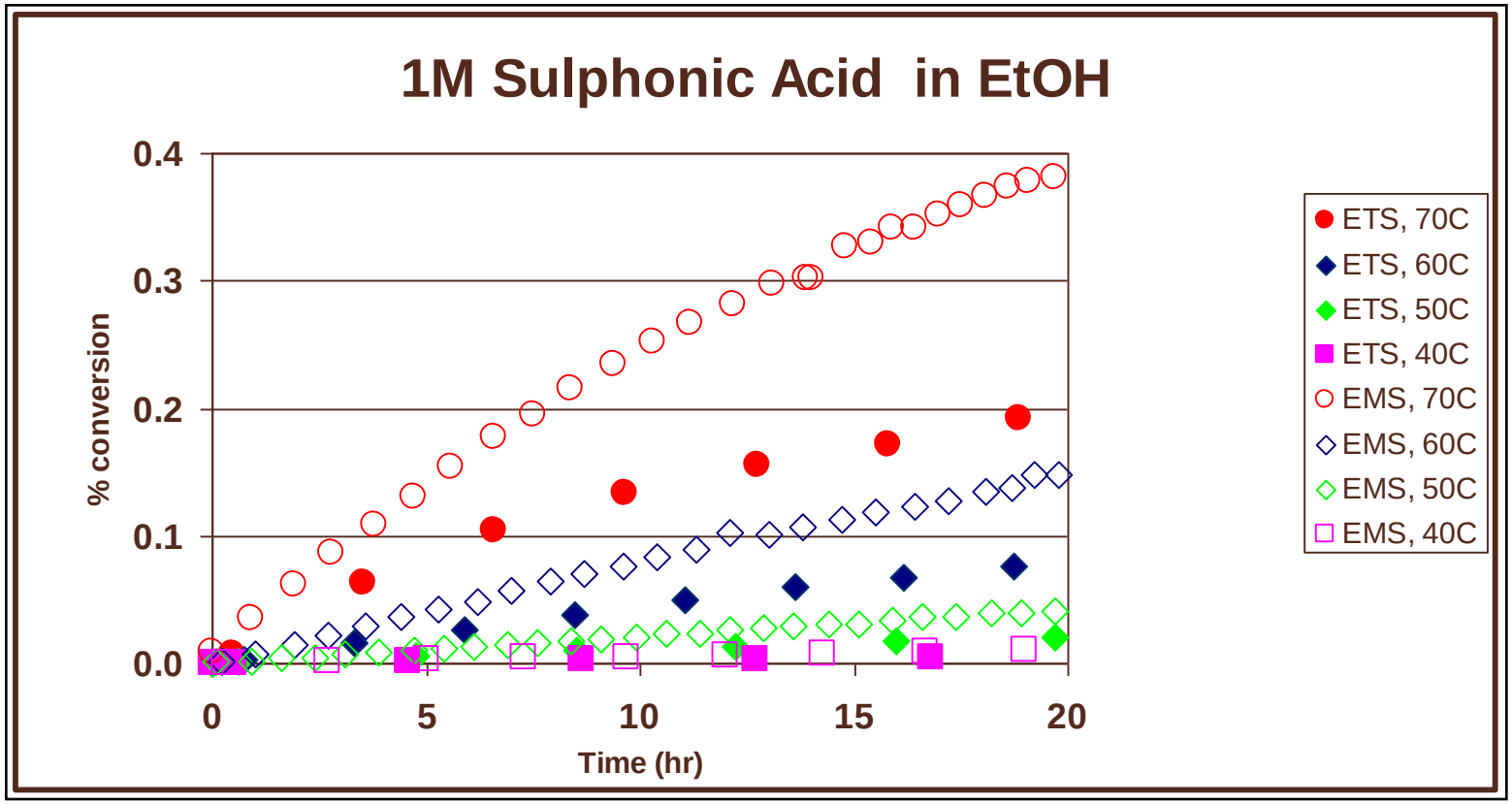
Ethyl Tosylate vs Ethyl Mesylate



- NB TsOH.H2O available commercially as the monohydrate

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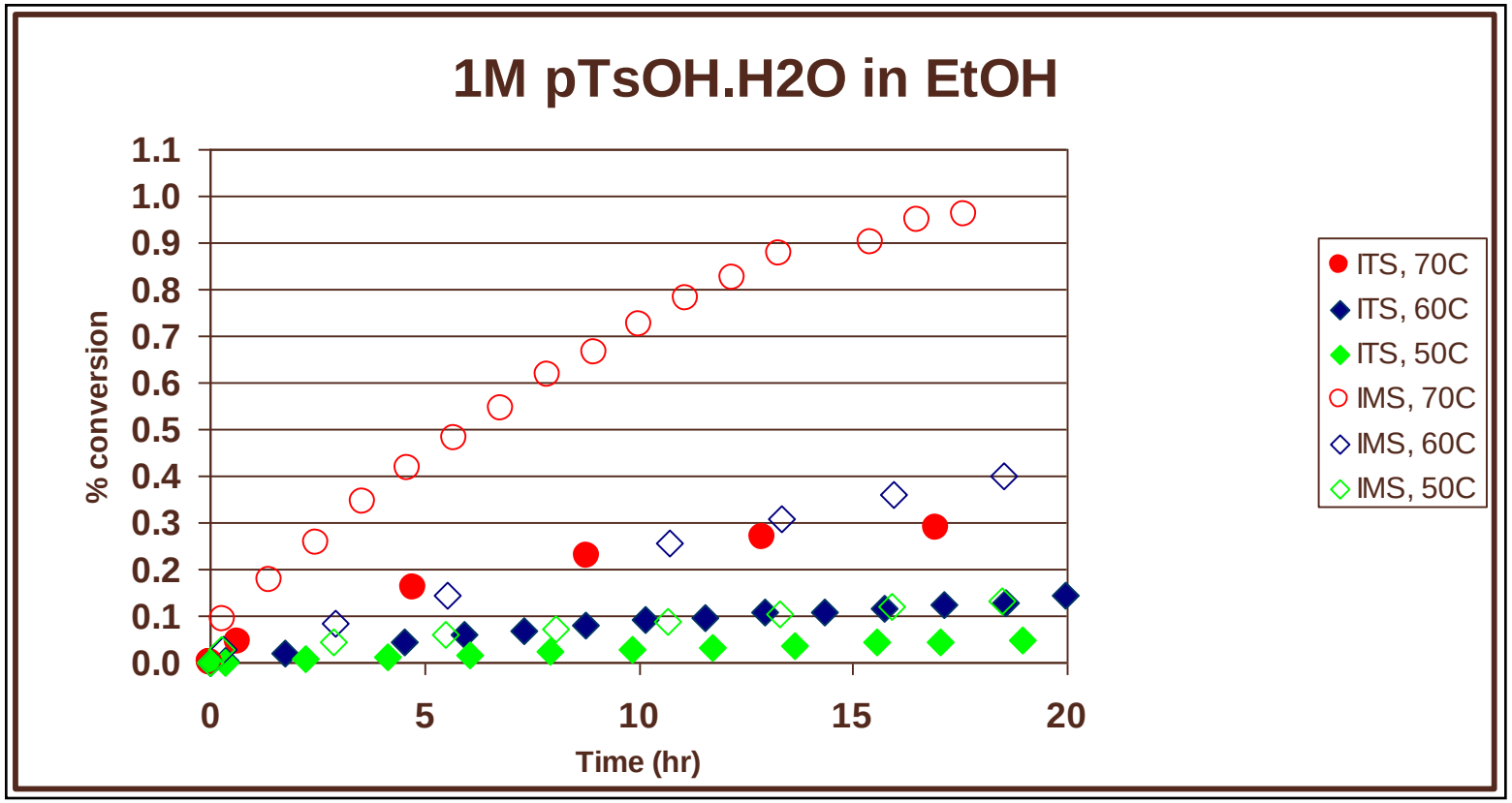
2-Propyl Esters: Tosylate vs Mesylate



- Again, no observable reaction seen in presence of lutidine

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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 stoichiometery.

- 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.

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Learning for Process Design…

- 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.

Viracept

- A common challenge to this work is – ‘what about Viracept – doesn’t this disprove your findings?’

- Background – In Spring 2007 Roche received reports of patients complaining of tablets smelling + nausea
- Tablets ultimately found to be contaminated with EMS
  - Up to 2300ppm.

- Root cause analysis showed that neither MSA nor the manufacturing process itself could be major contributors to the EMS contamination.
- MSA hold tank cleaned with ethanol but, crucially, no tank drying was performed.
- Tank then filled with neat MSA.
  - This created a highly acidic environment

- **REMEMBER mechanism H^+ mediated**
  - EMS formed over several months leading to significant levels in MSA.

Conclusion

- Based on the thorough understanding of the reaction between sulfonic acids and alcohols developed through the PQRI studies it is entirely possible and straight forward 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**

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Acknowledgements

- PQRI
- PQRI Team
  - Steve Eyley / Andrew Teasdale (AZ) - Team Leader.
  - Andrew Lipcynski / Karen Taylor Worth (Pfizer).
  - Kevin Facchine / Dave Elder (GSK)
  - Van Reif (Schering Plough)
  - Rolf Schulte-Oestrich (Roche)
  - Ed Delaney (formerly BMS) - employed as a consultant to the project
  - Simon Golec (Wyeth)
- RIC
  - Karine Jacq / Frank David
- FDA
  - Rick Lostritto

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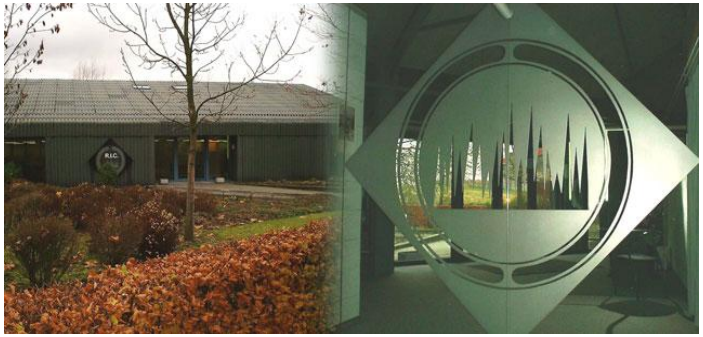
Back Up Slides – For Reference

Research Institute of Chromatography



- RIC is based in Kortrijk, Belgium
  - Director: Prof Pat Sandra.
- *"…involved in the development and promotion of chromatographic know-how…"*
- Particular skills in trace analysis
  - existing methodology developed by RIC in conjunction with Pfizer, employing HS-GC-MS after derivatisation
- RIC Project Personnel
  - R&D Manager: Dr Frank David
  - Analyst: Karine Jacq

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Instrument Design

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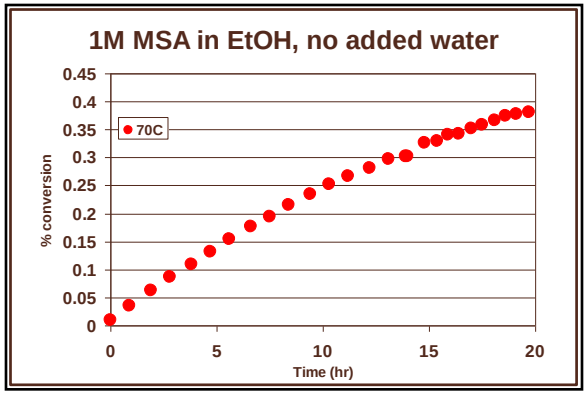
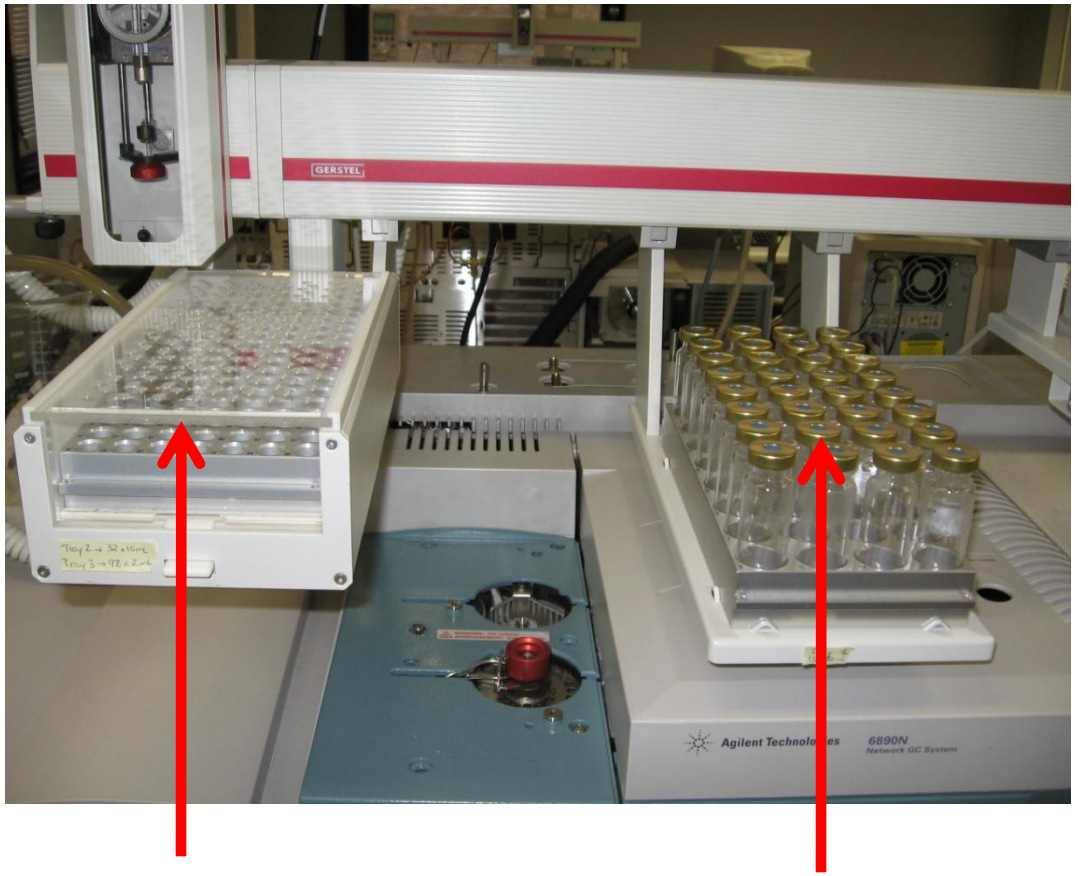
Each point is a separate experiment to build the reaction profile.

- Shown to provide highly robust data…





Heated samples
(MSA solutions)

SHS vials with 2 mL solvent
(MSA, DS and IS added there
before incubation)

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Validation Data for analytical procedure

- Method validation was performed using 1 M solutions of MSA in ethanol spiked with EMS
  - concentration of the EMS was in the range of 5 to 500 µg/mL. (corresponds to a 0.005 to 0.5 % (potential) conversion of MSA into EMS).
  - Using spiked solutions, a 6 level (+blank) calibration curve was made. The results are summarized in Table 1.

Validation Data for analytical procedure

Key Data:

Linearity: Linear over the range 5 –500 μg/ml EMS (R^2 >0.999).

Precision:

RSD for EMS (as Et-TPFB derivative) measured relative to the internal standard 2 (d5-Et-TPFB) was:

- 3 % at 5 μg level and better than 1 % at the 50 μg level.

Limit of Detection: 0.5μg/ml

Limit of Quantification: 1 μg/mL, corresponding to 0.001 % conversion.

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Validation Data for analytical procedure

Table 1: Validation of derivatisation-SHS-GC-MS method

The table shows the raw peak areas for IS1 (column 2), for MMS derivative (column3), for IS2 and EMS derivatives (columns 4 and 5) and the relative peak area (Et-TPFB versus IS2) (column 6) in function of EMS concentration spiked in reaction mixture, at room temperature (column 1). Relative standard deviations (RSDs) at all levels and at 5 and 50 µg/mL, and linearity data are given. EMS and d5-EMS were not detected.

EMS (µg)	PFA	Me-TPFB	Et-TPFB d5	Et-TPFB	Rel Area
0	280134	2016	200163	333	0.002
5	300742	7741	223447	5937	0.027
5	294712	1922	222579	6252	0.028
5	307885	2030	229717	6421	0.028
25	286297	1921	209304	26984	0.129
50	329687	2192	245241	61758	0.252
50	330967	6160	248046	62180	0.251
50	328756	2117	244613	61550	0.252
125	339988	3245	248132	163159	0.658
275	335488	2396	129735	179660	1.385
500	317337	4587	228441	582145	2.548
RSD all	14.3		15.5		
RSD 5µg	2.2		1.7	4.0	3.1
RSD 50µg	0.3		0.7	0.5	0.2
			slope		0.00509
			intercept		0.00138
			R^2		0.99988

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Publications

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Development and validation of an automated static headspace gas chromatography–mass spectrometry (SHS-GC–MS) method for monitoring the formation of ethyl methane sulfonate from ethanol and methane sulfonic acid

Karine Jacq[a], Ed Delaney[b], Andrew Teasdale[c], Steve Eyley[c], Karen Taylor-Worth[d], Andrew Lipczynski[d], Van D. Reif[e], David P. Elder[f], Kevin L. Facchine[g], Simon Golec[h], Rolf Schulte Oestrich[i], Pat Sandra[a], Frank David[a,*]

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Article

Mechanism and Processing Parameters Affecting the Formation of Methyl Methanesulfonate from Methanol and Methanesulfonic Acid: An Illustrative Example for Sulfonate Ester Impurity Formation

Andrew Teasdale, Stephen C. Eyley, Ed Delaney, Karine Jacq, Karen Taylor-Worth, Andrew Lipczynski, Van Reif, David P. Elder, Kevin L. Facchine, Simon Golec, Rolf Schulte Oestrich, Pat Sandra, and Frank David

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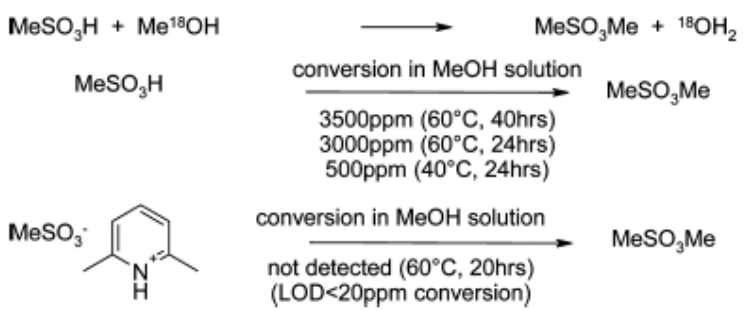

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