

Feasibility of iChemExplorer for Solution Stress Studies

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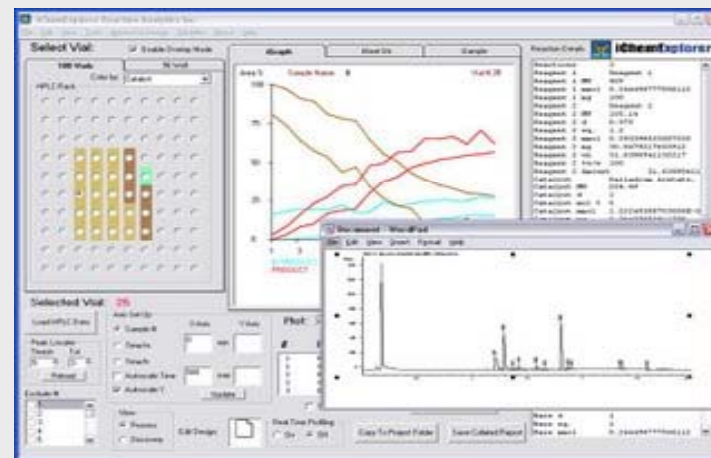


- Evaluate the feasibility of using iChemExplorer to improve efficiency of solution stress studies
 - Acid stress
 - Base stress
 - Oxidative stress



Hardware

- Sample tray with heating block
- T/stir control unit
- T range: ambient to 150 °C
- Compatible with Agilent 1100/1200
- Standard HPLC vials

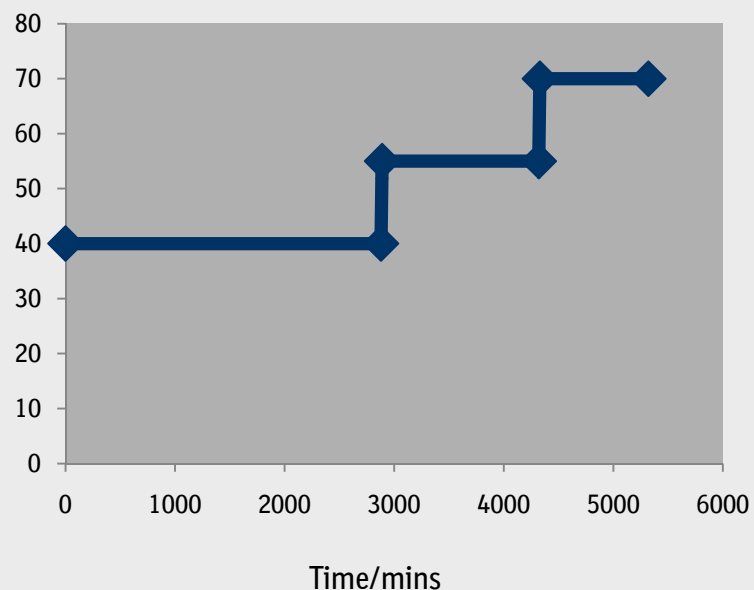


Software

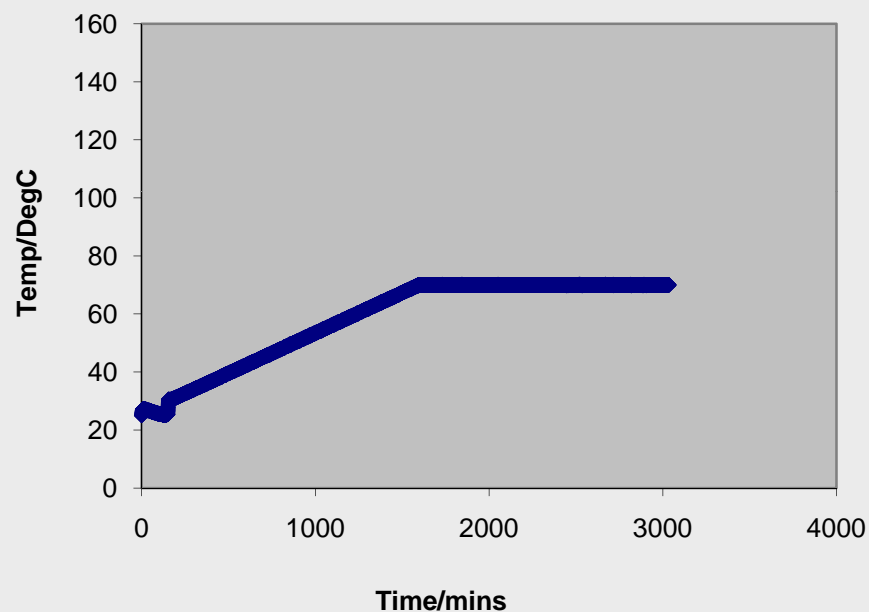
- Add-in to ChemStation
- Temperature programming
- Sample queue
- Real time monitoring
- Automatic workbook for each vial
- Kinetic analysis (e.g., activation energy)

- Conventional approach
 - 5-20% degradation, or
 - 40°C for up to 2 weeks (maximum duration)
 - Stress duration: a few days to 2 weeks
- iChemExplorer
 - 5-20% degradation, or
 - Kinetically equivalent to 40°C for up to 2 weeks
 - Two day program: see next slide
 - Four day program: see next slide
 - Stress duration: no more than 2 days or 4 days depending on the T program
- Potential benefit of using iChemExplorer
 - Potentially reduce the study duration from up to 2 weeks to up to 2 days

Two iChemExplorere temperature programs evaluated for accelerated solution stress



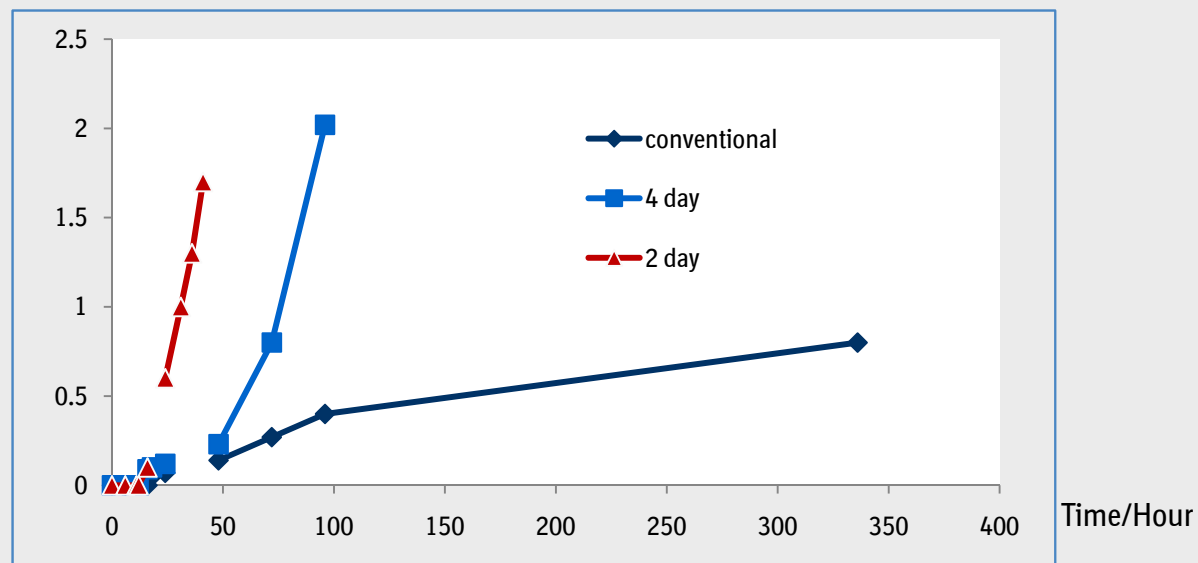
4 day isothermal
program



2 day program
1 day non-isothermal
+ 1 day isothermal

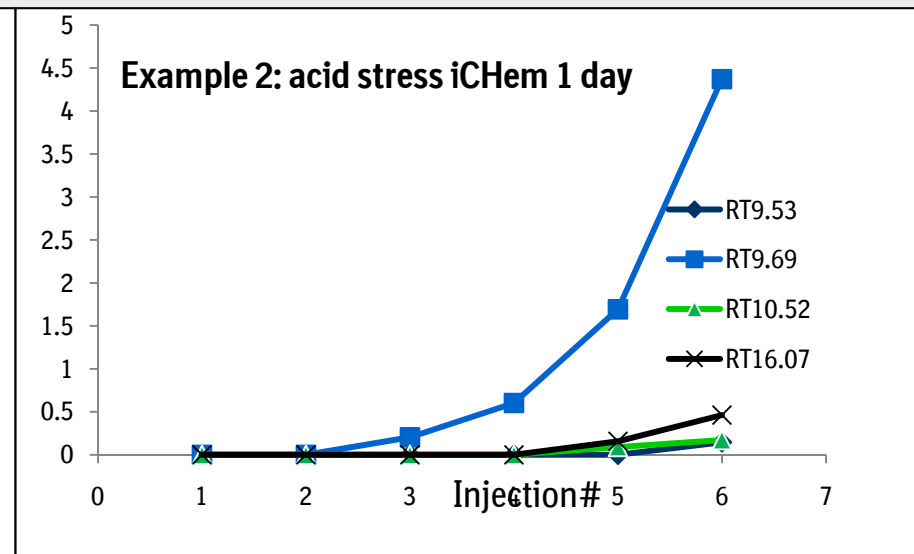
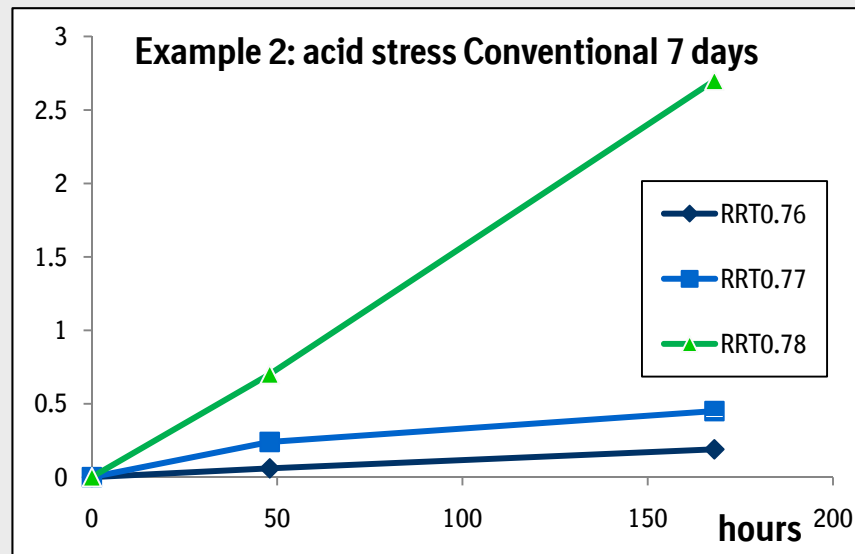
Example 1: Stable compound (in solution)

- Degradation pathways
 - 1 degradation product observed under acid stress
 - Degradation pathway under the 2 day or 4 day iChemExplorer experimental designs is consistent with the conventional approach, regardless the higher T
- Percent degradation under acid stress
 - Both the 2 day and 4 day iChemExplorer programs yielded more degradation products than the 14 day conventional approach
- Assessment
 - No risk to use the 2 day iChemExplorer program to replace the 14 day conventional approach



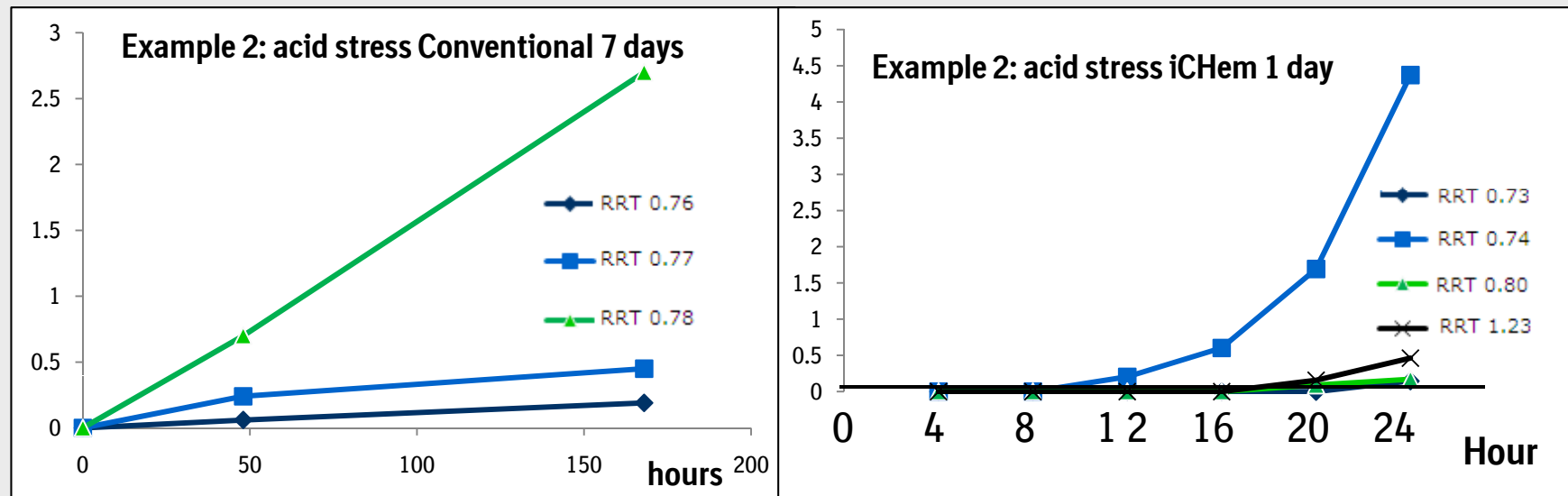
Example 2: Not so stable compound (in solution)

- Degradation pathways
 - After the 1 day T ramping, similar degradations observed with those observed after 7 days of conventional approach
- Percent degradation
 - Comparable degradations observed after the 1 day T ramping with those observed after 7 days of conventional approach
- Assessment: Low risk to use a 1 day iChem program to replace a 7 day conventional study



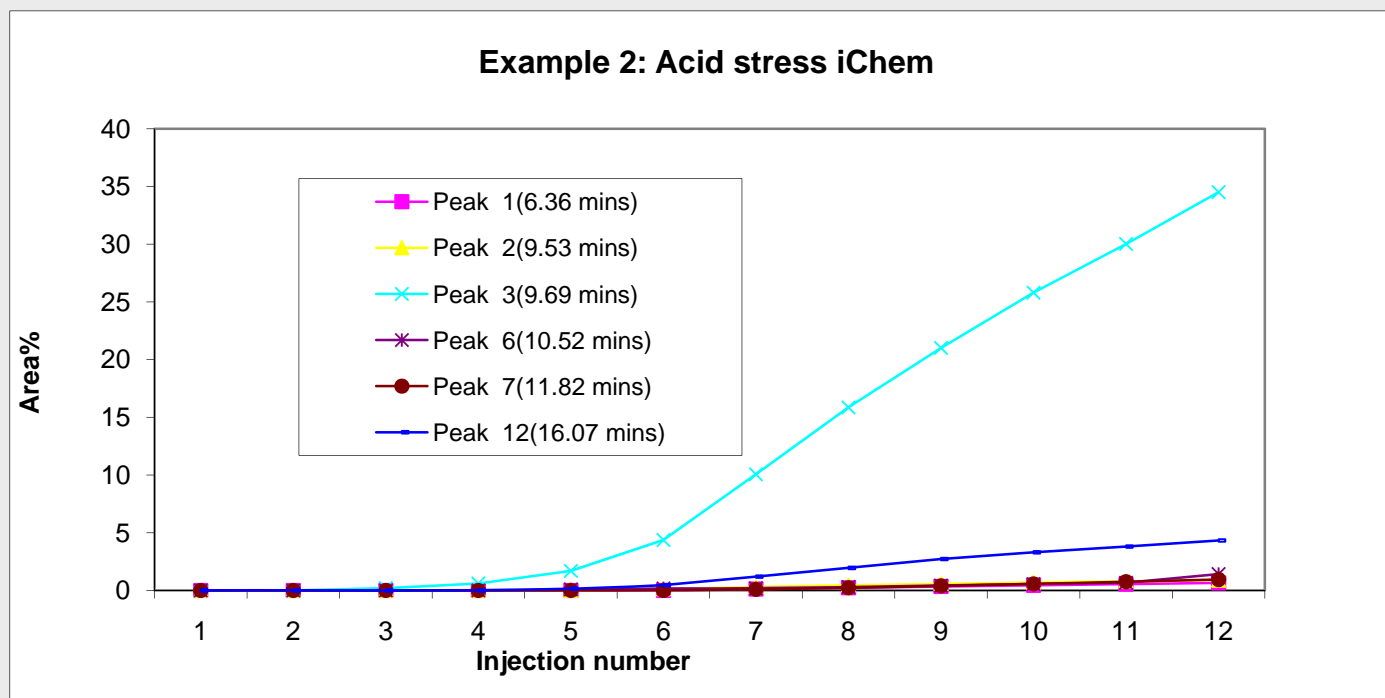
Example 2: Not so stable compound (in solution)

- Degradation pathways
 - No degradation observed under basic and neutral conditions with both manual and iChem
 - After the 1 day temperature ramping, similar degradations observed with those observed after 7 days of conventional approach
- Percent degradation
 - Comparable degradations observed after the 1 day temperature ramping with those observed after 7 days of conventional approach
- Assessment: Low risk to use a 1 day iChem program to replace a 7 day conventional study



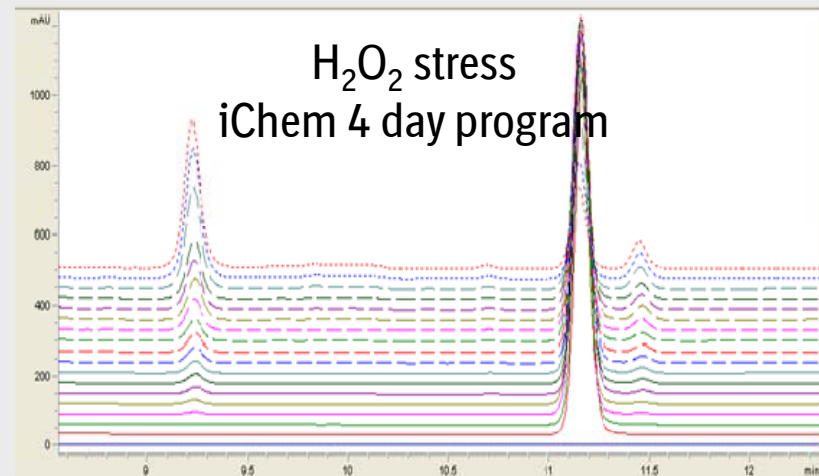
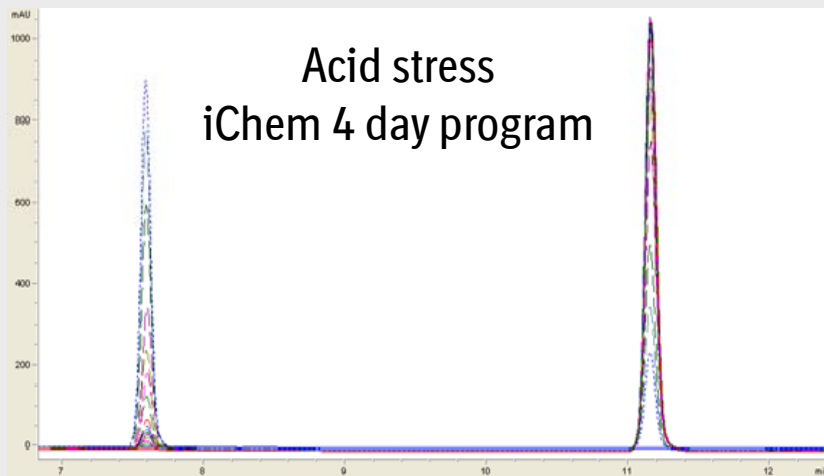
Example 2: Not so stable compound

- After the stress using the full 2-day iChem study, a couple of more degradation products were observed at very low levels on the second day, however, the main degradation products remain unchanged
- For MV, the 1 day stress can be sufficient; for elucidation of unknown degradation products, the 2 day program can be useful for this kind of compound



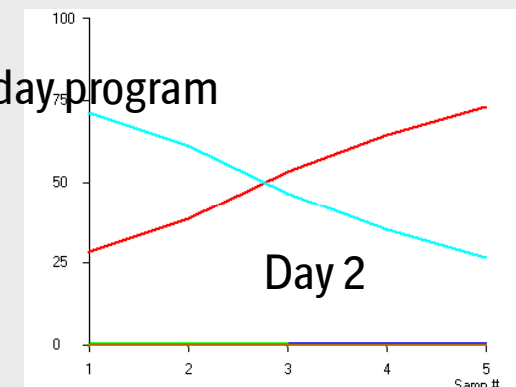
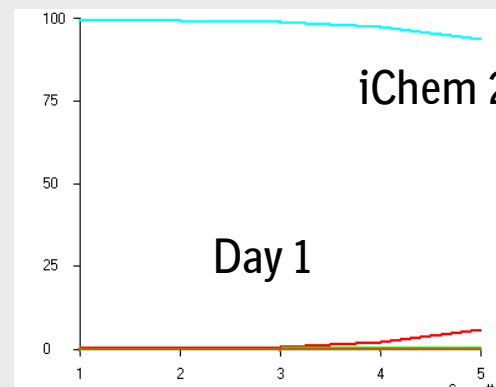
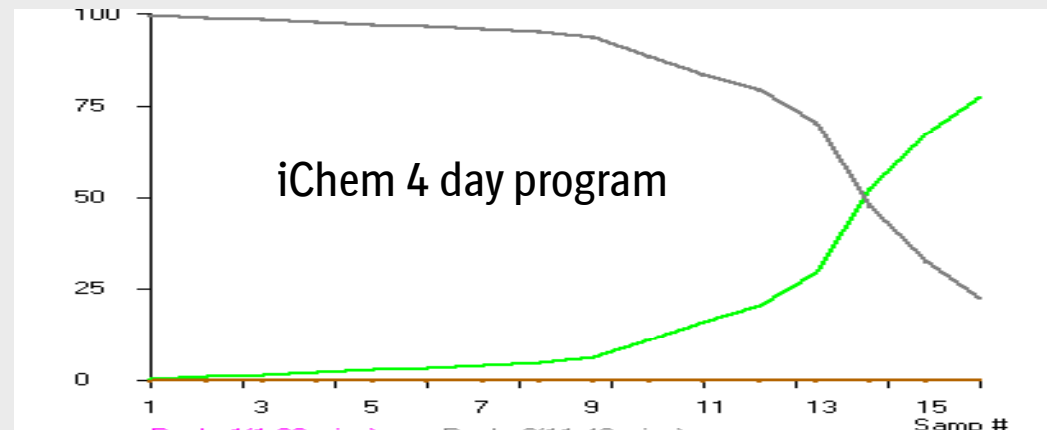
Example 3: Unstable compound (in solution)

- Compound 3 is stable in basic solution, but unstable in acidic and H_2O_2 (0.3%) solutions
- However, these hydrolysis and oxidative degradation pathways are very specific, increase T does not increase the numbers of degradation products
- Assessment: No risk to use iChemExplorer for solution stress studies for this kind of compound



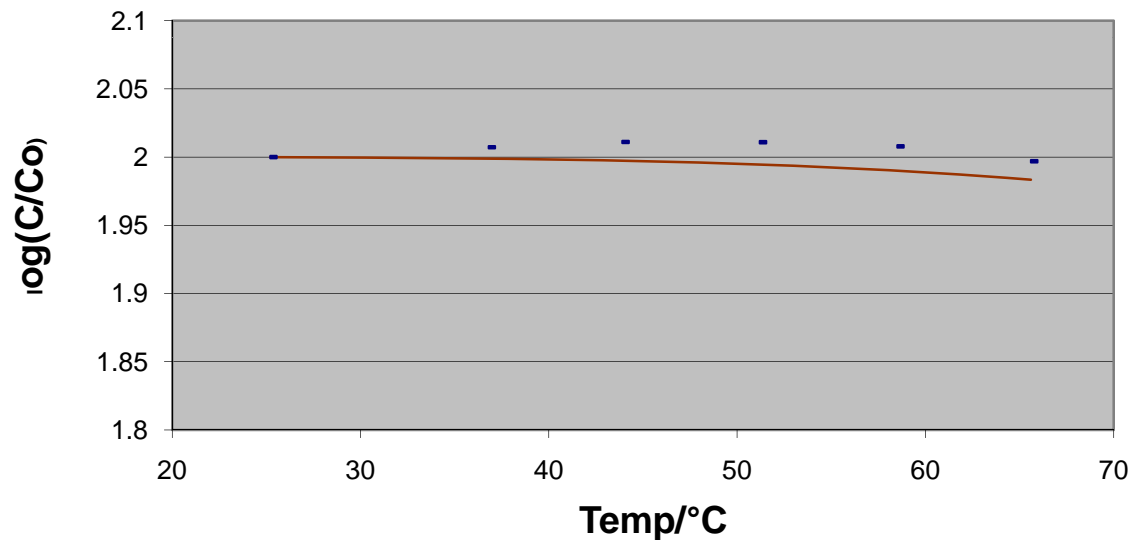
Example 3: Unstable compound(in solution)

- The 2-day iChem stress result is equivalent to the 4-day result
- For MV purpose, an 1-day T ramping is sufficient



Example 3: Unstable compound(in solution)

Example 3: Acid stress kinetics



SumSquares=1.2E-07

$t_{1/2}(25)=1.6E+03$ h

$t_{1/2}(50)=1.2E+02$ h

$t_{1/2}(75)=1.3E+01$ h

$t_{1/2}(100)=1.9E+00$ h

$k(25)=4.2E-04$ h⁻¹

$k(50)=5.8E-03$ h⁻¹

$k(75)=5.4E-02$ h⁻¹

$k(100)=3.7E-01$ h⁻¹

$k=Ae^{-Ea/RT}$

$A=1.82E11$ h⁻¹

$Ea=83.46$ KJ/mole

- The feasibility studies with compounds of different stability demonstrated that iChemExplorer can be a simple yet practical tool in improving efficiency of solution stress stability studies
- The non-isothermal T ramping program utilized both the T for accelerated stress and offered the complete trending information to prevent overstress (e.g., formation of secondary degradation products at higher T); the second day 70°C isothermal stress of the two day iChem program is only necessary for relatively stable compounds
- If used properly, the stress duration can be reduced from up to 2 weeks to up to 2 days

Acknowledgement



Mike Lopez, Reaction Analytics Inc.