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Quantitative Gas Evolution Analysis via Combination of Online Thermal Mass flow and Mass Spectrometry Data

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Introduction

- **Gas evolution from chemical reactions are one of the key hazards of concern when scaling up Pharmaceutical processes from the laboratory to large pilot plant and/or manufacturing equipment.**
- **The gas is often produced from the intended synthetic reaction, but may also be generated by side reactions, process quenching, and/or waste stream decomposition.**
- **The hazards associated with gas evolution are reactor pressurization due to inadequate venting, emission of toxic or environmentally harmful species, and generation of flammable atmosphere.**
- **Mitigation techniques often include appropriately sized vents, effluent scrubbing, thermal oxidizers, and inerted exhaust.**
- **We’ve developed a multi-instrument technique to identify and quantitate evolved gases resulting from our chemical processes during hazard evaluation studies.**

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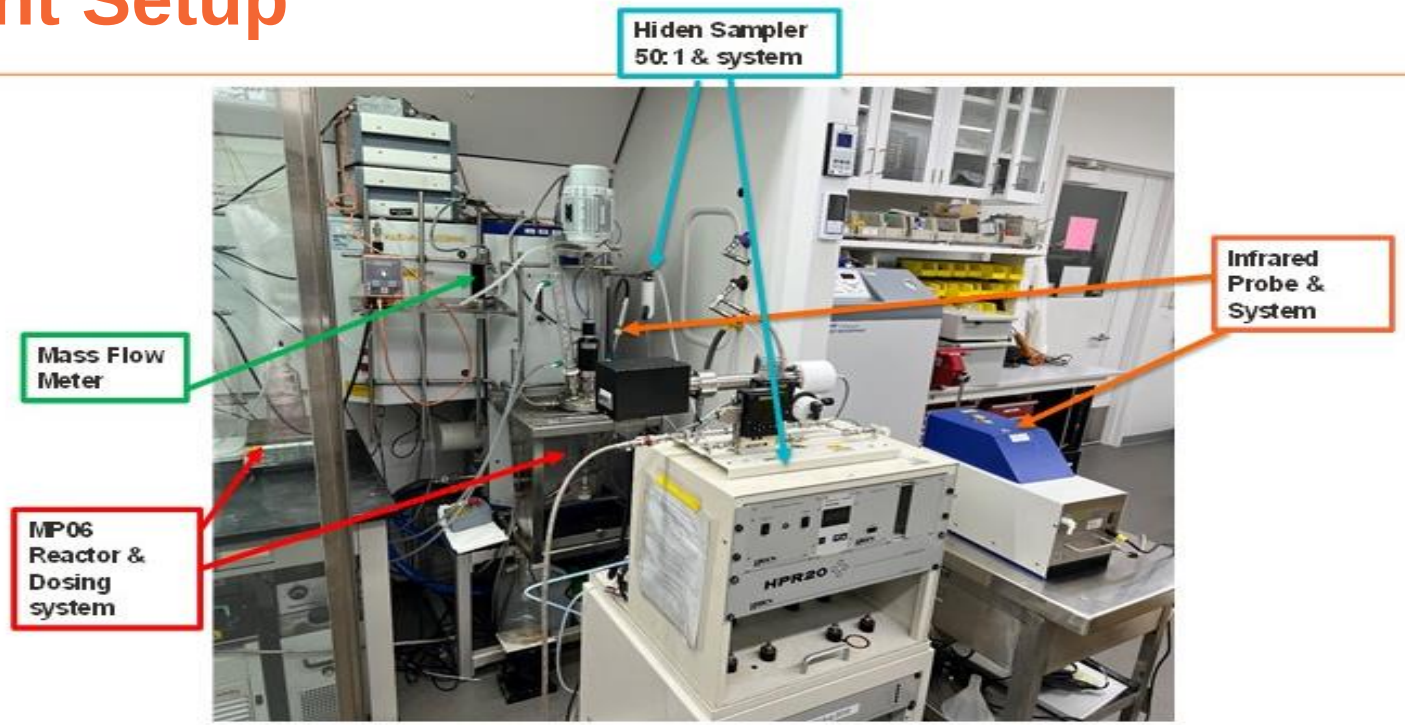
Instrument Setup

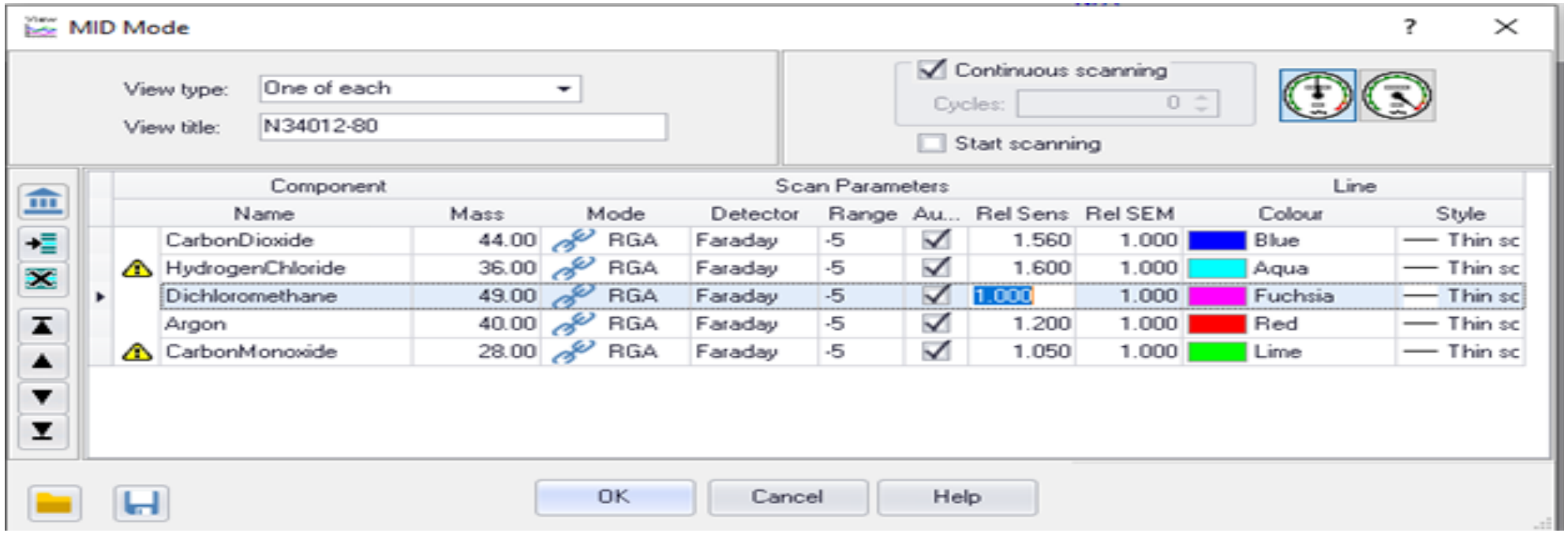


- **The Mettler Toledo reaction calorimeter (RC1) is the primary reactor used for our hazard evaluations.**
- **Total gas evolution rate is measured via thermal mass flow meter (TMFM), a Sierra Instruments model in this illustration.**
- **The Hiden Mass spectrometer (Hiden) is employed concurrently with the TMFM to identify and quantitate individual component gases.**
- **The Mettler Toledo infrared spectrometer is also used to monitor the reaction progression, by monitoring unique IR frequencies for the reaction's constituents.**

Experimental Setup

- **The ability to synchronize data points collected concurrently from the RC1, Hiden and TMFM is critical.**
- **This synchronization brings together fractional gas output data (from the Hiden) and the total gas flow from TMFM which are adjusted for relative sensitivity and specific k-factors during post-run evaluation, respectively.**
- **The RC1 head space is swept with a carrier gas (Argon /Nitrogen) that transports gas generated from the reaction through the TMFM, then through the Hiden via a 50:1 slipstream loop.**
- **The gas stream within the Hiden is ionized at the source and the base peak of individual gases (maximum ion abundance) is measured.**
- **The Hiden is set up in multiple ion detection mode and the appropriate ions for the carrier gas (Argon /Nitrogen), solvent, and expected reaction off-gases are monitored.**

Experimental Setup



- **The response factor, or the propensity of a molecule to ionize in this system (i.e. relative sensitivity), has been pre-determined experimentally or given a default value of 1.**
- **Note: The caution symbol next to hydrogen chloride and carbon monoxide gases indicate that these gases generate an ion common to other gas components in the reaction mixture (overlap).**
- **Overlapping ions present a significant challenge in performing accurate component quantitation.**

Evaluation

Follow the instructions in the blue cells below. Green Cells require user input. If you need to restart the macro, type a new value in cell F4

1) Enter the number of MS components and press enter:	5
2) Use the pulldown menu below in the green highlighted cells to select your MS components	
3) After selecting MS components, click Calculate:	Calculate
4) If required, select another MS Peak after evaluating overlaps and dick Recalculate. Use the "Working" worksheet to help select a new peak. New overlaps will be calculated using MS peak entered:	Recalculate
5) If Hiden Experiment has already been performed, dick Adjust to begin processing data:	Adjust

MS Component	MS Peak (m/z)	K-Factor	Overlaps
CarbonMonoxide	28	1.00128	Overlaps with CarbonDioxide (98/1000) Overlaps with Dichloromethane (2/1000)
HydrogenChloride	36	1.0034	Overlaps with Argon (3/1000) Overlaps with Dichloromethane (23/1000)
Argon	40	1.4573	No Overlaps
CarbonDioxide	44	0.7382	No Overlaps
Dichloromethane	49	0.53205	No Overlaps

- **An Excel macro was developed in-house to identify and resolve overlapping ions.**
- **Implementation of this tool has significantly improved our capability to quantitate gas evolution components.**

Evaluation

Time (hrs)	Hiden Mass Spectrometer Ion Abundance (Mass to Charge Ratio)					RC1/TMFM (L/min-kg)	Infared Spectrometry (λ)		
Time	CarbonDioxide	HydrogenChloride	Argon	CarbonMonoxide	ichloromethan	Gas Flow	Stearic acid	Oxalyl chloride	Product
0.004302778	1.86E-11	1.07E-09	1.15E-07	5.72E-10	1.33299E-08	0.8346624	1.16888917	0.011304995	0.002681725
0.022705556	1.35E-11	1.57E-09	1.33E-07	6.45E-10	1.42974E-08	0.8426688	1.168801627	0.011275914	0.002631911
0.037150556	1.05E-11	1.78E-09	1.47E-07	7.06E-10	1.53724E-08	0.8462336	1.168679176	0.011618128	0.002491811
0.066039722	2.76E-11	2.12E-09	1.73E-07	8.36E-10	1.81674E-08	0.8248768	1.168942154	0.012348859	0.002674711
0.080484722	2.51E-11	2.23E-09	1.80E-07	8.75E-10	1.90274E-08	0.8141952	1.168954808	0.011780011	0.00347841
0.094929167	1.98E-11	2.33E-09	1.87E-07	9.22E-10	1.97799E-08	0.8293248	1.16867152	0.011249146	0.002370244
0.109374167	2.22E-11	2.42E-09	1.93E-07	9.47E-10	2.06399E-08	0.7972928	1.168698232	0.011426708	0.001916208
0.123818611	2.68E-11	2.49E-09	2.00E-07	9.80E-10	2.16074E-08	0.831104	1.168891579	0.011441126	0.002585659
0.138263333	3.95E-11	2.61E-09	2.07E-07	1.02E-09	2.23599E-08	0.807968	1.168864205	0.011202329	0.003098432
0.152708333	3.64E-11	2.67E-09	2.15E-07	1.06E-09	2.33274E-08	0.7937344	1.168649682	0.011818371	0.0025284
0.167152778	3.97E-11	2.81E-09	2.22E-07	1.10E-09	2.42949E-08	0.8364416	1.168880133	0.011782803	0.003024917
0.181597778	4.02E-11	2.92E-09	2.30E-07	1.13E-09	2.54774E-08	0.8302144	1.169472201	0.011741186	0.002305737
0.196042222	3.47E-11	3.03E-09	2.38E-07	1.18E-09	2.63374E-08	0.8364416	1.168880971	0.01135804	0.00164554
0.209611944	3.67E-11	3.16E-09	2.48E-07	1.22E-09	2.76274E-08	0.8275456	1.168848357	0.011529909	0.002070565
0.224931944	4.83E-11	3.43E-09	2.65E-07	1.32E-09	2.97774E-08	0.8115264	1.169073902	0.011456461	0.002760353
0.239376389	5.42E-11	3.54E-09	2.75E-07	1.38E-09	3.11749E-08	0.8017408	1.169388198	0.01129453	0.003182056
0.253821389	5.87E-11	3.70E-09	2.86E-07	1.42E-09	3.25724E-08	0.8168704	1.169634208	0.011661539	0.003093377
0.268265833	3.99E-11	3.91E-09	2.97E-07	1.51E-09	3.42924E-08	0.8052992	1.16890266	0.011860864	0.001932276

- **Synchronized data spreadsheet example from the Hiden (overlap corrected), TMFM and IR spectrometer.**

Evaluation

Data	Normalized MS Components (NIA)											
Time	CarbonDioxide	Dichloromethane	Adj CarbonMonoxide	Adj HydrogenChloride	Argon	K-Factor	Total Flow L/min-kg	CO2 CO2 (L/min-kg)	DCM DCM (L/min-kg)	CO CO (L/min-kg)	HCl HCl (L/min-kg)	Argon Argon (L/min-kg)
0:00:15	0.000144187	0.103134029	0.004205833	0.003258745	0.88925721	1.358374445	1.133784075	0.000163477	0.11693172	0.004768507	0.003694713	1.008225659
0:01:21	9.05018E-05	0.095909992	0.004126711	0.005674831	0.89419796	1.364036511	1.14943101	0.000104026	0.110241919	0.00474337	0.006522827	1.027818869
0:02:13	6.41238E-05	0.093704728	0.004107005	0.006027417	0.89609673	1.365944847	1.155908425	7.41212E-05	0.108314085	0.004747322	0.006967143	1.035805755
0:03:02	0.000127716	0.092652868	0.004127868	0.006221099	0.89687045	1.366774925	1.159042632	0.000148028	0.107388624	0.004784375	0.007210519	1.039511086
0:03:57	0.000142906	0.094051462	0.004123957	0.006149448	0.89553223	1.365504259	1.126372783	0.000160966	0.105937007	0.004645113	0.006926571	1.008703127
0:04:49	0.000124964	0.094610668	0.004150333	0.00622741	0.89488663	1.364952341	1.111337644	0.000138878	0.105144397	0.004612421	0.006920755	0.994521194
0:05:41	9.46625E-05	0.094662494	0.004213999	0.006277104	0.89475174	1.364874589	1.131924345	0.000107151	0.107150782	0.004769928	0.007105207	1.012791277
0:06:33	0.000102555	0.09548577	0.004177836	0.006294871	0.89393897	1.364115604	1.087599549	0.000111539	0.103850281	0.004543813	0.006846299	0.972247618
0:07:25	0.000119225	0.096269351	0.00416367	0.00620038	0.89324737	1.363427958	1.13315043	0.0001351	0.109087656	0.004718065	0.007025963	1.012183646
0:08:17	0.000170482	0.096471283	0.004169804	0.006363428	0.892825	1.363127458	1.101363366	0.000187762	0.106249936	0.004592469	0.007008447	0.983324751
0:09:09	0.000151453	0.097029145	0.004207021	0.006194143	0.89241824	1.362684845	1.081609838	0.000163813	0.104947678	0.004550355	0.006699646	0.965248346

- **The adjusted (overlap corrected) ion abundance for each gas is normalized against the total ion abundance for each time point (summing of the partial pressure of all gases measured). This gives us the normalized gas fraction for each gas in the ion source:**

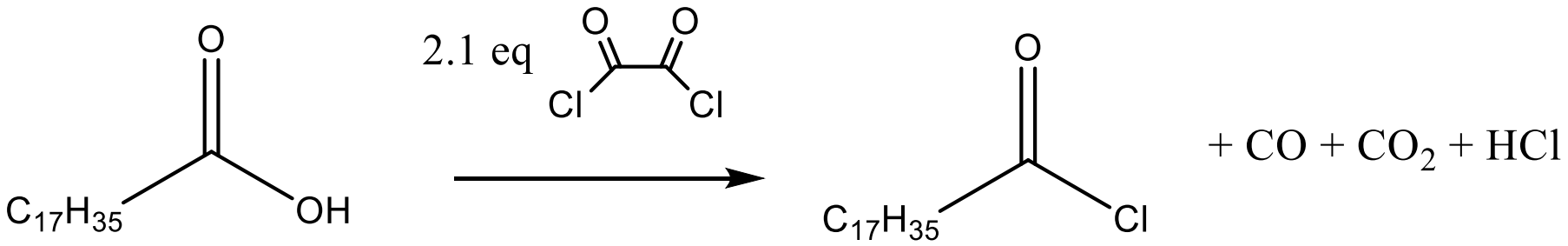
  Σ Individual Ion Abundance, for each gas /Total Ion Abundance (all gases) = Normalized Ion Abundance, for each gas (NIA)

- **The k-factor (the unique thermal conductivity coefficient for each gas) is determined from the TMFM data at each time point:**
- ***k-factor*** $_{gas(x)}$ ***+ k-factor*** $_{gas\ (y)}$ ***+ * k-factor*** $_{gas(z)}$ ***…=k – factor***
- **Multiplying the Total Gas Flow (from the TMFM), the k-factor (corrected), and the NIA will give the gas flow in (L/min-kg) for each gas at each time point:**

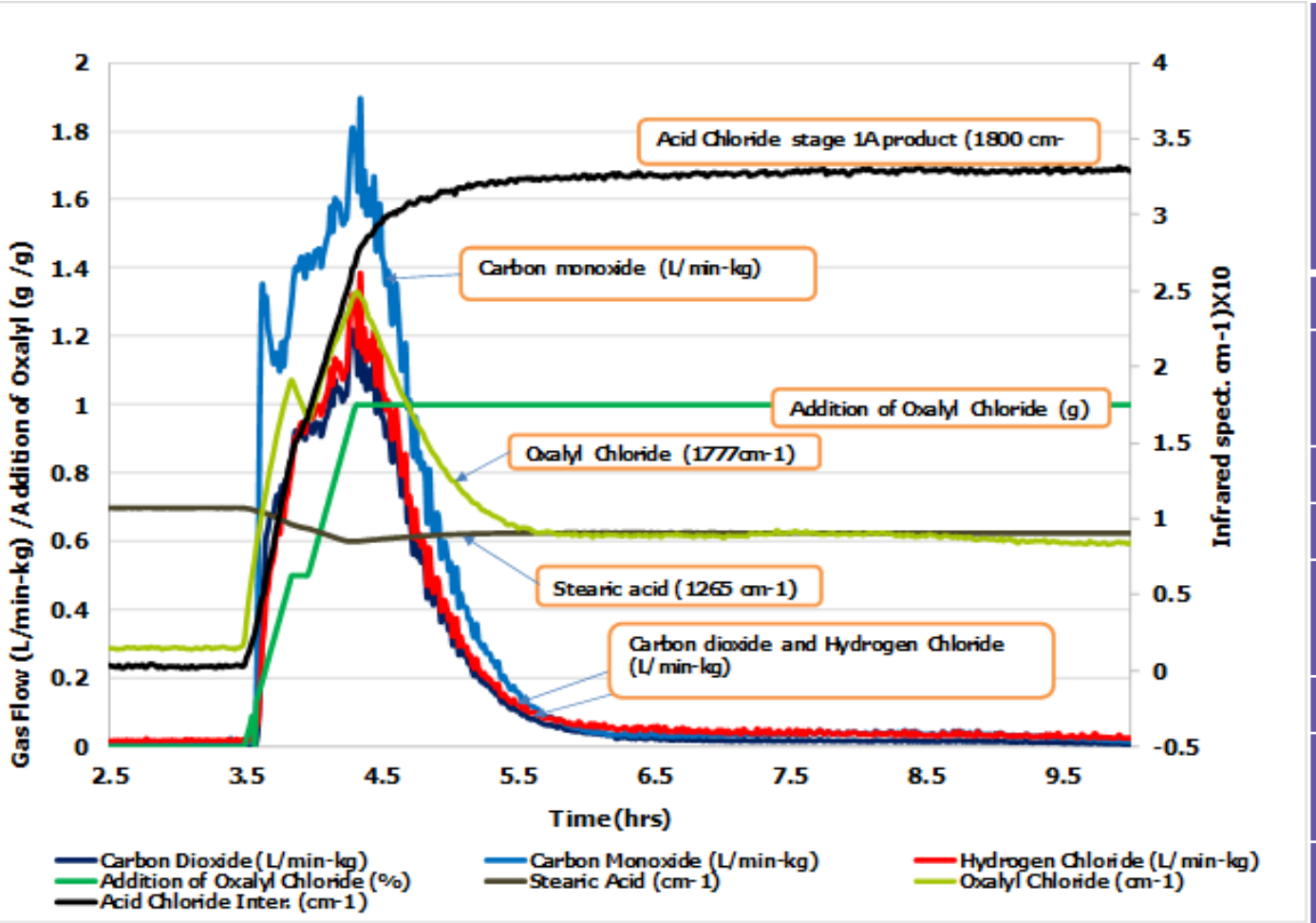
  NIA*k factor (corr.)*Total Gas Flow (via TMFM) = Individual gas flow per time point (L/min-kg)

Example 1: Conversion of Stearic acid to the acid chloride

- **Example 1 involved the synthesis of an acid chloride from stearic acid using oxalyl chloride. This acid chloride is subsequently used in the synthesis of an investigational medicine to combat HIV infections.**
- **Based on the scheme below, a total of 3 equivalents of gas are predicted from the intended reaction: carbon monoxide (a flammable gas), carbon dioxide (an asphyxiating gas) and hydrogen chloride (a corrosive gas), one equivalent each.**



Example 1 - Results

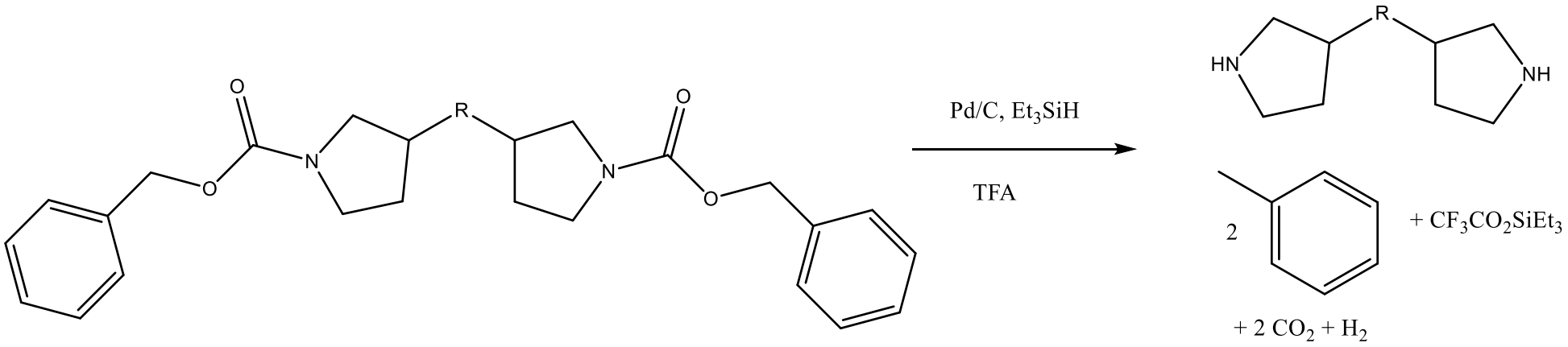


Average (L/min-kg)	Volume (L/kg)	Theoretical (%)	Maximum Rate (L/min-kg)	Solubility in DCM (mole fractions) *IUPAC series*
Carbon Dioxide				
0.359	77.52	71.25	1.28	0.0125
Carbon Monoxide				
0.557	120.22	110	1.89	0.006*
				Estimated from CHCl3 DCE
Hydrogen Chloride				
0.385	83.07	76.36	1.39	0.013

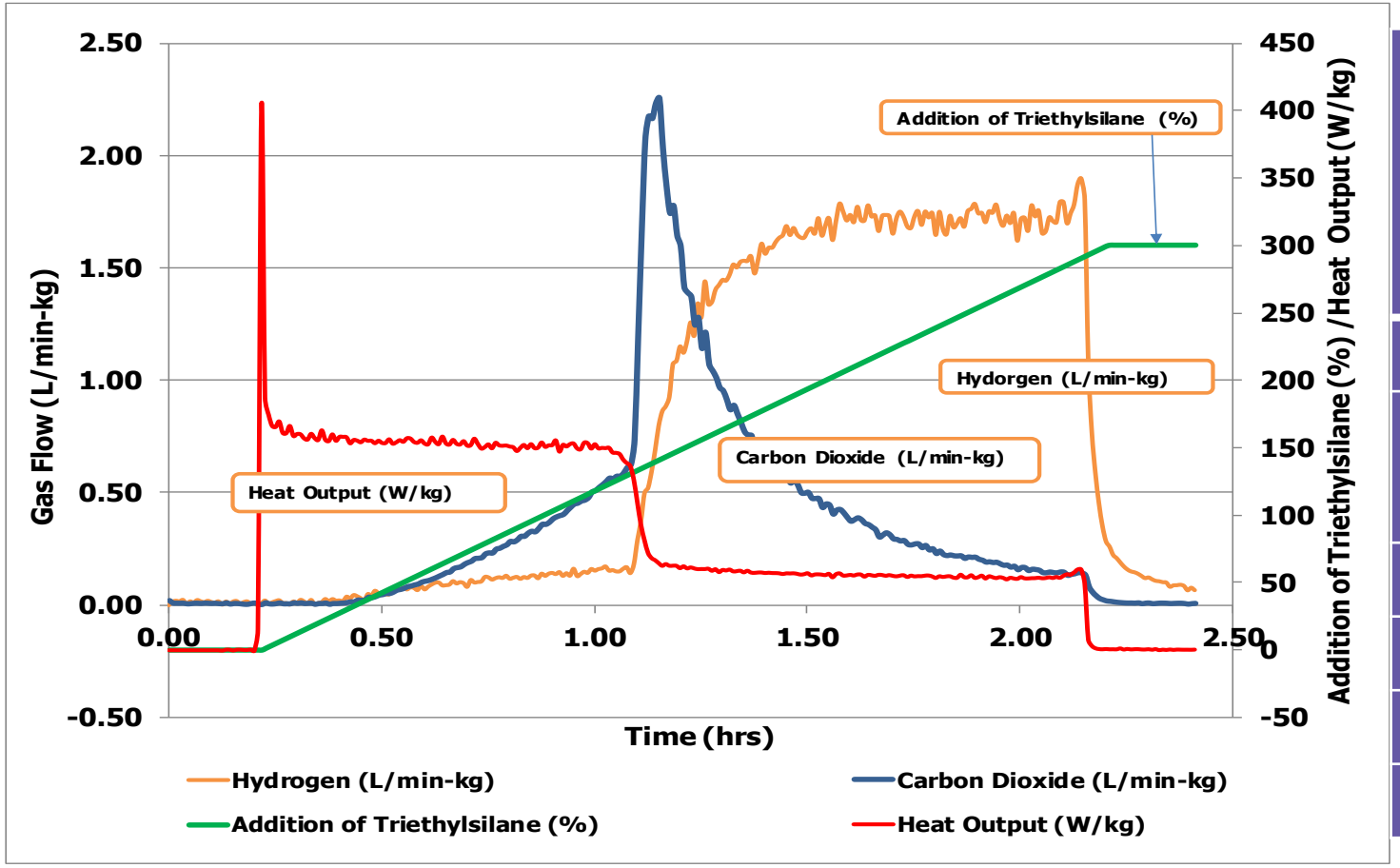
- **Gas observed vs theoretical amount in good agreement.**
- **Individual component solubility differences in reaction solvent reflected in observed ratios.**

Example 2: Deprotection reaction

- **Example 2 involved the deprotection (Cbz removal) of a pharmaceutical intermediate via palladium catalyst mediated triethyl silane reduction. This diamime is subsequently used in the synthesis of an investigational medicine to combat Hepatitis C infections.**
- **Based on the scheme below, a total of 3 equivalents of gas are predicted from the intended reaction: 2 equivalents of carbon dioxide (an asphyxiating gas) and one equivalent of hydrogen (a flammable gas).**



Example 2 - Results



Average (L/min-kg)	Volume (L/kg)	Theoretical (%)	Maximum Rate (L/min-kg)	Solubility in Ethyl acetate (mole fractions) *IUPAC series*
Carbon Dioxide				
0.44	47.82	48.85	2.26	0.023
Hydrogen				
0.86	106.83	109.13	1.70	0.003

- Gas observed vs theoretical amount in good agreement.
- Individual component solubility differences in reaction solvent reflected in observed ratios.

Conclusion

- **The combined use of reaction calorimetry (RC1), mass spectrometry (Hiden), and thermal massflow (TMFM) instruments provides a powerful hazard evaluation methodology, individual gas component quantification, in conjunction with total output.**

- **Careful equipment and experimental set up is required to ensure accurate results are obtained; an Excel macro has been developed to enable resolution of ion overlap conflicts during Hiden mass spec. data evaluation.**

Acknowledgment

- **Roy Flanagan – WW Process Safety Director GSK**

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