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Determination of Reaction Heat: A Comparison of Measurement and Estimation Techniques

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Abstract:

The heat of reaction is an important parameter in the safe, successful scale-up of chemical processes. Reaction heat data is used to calculate the potential adiabatic temperature rise of the desired reaction, providing a worst-case scenario for rapid reaction of the entire batch with no heat loss to the surroundings. The data is used in parallel with information regarding the thermal stability of reaction mixtures/components and an intimate knowledge of the process to analyze the risk associated with running it on-scale. If the level of risk is judged to be unacceptable, the analysis can be used to make rational process changes in order to reduce the risk to an acceptable level. The Pfizer global process safety network provides a heat of reaction for all processes run in our kilo laboratories, pilot plant, and manufacturing facilities. In general, there are two methods used to determine reaction heats: (1) experimental measurement using some form of calorimetry, or (2) estimation techniques. Since experimental measurement is not always practical, accurate, or necessary, we set out to show that estimation techniques could be used reliably and efficiently to provide heat of reaction data for a wide range of chemistry. To gain confidence in our ability to accurately predict reaction heats, we carried out a comparative study of measured versus estimated values. The results of this study will be discussed in detail, including rationalization of any significant disparity through further analysis to more fully understand the limitations/advantages of both techniques. To help ensure consistent application of measurement/estimation across the Pfizer global process safety network, we developed a decision tree to determine whether estimation or measurement should be considered for a particular reaction. In order to maximize the efficiency gain and to ensure accuracy in our estimations, we have created a heat estimation database that allows for (1) rapid archival/retrieval of model compounds, (2) calculation of reaction heat and adiabatic temperature rise, and (3) reporting/documentation of the results.

Introduction

Theoretical prediction of reaction heats using eq 1 has a long history in process safety analysis.[1–9] For the hypothetical reaction $a\mathrm{A} + b\mathrm{B} \rightarrow c\mathrm{C} + d\mathrm{D}$

$$\Delta_r H = c\Delta_f H°(\mathrm{C}) + d\Delta_f H°(\mathrm{D}) - a\Delta_f H°(\mathrm{A}) - b\Delta_f H°(\mathrm{B}) \quad (1)$$

The reaction enthalpy, $\Delta_r H$, is calculated from the standard heats of formation, $\Delta_f H°$, of the reactants and products. The standard heat of formation is the enthalpy change upon formation of the material from the elements in their standard states at the temperature *T*. Frurip and co-workers have reported a seven-step process to successfully estimate the heat of reaction using eq 1:[10]

(1) **Define and balance the chemical equation**. It is critical to have the reaction written down correctly with the states of all species defined.

(2) **Reduce complex chemical structures to model compounds**. The Analog Reaction Hypothesis states that the heats of reaction for structurally similar reactions are identical.[11] Chemical groups that do not change throughout the reaction cancel across eq 1 and, therefore, do not significantly affect the thermodynamics. This step is performed because the $\Delta_f H°$ data are available for thousands of small molecules but not for larger ones.

(3) **Make simplifying assumptions**. There are three basic assumptions that are used for most estimations: (a) the heat of dissolution of most organic liquids in organic solvent is small, and therefore $\Delta_f H°$ for the liquid instead of the solution is used; (b) most reaction heats are weakly dependent on temperature, so temperature effects can be ignored; and (c) most reaction heats are weakly dependent on pressure, so pressure effects can be ignored.

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(4) **Obtain the literature $\Delta_f H°$ data for the compounds or model compounds if available**. There are a few key sources for $\Delta_f H°$ data.[11–14]

(5) **Estimate $\Delta_f H°$ data for compounds and model compounds for which literature data does not exist**. If literature data does not exist, then the $\Delta_f H°$ can be estimated. Benson's method is preferred over bond energy approaches.[15–18]

(6) **Perform the calculation based on eq 1**.

(7) **Perform a reality check**. Is an endothermic prediction reasonable on the basis of reaction temperature or favorable entropy change? Is the estimation conservative compared to observations made in the laboratory? How does the estimation compare with similar chemistry that has been measured?

The appearance of several practical and reliable calorimeters brought on a new era of experimental measurement, and as these instruments became more popular, the use of heat estimation decreased. This is unfortunate because experimental testing and estimation techniques are complimentary, and experimental measurement is not always practical, accurate, or necessary.

In the Pfizer global environment it is essential for processes to be transferred between facilities with minimum delays caused by different site practices and procedures. Therefore, we were challenged with implementing a globally accepted strategy on the assessment of chemical reaction hazards that aid these process transfers, while at the same time satisfying country-specific regulations along with Pfizer internal standards. This approach should be time- and material-efficient without compromising safety. Toward this end, we were interested in incorporating estimation techniques as a way to gain efficiency and broaden the scope of our toolbox for determination of reaction heats. Estimation techniques had previously been used for several years at our Kalamazoo facility to satisfy the energy balance requirement of the OSHA 29 CFR 1910.119 process safety standard. We decided to build on this experience and investigate the role of estimation globally. The goal was to develop a system where a heat of reaction, either measured or estimated, is available for all processes. Therefore, we set out to show that estimation techniques could be used reliably and efficiently in our hands to provide heat of reaction data for a wide range of chemistry. This paper describes the results of a comparison between measured and estimated heat of reaction data for chemistry that was run in our scale-up facilities. A general overview of the errors associated with both techniques is provided, along with detailed discussion of the errors that we made while learning to perform estimations competently.

Experimental Section

Reaction heats were measured using either a Mettler Toledo RC1 or an Omnical SuperCRC. Reaction heats were normalized to 100% conversion, and the sensible heat of dosing has been removed unless otherwise stated. For RC1 experiments, the reaction temperature was maintained isothermally by allowing the jacket temperature to fluctuate, unless otherwise stated. Calibrations were performed before additions and after reaction completion to obtain heat capacities and heat transfer coefficients. The heat flow curve was analyzed using WinRC NT version 7.11 (SR-6) with the following equation: $Q = Q_{\text{accum}} + Q_{\text{flow}} + Q_{\text{dose}}$. Heat transfer coefficients were interpolated proportionally to virtual volume, heat capacities were interpolated proportionally to the reaction mass, and the baseline was interpolated proportionally to conversion. Total off-gas volume and rate were measured using a Ritter gas flow meter. For SuperCRC experiments, the reaction temperature was maintained isothermally by (1) equilibrating the dose to the reaction temperature prior to injection and (2) adding the dose in a controlled manner, unless otherwise stated. Total off-gas volume was measured by reading the volume from a syringe connected to the vent line.

Results and Discussion

Comparison of the measured and estimated heat of reaction for 50 reactions was carried out across our global process safety network, as shown in Table 1. Inspection of the reactions reveals a broad range of reaction types including a variety of substitution, reduction, oxidation, addition–elimination, electrocyclic, and salt-forming reactions. The reactions are grouped by class in the table: entries 1–7, transition metal catalyzed hydrogenation; entry 8, $LiBH_4$ reduction of an ester; entries 9–13, nucleophilic aromatic substitution; entries 14–16, Pd-catalyzed coupling of an aromatic halide with various nucleophiles; entries 17–30, a variety of addition–elimination reactions; entries 31–36, S_N2-type substitution reactions; entries 37–41, halogenations; entry 42, H_2O_2 oxidation of a sulfide; entries 43–46, alkali metal salt formation; entries 47 and 48, amine salt formation; and entry 49, a Diels–Alder reaction. There are three general trends that appear: (1) Estimation tends to be more conservative than measurement. More discussion will follow regarding the error associated with estimations and measurement. (2) The transition metal catalyzed hydrogenations tend to show excellent agreement between the measurement and the estimation. The percent difference is less than 6% in all but one example, entry 6, which has a −13% difference on a small $\Delta_r H$, −57.3 kJ/mol. This close correlation is likely due to reaction heats that tend to be fairly large, reliable measurement due to straightforward processing, and reliable estimation due to simple models that have accurate, thoroughly studied $\Delta_f H$ data. (3) The estimated alkali metal and amine salt formations tend to be very conservative since these equilibrium reactions are assumed to go to 100% conversion in the estimation. No other trends appear in the data. Relatively large percent differences ($> \pm 15\%$) can be explained by a variety of observations as described in the footnotes of Table 1.

In order to rapidly assess the overall correlation, the estimated value was plotted against the measured value, as shown in

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Table 1. **Comparison of estimated and measured heats of reactions for 50 reactions**

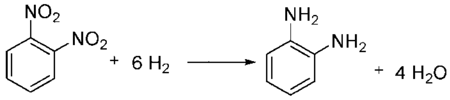
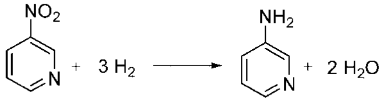
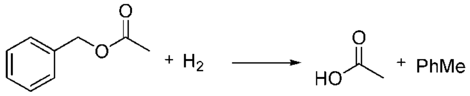
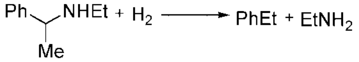
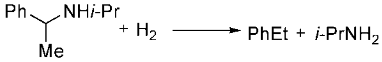
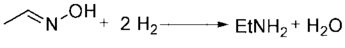
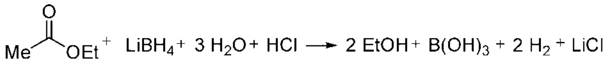
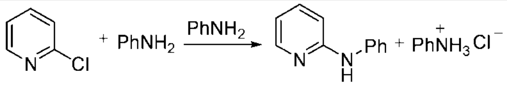
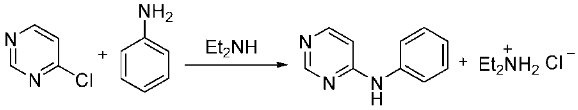
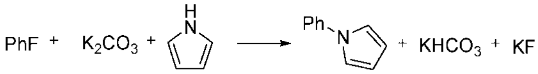
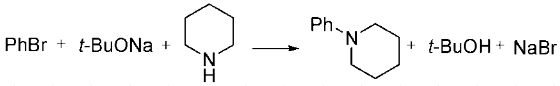
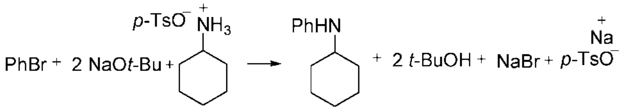
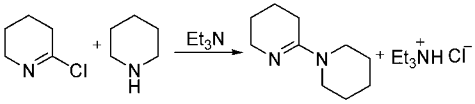
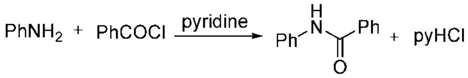
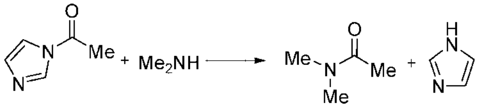
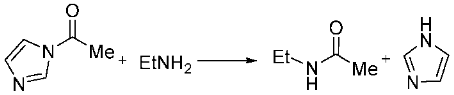
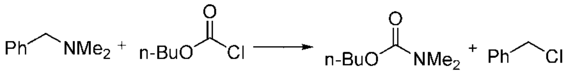
Entry	Model Compounds used for the Estimation[a]	Δ_rH Estimated Measured (kJ/mol)	Δ_rH Diff (%)[b]
1	$PhNO_2 + 3\ H_2 \longrightarrow PhNH_2 + 2\ H_2O$	-552.9 -569.2[c]	3
2		-1122.8 -1133.6[c]	1
3		-557.0 -565.2[c]	1
4		-116.1 -112.9[c]	-3
5		-65.7 -69.7[c]	6
6		-64.6 -57.3[c]	-13
7		-299.0 -310.0[d]	4
8		-385.0 -342.0[d]	-13
9		-107.1 -42.0[c,e] -139.7[c,f]	-155 23
10	$PhF + MeOK \longrightarrow PhOMe + KF$	-194.0[g] -139.0[d]	-40
11		-126.1 -118.9[d]	-6
12	$PhF + PhNH_2 + Et_3N \longrightarrow Ph_2NH + Et_3\overset{+}{N}H\ F^-$	-165.5 -126.6[d,h]	-31
13		-105.7 -103.0[c]	-3
14		-204.0 -135.4[d,i]	-51
15		-213.4 -174.0[c,j]	-23
16	$PhI + PhSH + KOH \longrightarrow Ph_2S + KI + H_2O$	-143.5 -87.8[c,k]	-63
17		-208.6 -164.0[d,l]	-27
18		-91.2 -94.9[c]	4
19		-41.5 -38.2[c]	-9
20		-24.3 -22.7[d]	-7
21		-95.0 -63.4[c,m]	-50

Table 1. **Continued**

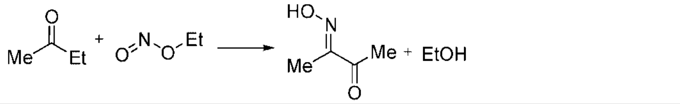
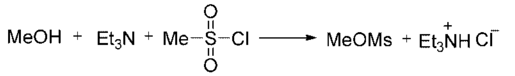
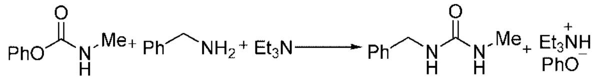
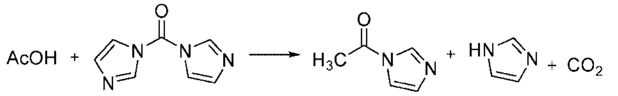
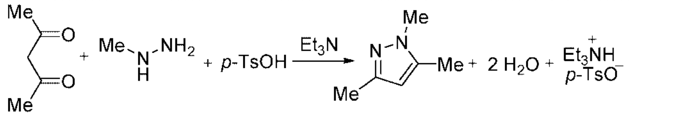
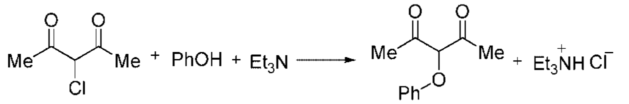
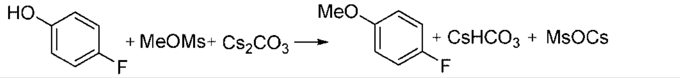
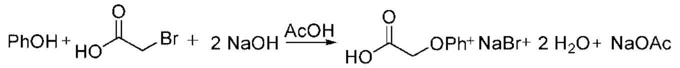
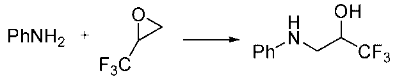
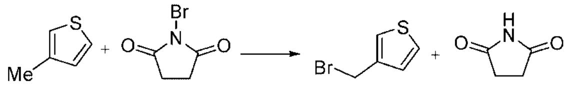
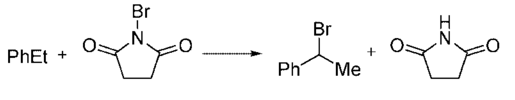
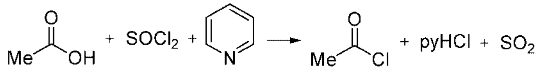
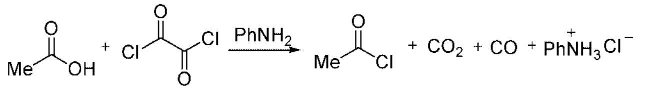
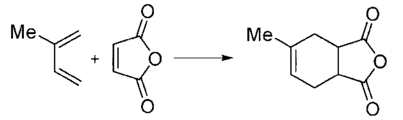
22		-136.4 -121.9[c]	-12
23	 MeOH + Et_3N + $Me{-}\overset{O}{\underset{O}{S}}{-}Cl$ $\longrightarrow$ MeOMs + $Et_3\overset{+}{N}H\ Cl^-$	-201.6 -224.0[c]	10
24	*i*-PrOH + AcCl $\longrightarrow$ *i*-PrOAc + HCl	-41.8 -42.6[d]	2
25	PhOH + AcCl $\xrightarrow{Et_3N}$ PhOAc + $Et_3\overset{+}{N}H\ Cl^-$	-180.2 -115.2[c,n]	-56
26	*i*-PrOH + Ac_2O + Et_3N $\longrightarrow$ *i*-PrOAc + $Et_3\overset{+}{N}H\ AcO^-$	-80.0[o] -80.0[d]	0
27	EtOAc + NaOH $\longrightarrow$ NaOAc + EtOH	-53.6 -21.7[d,p]	-147
28		-35.3 -33.9[c]	-4
29		-18.0 -6.9[c,q]	-161
30		-159.1 -165.5[c]	4
31		-125.2 -45.5[c,r]	-175
32		-117.0 -64.4[c,s]	-82
33		-136.8 -131.9[d]	-4
34		-117.9 -109.4[c]	-8
35		-81.7 -88.0[c]	7
36		-100.5 -88.0[d]	-14
37		-97.8 -122.2[c,t]	20
38		-118.0 -113.6[c]	-4
39	EtOH + $SOCl_2$ $\xrightarrow{Et_3N}$ EtCl + $Et_3\overset{+}{N}H\ Cl^-$ + SO_2	-184.8[u] -107.0[c]	-73
40		-120.6 -136.2[c]	11
41		-162.8 -93.5[d,v]	-74
42	Ph_2S + 2 H_2O_2 $\longrightarrow$ Ph_2SO_2 + 2 H_2O	-579.1 -565.9[c]	-2
43	MeOH + *t*-BuOK $\rightleftharpoons$ MeOK + *t*-BuOH	-155.3[w] -58.0[d]	-168
44	EtOH + *t*-BuOK $\rightleftharpoons$ EtOK + *t*-BuOH	-150.8[w] -58.0[d]	-160
45	*i*-PrOH + *t*-BuOK $\rightleftharpoons$ *i*-PrOK + *t*-BuOH	-97.3[w] -58.0[d]	-68
46	MeOH + $(i\text{-}Pr)_2NNa$ $\longrightarrow$ MeONa + $(i\text{-}Pr)_2NH$	-85.2 -63.9[d,x]	-33

***Table 1.* Continued**

47	$Et_3N + AcOH \rightleftharpoons Et_3\overset{+}{N}H\ AcO^-$	-83.9 -4.0[d,y] -33.1[d,y]	 -1998 -154
48	$Et_2NH + AcOH \rightleftharpoons Et_2\overset{+}{N}H_2\ AcO^-$	-86.5 -17.6[d,z]	 -391
49		-149.4 -136.0[c]	-10

[a] In most cases, these schemes represent the model compounds used in the estimations, not the real chemical compounds used in the measurements. The real chemistry is not shown to protect our proprietary intellectual property. Reactants that appear over the arrow indicate that the reactant was not used in the measurement but only used in the estimation to mimic a secondary reaction that takes place in a remote location on the real compound. The phases have been left out for clarity but are important per the discussion in the text. [b] % difference = (estimated Δ_rH – measured Δ_rH)/absolute value of measured Δ_rH. Therefore, a negative % difference indicates that the estimation is more conservative (more exothermic). [c] Measured using a Mettler Toledo RC1. http://us.mt.com/mt/filters/products-applications_autochem_RC1-MultiMax/Level_2_ALR_Calorimeters_RC1_LabMax_FilterHierarchy-ProductFamily_1173125415003.jsp. [d] Measured using an Omnical SuperCRC. http://www.omnicaltech.com/. [e] Reaction run in toluene/ACN. Large endotherm upon start of dosing indicates a significant endothermic heat of solution. Assay of the starting material was questionable. The reaction formed a very thick slurry and the heat transfer coefficient was unusually low, making the value questionable. [f] Reaction run in THF/*t*-BuOH. Unusual heat flow observed several hours after dosing, which may be a heat of crystallization. [g] The estimation from the coupling of KOMe to PhF, −96.7 kJ/mol, was adjusted by adding the heat that is contributed by driving the equilibrium between KO *t*-Bu and MeOH to give KOMe and *t*-BuOH to completion, −97.3 kJ/mol. This heat is known from a measurement as explained in the main body of the text. In the absence of this measured data, all of the heat from the equilibrium could be estimated, −155.3 kJ/mol, and added to the heat from the coupling to arrive at a conservative estimate, −252.0 kJ/mol. [h] The conversion is unknown for this experiment. [i] Pd-catalyzed reaction performed isothermally at 90 °C in toluene, which may have resulted in significant heat loss. [j] Pd-catalyzed temperature ramping experiment to 90 °C in toluene, which may have resulted in significant heat loss. Unknown conversion. [k] Pd-catalyzed temperature ramping experiment to 75 °C in NMP. The measured heat may reflect the heat of solution of KOH in NMP and the deprotonation of the thiol, not the actual coupling. [l] Reaction of Et_3N with HCl to give triethylammonium chloride assumed to go to 100% conversion in the estimation, and may be the cause of the overestimation. [m] The conversion is unknown for this experiment. [n] The entire heat flow curve was not integrated due to technical difficulties. The conversion is unknown. [o] The original estimation of −68.0 kJ/mol, which assumes no reaction between acetic acid and Et_3N, was adjusted using a measured heat of reaction between acetic acid and Et_3N, −19 kJ/mol, and a measured heat of mixing between isopropanol and acetic anhydride, +7 kJ/mol. Note that in the absence of this measured data, all of the heat from the equilibrium between acetic acid and Et_3N could be estimated, −90 kJ/mol, and added to the heat from reaction of isopropanol with acetic anhydride to give a conservative estimate, −158 kJ/mol. [p] Reaction performed at 50 °C in acetone, which may have resulted in significant heat loss. Large endotherm upon start of dosing indicates the dose may not have been equilibrated to the reaction temperature, or there may be a significant heat of mixing. [q] The estimation assumes all gas stayed in solution, but 60% of the theoretical off-gas was observed during the measurement. The estimation gives −7.1 kJ/mol when corrected for this observation. [r] Reaction performed at 78 °C in acetonitrile, which probably resulted in significant heat loss. The baseline heat was also poor, which made integration questionable. [s] Temperature ramping experiment and questionable Δ_fH data for MsOCs may be to blame for the relatively large error. [t] The reaction mixture was not assayed, and therefore the level of impurities that were formed is unknown. [u] No gas was observed in the measurement. The heat of solution of SO_2 in THF was not accounted for in this estimate. There may be a competition between HCl and SO_2 complexation to Et_3N. Only the heat of reaction of HCl with Et_3N was considered in this estimation. [v] The estimation assumes all gas stayed in solution, but 76% of the theoretical off-gas was observed during the measurement. [w] These are equilibrium reactions, but the estimation assumes 100% conversion and is therefore conservative. [x] The estimation used $NaN(i\text{-}Pr)_2$ as a model for $NaN(SiMe_3)_2$, and therefore the relatively large error is not surprising. [y] These experiments are NOT repeats of the same chemistry. The conversion is unknown in each case. Failure of the salt to precipitate in these small-scale experiments may be the cause of the large errors. [z] The conversion is unknown. Failure of the salt to precipitate in this small-scale experiment may be the cause of the large error.

Figures 1 and 2. Perfect correlation is indicated by the solid line running through the data points. The points that fall below the line indicate those instances where the estimated reaction heat is greater (more negative) than the measured reaction heat. Conversely, the points that fall above the solid line indicate those instances where the measured reaction heat is greater than the estimated reaction heat. Twenty-two of the comparisons have a percent difference of 10% or less, and we will assume that those are identical within experimental error. Estimation is more conservative for 26 out of the remaining 28 comparisons, or 93%. From a process safety perspective, the use of conservative values is desirable, assuming the number is not so overly conservative that unnecessary controls are put in place. In all examples shown in Table 1 and Figure 1, the final safety recommendation was independent of approach. More detail regarding our application of estimated reactions heats to process safety analysis will be provided later.

Checklist of Factors that Lead to an Accurate Heat Estimation. As with any new tool, a beginner must learn several basic guidelines in order to use heat estimation successfully. We have developed several guidelines that lead to an accurate heat estimation. The following guidelines should be used in parallel with Frurip's seven-step process to successfully estimate a heat of reaction (discussed in the Introduction). These may be a little overwhelming at first, but with a little persistence and practice the technique will become as familiar as your favorite calorimeter.

(a) Start with an accurate, balanced equation. As mentioned previously, the key to accurate prediction of reaction heats is a balanced chemical equation. Be on the lookout for chemistry that may be perfectly correct in its own right but does not accurately represent the chemistry that is occurring in the process of interest. If chemistry is not your strong suit, consult a trusted colleague that excels in chemistry and then double check it with another trusted colleague. Be wary if the chemist has a hard time coming up with a balanced equation. Keep in mind that just because the equation balances does not mean it is right. It is very important to identify reaction products that react further with other components in the reaction mixture. Acid–base reactions are the most common. For example, formation of HCl as a byproduct in the presence of an amine will usually result in the formation of the HCl salt of the amine. This acid–base reaction can generate a significant amount of heat and must be accounted for in the estimation. Is the fate of materials, reagents, and excess reagents really known? It can be quite complicated to predict in some cases, so do not attempt an estimation if there are too many species to track with reasonable confidence. Also be aware that too many telescoped steps can be problematic because it may be difficult to keep track of what goes in which phase and what stays behind.

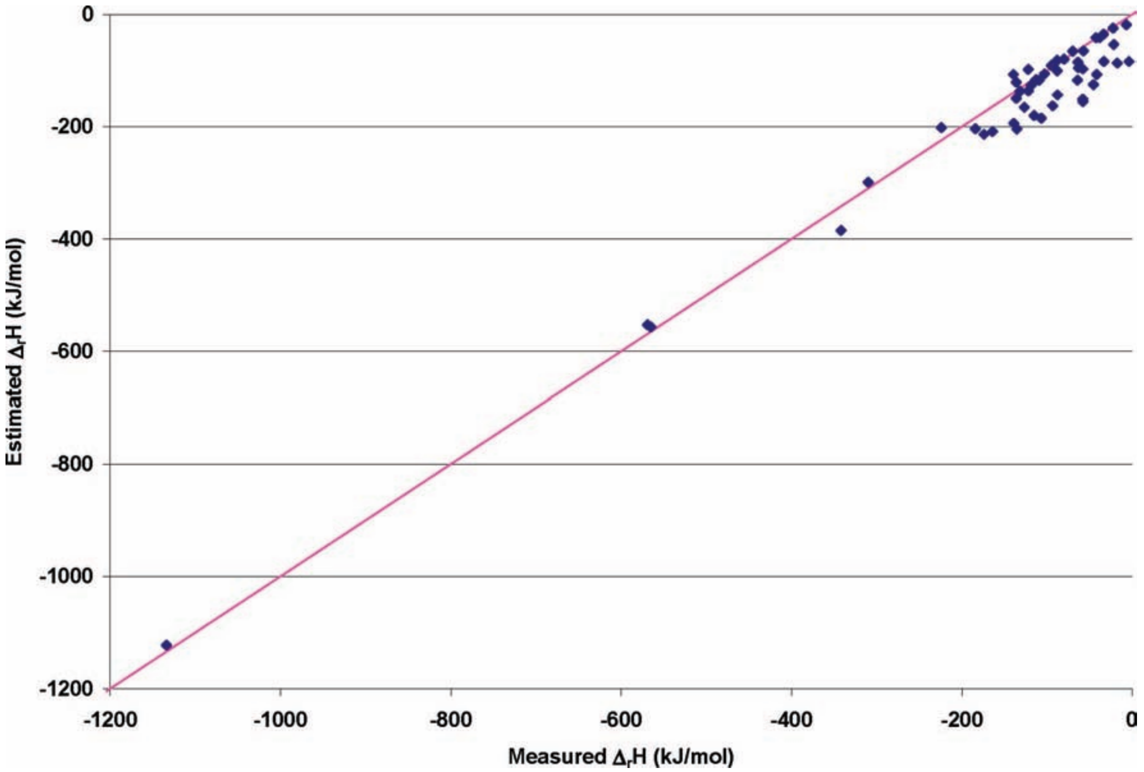


Figure 1. **Graph of the estimated $\Delta_r H$ data versus the measured $\Delta_r H$ data. The blue dots represent the 50 individual comparisons, and the red line indicates a perfect 1:1 correlation.**

(b) Only estimate reactions that have a high yield or known side reactions that can be estimated. Exothermic side reactions that are not accounted for in the estimation will result in a predicted reaction heat that is too low. We perform estimations for reactions that have 90% or greater conversion to the desired or known products. Since the conversion is typically based on nonvalidated analytical methods (usually area/area), a judgment must be made on the quality of the data. In cases where the conversion is below 90%, but calorimetric measurement is not possible or practical, we would carefully consider an estimation approach.

(c) Know when the reaction heat is released. Be on the lookout for intermediates that cannot be represented in an estimation. You might be able to estimate the overall reaction without using the intermediate, but if the chemistry occurs in semidiscrete steps there will likely be individual heats associated with those steps. Estimation of the overall reaction leaves these individual heats unresolved, and you can miss a significant exotherm. For example, if the formation of an unisolated intermediate is highly exothermic and the next step is endothermic, estimation of the overall sequence would result in a prediction that is a combination of the two heats. This prediction would suggest a reaction that is only mildly exothermic even though the formation of the intermediate is highly exothermic.

(d) Identify equilibrium reactions. Heat estimation assumes 100% conversion to products and, therefore, estimation of an equilibrium reaction gives conservative results. However, if the equilibrium reaction is the first part of a two-step reaction, then the estimation of the second reaction may be erroneously lower than the measured value which includes the heat from driving the first step equilibrium to completion. To be conservative in these situations, the estimated exotherm from the equilibrium should be added to the estimated exotherm from step two. A specific example will be presented later.

(e) Identify potential physical phenomenon that may produce heat. Exothermic heats of solution/mixing/coordination need to be considered. For example, water formed in the presence of alcohols, H_2SO_4, DMSO, etc. can have relatively large exothermic heats of solution and must be considered in the overall estimation. Most common heats of solution can be found in the literature. It may be possible to ignore heats of solution if they are expected to cancel out on both sides of the equation. Neat reactions can have physical interactions that are extreme and dominating and, therefore, we do not recommend heat estimation unless the effect of physical interactions is known, or measurement is not possible/practical. Heats of crystallization can be significant, especially if released suddenly at reflux. Consider a case where the product supersaturates and then precipitates quickly during a reflux reaction. The sudden exotherm from crystallization can overwhelm the condenser, pressurize the vessel, and lead to release of the reaction mixture. Unfortunately, it is difficult to know the likelihood of supersaturation, and estimation of the crystallization heat is usually not practical since the heat of fusion of the product is rarely known.

(f) Be aware of off-gassing. Estimation may be used for reactions that off-gas if (1) the estimation is being used as a conservative backup for a measured value, or (2) the total theoretical amount and/or rate of off-gassing are not considered to pose a significant overpressurization hazard. Off-gassing can affect both measurements and estimations, so care should be taken when working with reactions that have the potential to produce noncondensable gases. Off-gassing tends to lower measured values due to the heat loss/evaporative cooling, so

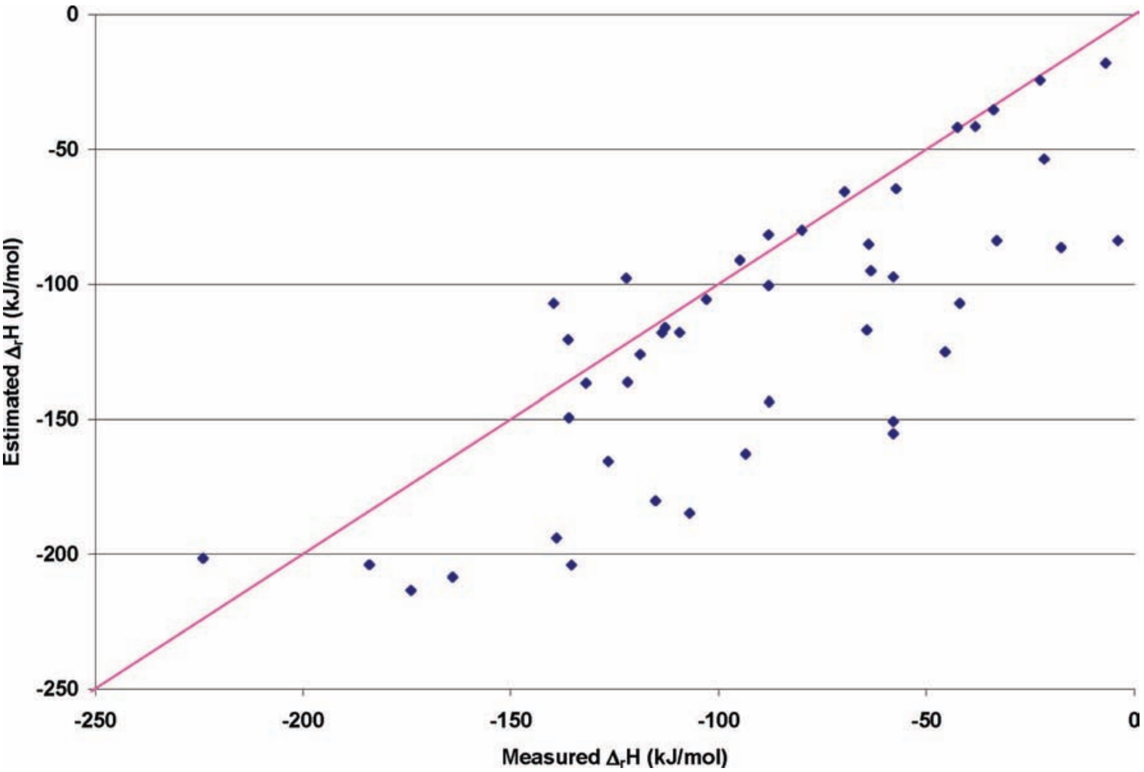


Figure 2. **The data from Figure 1 zoomed in to −250 kJ/mol on both axes.**

care should be made to retain potential off-gases if a measurement of the actual heat of reaction is desired. Similarly, the use of gaseous heats of formations for by-products lowers estimated reaction heats. Therefore, the use of liquid or solution phase heats of formation for gaseous by-products generally gives a conservative estimation of the reaction heat. Since heat loss due to evaporative cooling will most likely not scale linearly, this conservative estimation may be useful for the development of a worst-case scenario even if a measurement is available. If the solubility of the by-product is unknown we generally error on the side of caution and assume that all of the ”gaseous” by-product stays in solution. Also remember to consider the generation of a condensable by-product above its boiling point that could lead to a nasty surprise if not thought through properly (e.g., methanol in water at 100 °C).

(g) Match calculation to production process operations. It is important to consider the details of how the process will be run on-scale in order to maximize accuracy. This is closely related to the section above for knowing when the reaction heat is released. For example, if NaOH pellets are added to an aqueous reaction mixture, the heat of solution must be added to the estimation, but if dilute caustic will be made in separate tank before addition to the reaction mixture, you may be able to use the smaller heat of dilution.

(h) True catalysts should not be entered into the heat of reaction estimation. Catalysts may need to be taken into account if they are used stoichiometrically (i.e., large amounts of in-situ intermediates generated before desired reaction initiates). Some catalysts are actually precursors and must be activated, releasing a significant amount of heat. These types of heat may be unknown or difficult to estimate.

(i) Preserve estimation technique across the equation. Here, ”estimation” refers to estimation of the heat of formation, not the heat of reaction. There are several different techniques that can be used to estimate heats of formation including Benson groups, bond energies, and quantum mechanics.[15,16] If you use a Benson group approach to estimate $\Delta_f H$ in the gas phase for a starting material, then use a Benson group approach to estimate $\Delta_f H$ in the gas phase for the product. Do not use a Benson group approach for one and a bond energy approach for the other. By not mixing techniques, the inherent assumptions in the estimation technique are potentially carried across the equation and, therefore, potentially cancel. For example, if there is a ring structure in an estimated molecule, the $\Delta_f H$ contribution of the ring may not be the same for different estimation techniques, therefore creating a difference across the equation that is not real. By using the same technique you can ensure that those auxiliary structural pieces are the same and cancel across the equation. However, it is acceptable to mix literature values with estimated values. It is always a good idea to cross-check literature values against an estimation technique to check for consistency. Large inconsistencies should be investigated further.

(j) For thermally neutral reactions, what is the effect of a 40 kJ/mol error? Be wary of estimations that suggest thermal neutrality, especially for reaction masses that provide a small heat sink, because even a small exothermic heat of reaction could result in a very large adiabatic temperature rise. There can easily be a 20–40 kJ/mol error in an estimation, so it is prudent to check the adiabatic temperature rise for a worst-case reaction heat, −40 kJ/mol, rather than 0 kJ/mol. For dilute systems the ATR will likely not be a concern, but for a concentrated one the difference could produce a significant temperature rise.

(k) Choose model compounds carefully. The vast majority of proprietary compounds will not have known heats of formation. Accuracy can be maintained by using smaller, easier to estimate model compounds. Model compounds will be discussed in detail in the next section.

Compound Modeling. The vast majority of proprietary compounds will not have known heats of formation and must be modeled for use in heat estimation. There will likely be several reasonable model compounds for any given molecule. There are two basic rules to follow for choosing a good model. First, focus on the functional groups that are reacting. Try to ensure all neighboring effects to the reaction site are taken into account. For example, if the reaction site is a ketone that is attached to two aliphatic carbons, acetone is a good model compound. If the reaction site is a ketone that is attached to one aromatic ring and one aliphatic carbon, phenyl acetone is a good model. That is not to say that you could not use acetone as a model compound, but it may not be as good. We have found that adding anything past the first neighbor to the reacting centers does not add accuracy to the estimation, but only complicates the search for a heat of formation. Also keep in mind that a complex model used for the starting material requires an even more complex model for the product. A new model must be chosen if a value for the heat of formation cannot be found for either the reactant or product. The second rule is to avoid the first compound in a series unless the actual species in the reaction is the first member in the series.[10] For example, do not choose methanol, methyl amine, or formic acid as models for an alcohol, amine, or carboxylic acid, respectively, unless the actual compound in the reaction is methanol, methyl amine, or formic acid. This is because the first compound in a series usually has a heat of reaction that is slightly out of line with the rest in the group. If necessary, you can use the first compound in a series, but the error will be slightly larger.

Determination of Heats of Formation. Once you have decided on a model compound you must find a reliable value for the heat of formation. Keep your model compounds as simple as possible and there is a good chance that you will find a literature value for the heat of formation. As mentioned above, nothing is gained by making the model compounds overly complex. Many reagents have known heats of formation and can be found in the literature.

The physical phase of the heats of formations should match the components of the planned experimental run. In most cases a heat of formation in the liquid phase is preferred. If the reaction involves solids or gases then you may want to use a heat of formation in the in liquid or solid phase. The phase can have a large effect on the heat of reaction, particularly gas verses condensed, so choose carefully. If the phase is unclear, we typically choose the value that will make the estimation more conservative.

If a literature value cannot be found then the heat of formation can usually be estimated using a Benson group approach.[15,16] CHETAH and the NIST Web site are the two most common software packages used to estimate $\Delta_f H$.[14,19] The Benson group approach gives the estimated heat of formation in the gas phase. Gas phase heats of formation can be adjusted to the liquid phase by subtracting the enthalpy of vaporization, $\Delta_{vap}H$. The $\Delta_{vap}H$ can be found in the literature or estimated using a variety of techniques such as: (1) Advanced Chemistry Development (ACD/Laboratories) Software V9.04 for Solaris (The ACD software is integrated into SciFinder, therefore as long as the molecule can be found in SciFinder, the calculated $\Delta_{vap}H$ is usually readily available), (2) Frurip's rules of thumb for estimation of $\Delta_{vap}H$:[10] nonstrongly interacting species have a ΔH_{vap} close to 0.42 kJ/mol/Da, species with strong hydrogen bonding have a larger $\Delta_{vap}H$, typically 0.63–0.84 kJ/mol/Da, and halogenated species typically have a smaller Δ_{vap}H, 0.21–0.34 kJ/mol/Da (note: dalton (Da) is simply another name for an atomic mass unit, so multiply the molecular weight of your model compound by the appropriate factor to get the $\Delta_{vap}H$ in kJ/mol), (3) look up the $\Delta_{vap}H$ for a similar structural compound and adjust the value by multiplying the molecular weight difference (in daltons) between your model and the literature compound by the appropriate value using Frurip's rule's from (2) above. For example, pretend that you cannot find the $\Delta_{vap}H$ for *p*-xylene (MW = 106.17 Da), but you know the $\Delta_{vap}H$ = 38.0 kJ/mol for toluene (MW = 92.14 Da). Multiply the molecular weight difference, 14.03 Da, by 0.42 kJ/mol/Da to get the correction factor, 6 kJ/mol. Add the 6 kJ/mol to the $\Delta_{vap}H$ for toluene, 38.0 kJ/mol, to give the estimated $\Delta_{vap}H$ for *p*-xylene, 44 kJ/mol (literature value is 40 ± 6 kJ/mol), or (4) skip the $\Delta_{vap}H$ correction if there are small molecular weight changes and similar structures across the equation (again, changes in the ability to hydrogen bond can lead to significant errors).

When the $\Delta_f H$ in the liquid or gas phase cannot be found then it may be possible to find a $\Delta_f H$ for the solid phase in the literature. If the heat of fusion is also available, then an adjustment can be made by adding the heat of fusion to the solid phase heat of formation to give the liquid phase heat of formation. If the heat of fusion is expected to be small, then it may be possible to substitute the solid phase heat of formation for the liquid phase data.

The Decision To Estimate or To Measure. In order to help our Process Safety Network deliver a consistent global approach, we have developed a decision tree as an aid in deciding if estimation should be *considered* for any given process; see Figure 3. Only reactions that progress through this tree to the final box are generally considered as estimation candidates, although there are some exceptions, especially when measurement is not practical or possible. The decision tree is largely a graphical summary of the previous discussion on the checklist of factors that lead to an accurate estimation and, therefore, further discussion is not necessary. The decision to *apply* an estimation to support a scale-up run in our production facilities is discussed in the next section.

Application of Estimated Reaction Heats to Process Safety Analysis. Stoessel has described the risk associated with chemical processes using five scenarios; see Figure 4.[20] Risk is analyzed with regard to the relationship between the desired processing temperature (T_p), adiabatic temperature rise (ATR) associated with the desired reaction, boiling point of the reaction mixture (T_b), temperature at which the rate of decomposition

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(19) Chemical Thermodynamic and Energy Release Evaluation (CHETAH) Version 8.0 available through the ASTM website: http://www.astm.org/cgi-bin/SoftCart.exe/BOOKSTORE/PUBS/1026.htm?L+mystore+vkkc4412.

(20) Stoessel, F. *Chem. Eng. Prog.* **1993**, *89* (10), 68.

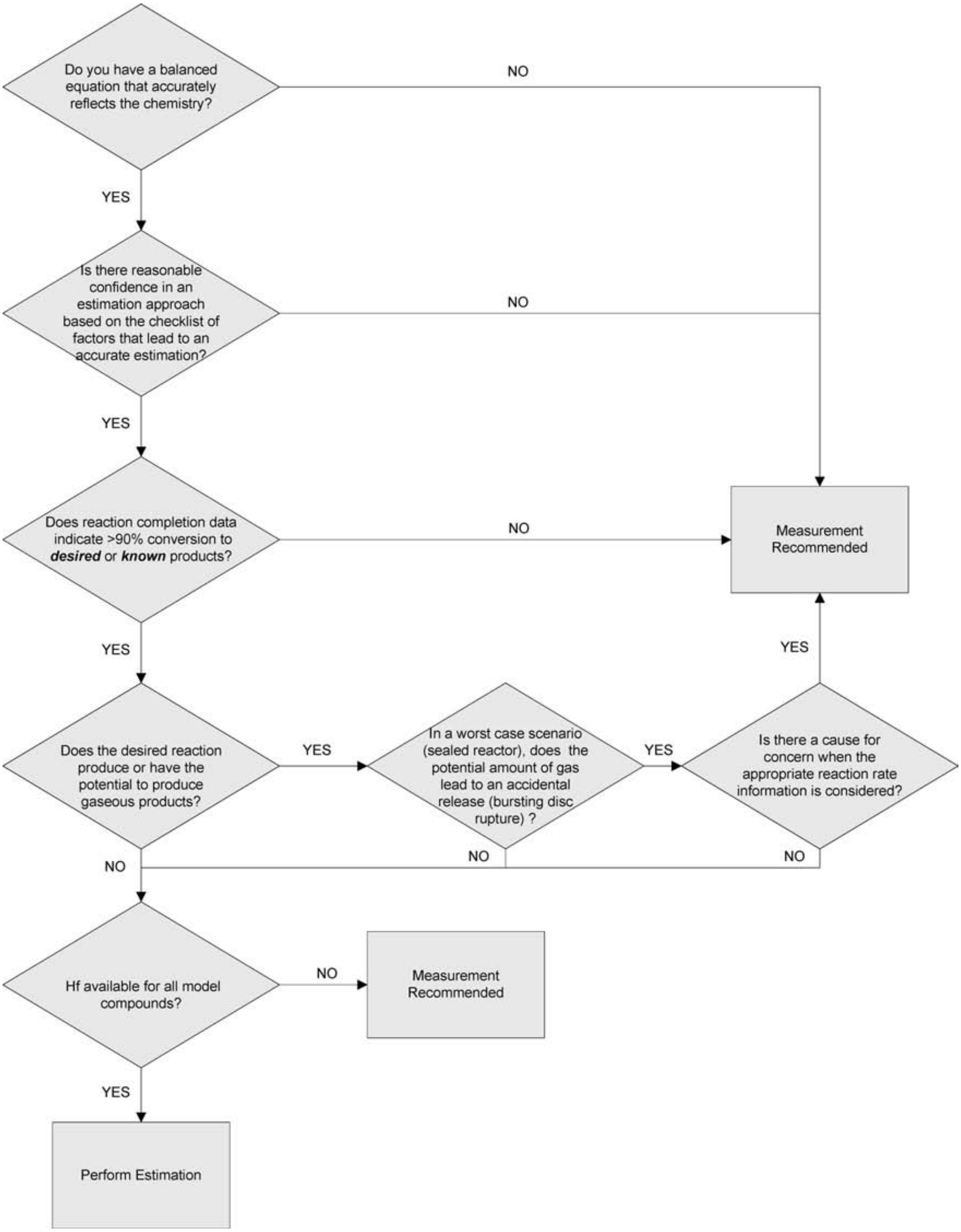


Figure 3. **Decision tree to help determine if a heat of reaction should be estimated or measured.**

becomes hazardous (T_d), and the maximum temperature of the synthesis reaction (MTSR). MTSR is the peak temperature attainable if all of the heat from the desired reaction goes into self-heating of the batch (MTSR $= T_p +$ ATR). The potential hazard increases from left to right, scenario A being the safest, and scenario E being the most hazardous.

We have created a second decision tree as an aid in deciding if estimation should be *applied* to support a scale-up run in a production facility; see Figure 5. Our approach is to apply estimations to processes that fall into scenarios A, B, and C based on the following rationale. In scenario A, the MTSR is below the boiling point that itself is below the temperature at which the rate of decomposition becomes hazardous (T_d). The rate of the reaction is not important because even if all of the heat is released instantaneously, the temperature will not reach the boiling point or T_d. This is considered to be a thermally safe process and will likely proceed to the kilo laboratory or pilot plant with a heat estimation unless there are concerns related to off-gassing.

For scenario B, although the MTSR is below the boiling point and T_d, T_d is below the boiling point. The rate of the reaction is not important, but overheating from some other source (e.g., heat input from the jacket) could lead to hazardous decomposition prior to boiling. Measures to prevent overheating

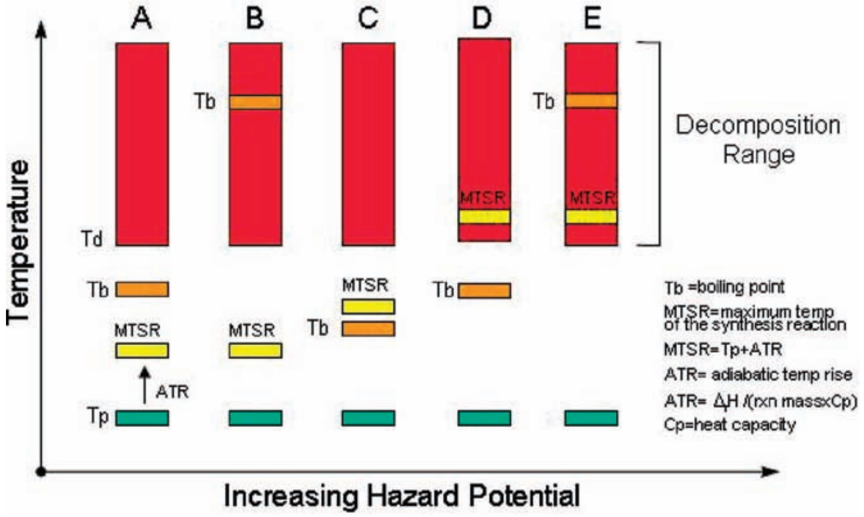


Figure 4. **Five scenarios that depict the relative risk associated with chemical processing.**

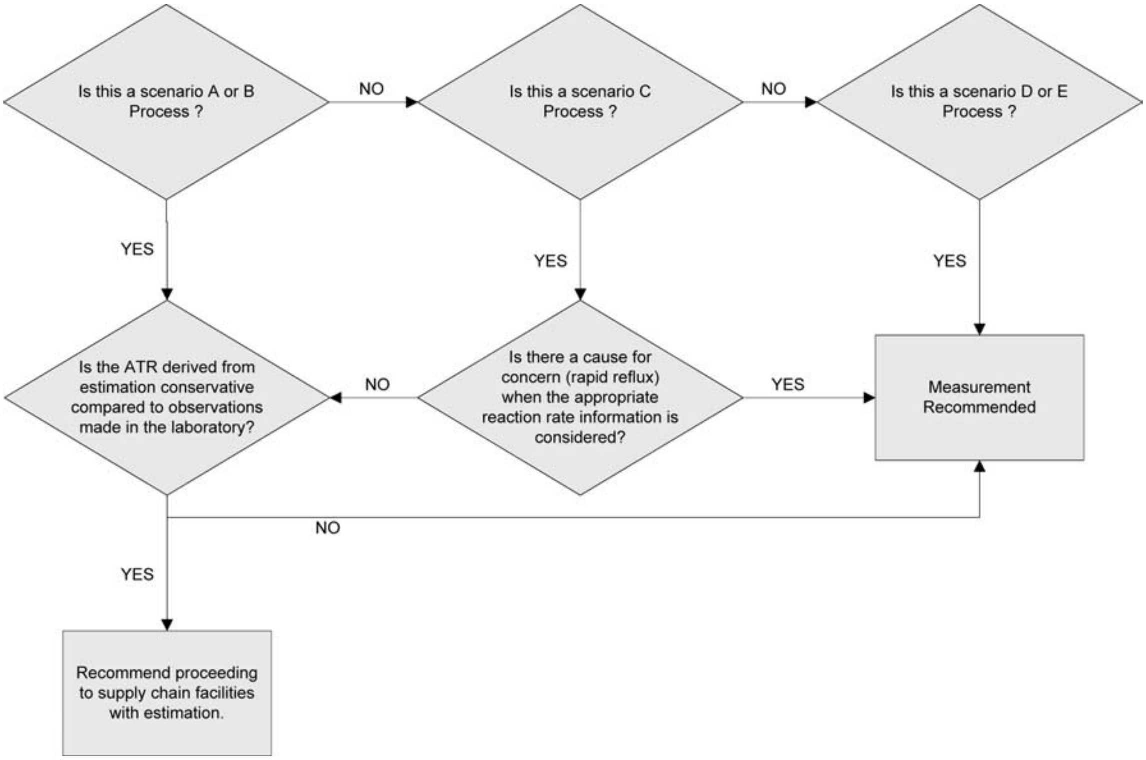


Figure 5. **Decision tree used to determine if an estimated heat of reaction should be applied to support a scale-up run in a production facility.**

should be applied. Use of a heat estimation is generally accepted in this scenario unless there are other specific concerns (e.g., off-gassing) to suggest that a measurement is necessary.

In scenario C, the MTSR exceeds the boiling point, but the temperature where the rate of decomposition becomes hazardous (T_d) is above both. Potential exists for overpressurization of the vessel due to vapor pressure effects. Measures to control the reaction rate may need to be applied. Use of a heat estimation may be acceptable if it can be shown that (1) the reaction is dose-controlled, (2) the reaction rate is sufficiently slow, or (3) historical T_r–T_j data from a laboratory, kilo laboratory, or pilot plant run does not show cause for concern. In the case of pressurized reactions, heat estimation may be acceptable if the operating pressure plus the vapor pressure of the reaction mixture at the MTSR is significantly below the maximum allowable working pressure of the vessel. It is important to note that estimation does not give any information regarding the reaction rate. We generally request conversion as a function of time from the project laboratory in order to derive the semiquantitative rate data.

Scenarios D and E are not good candidates for estimation. In D, The MTSR exceeds the boiling point and the temperature where the rate of decomposition becomes hazardous (T_d). Reaction control and/or protection must be applied. In the event of an uncontrolled reaction, evaporative cooling may prevent significant decomposition, since the boiling point is below T_d. In E, The MTSR exceeds T_d but not the boiling point. Loss of reaction control will initiate significant decomposition, which may lead to hybrid pressure effects (i.e., gases formed from decomposition will contribute to the pressure generation inside the reactor as well as vapor pressure effects associated with the solvent). Reaction control should be applied and/or protection should be designed to mitigate the consequences of the decomposition. Processes are only classified as D or E if the decomposition is considered to be severe. For example, if the decomposition is determined to have relatively low energy and does not produce a significant amount of gas, then the process is not classified as D or E, and estimation may be appropriate. The determination is made on a case-by-case basis by a process safety professional.

To check the validity of the heat estimation, the decision tree asks if the ATR is conservative compared to observations made in the laboratory. Obviously, if the estimation predicts a 5 °C ATR and a 10 °C rise is observed in the laboratory, additional scrutiny and analysis is needed. As an additional reality check, it is a good idea to compare the estimated $\Delta_r H$ to values from similar reactions that have been estimated, measured, or reported in the literature.

Errors in Measurement and Estimation. It is difficult, perhaps even impossible, to say which value, the estimate or measurement, most accurately represents the true heat of reaction, but a discussion of the sources of error for each method is valuable. In particular, we are concerned about erroneously low heats of reaction since that would result in an erroneously low adiabatic temperature rise. The false sense of security derived from such erroneous data could lead to severe consequences.

Errors that Cause a Measurement to be Too Low. Today's sophisticated calorimeters can provide very accurate reaction enthalpies, but carefully designed experiments are necessary in order to achieve a high level of accuracy. Heat loss from the calorimeter, either through the walls or lid, is a common source of error. Processes at or near reflux have a high potential for heat loss, and special precautions must be taken to ensure accurate measurement including: (1) careful insulation and/or heating of the lid, (2) suppression of the boiling point by pressurization of the reactor with an inert gas, and (3) lowering of the reaction temperature at least 10 °C below the reflux temperature. The latter strategy can be problematic if the reaction rate slows beyond a practical level.

Reactions that off-gas can also suffer from heat loss if the gas is allowed to exit the calorimeter. From a practical standpoint this is generally considered to be acceptable because this heat loss will also be experienced on-scale. The loss will likely not scale linearly, and therefore it may be desirable to prevent or estimate the loss in order to determine a worst-case scenario. Use of a sealed reactor is a potential solution if the reaction does not depend on loss of the gas to drive it to completion. A particularly difficult situation occurs with reactions at or near reflux that also off-gas. A combination of the above techniques, if possible, may be necessary to obtain an accurate measurement.

Reactions that have a heat flow near or below the sensitivity of the calorimeter present an obvious source of error. Today's modern calorimeters offer high sensitivity (microwatts can easily be detected), but slow reactions or those with relatively low enthalpy changes can lead to large errors in measurement. From a practical standpoint, the inability to accurately measure the reaction heat is not an issue because reactions with low heat flow do not raise significant process safety concerns. However, it is desirable to have an accurate assessment of the thermal *potential*, when possible, even if the reaction kinetics moderate the heat flow such that the practical concern is low.

Integration of the area under a heat flow curve provides the heat of reaction and another potential source of error. In order to accurately integrate the area, an accurate baseline heat flow is essential. Baseline shifts can cause large errors in the integration because the baseline can be drawn in many different ways, and the correct baseline is not always not obvious.

The heat associated with differences in temperature between the contents of the reactor and a component that is being charged is known as sensible or dosing heat. Mathematically, sensible heat is the product of the mass and heat capacity of the dose multiplied by the temperature difference. Sensible heat can usually be accounted for quite accurately, but there are instances when the sensible heat is unknown or inaccurate, leading to errors in the reaction enthalpy. In a general sense, if a hot component is being added to a cold reaction mixture, the reaction heat is determined by *subtracting* the sensible heat. Therefore, anything that makes the sensible heat erroneously high will result in a reaction heat that is too low. On the other hand, if a cold component is being added to a hot reaction mixture, the reaction heat is determined by *adding* the sensible heat. Therefore, anything that makes the sensible heat erroneously low results in a reaction heat that is too low. Some reaction calorimeters, such as the SuperCRC, attempt to eliminate the issue of sensible heat altogether by attempting to equilibrate the temperature of the dose to the reaction temperature. However, this approach may still lead to erroneously low reaction heats for reactions that are above ambient temperature. This situation occurs when the dose is colder than predicted on the basis of the block temperature and is usually the result of injecting the dose before it has time to thermally equilibrate up to the reaction temperature.

Poor analytical data is another potential source of error in calorimetric measurements. Reaction heats are typically normalized to 100% conversion. Overestimation of the conversion results in a reaction heat that is too low. Likewise, since reaction heats are generally reported on a molar basis, accurate assay of the starting materials is important. If the assay of the material is overestimated, a reaction heat quoted on a molar basis will be too low, assuming the impurities do not react with higher energy compared to the desired reaction.

The accuracy of a measurement is only as good as the accuracy associated with the instrument. Obviously, if an instrument is out of calibration or maintained poorly, then the measurement will suffer. Faulty thermocouples, inaccurate heat transfer coefficents, or contaminated heat transfer fluid are a few examples that lead to poor accuracy. Another factor that contributes to large errors in heat flow is inaccurate assessment of the heat transfer area. This is especially true for small reactors were small errors lead to large percentage errors. Routine calibration and maintenance is recommended to minimize this source of error. Hydrolysis of acetic anhydride is the standard that most calorimetrists use to check the accuracy of their reaction calorimeters.

Processes that incorporate a temperature ramp during a reactive step present a special challenge as temperature ramping often leads to combination of all the errors mentioned above.[21] When faced with such a process, the best approach is to make the process isothermal, if possible. This is usually accomplished by heating a mixture of all but one component to the desired reaction temperature, followed by careful dosing of the final component in order to maintain the batch temperature. In fact, in cases where the reaction kinetics are relatively fast compared to a reasonable addition time, this is known as a dose-controlled process. Not only are dose-controlled processes usually preferred from a process safety perspective, but in many cases they are also desirable from a chemistry perspective because they lead to higher chemical selectivity and improved yields. When limitations prevent a process from being made isothermal, special precautions must be taken to ensure accurate measurement.[21]

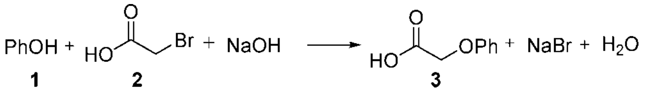
Errors that Cause an Estimation to be Too Low. Given eq 1, the most obvious source of error in an estimation is the error associated with measurement or estimation of the heats of formations themselves. A heat of formation for a product that is erroneously positive will result in a reaction enthalpy that is too low (erroneously positive). Likewise, a heat of formation for a reactant that is erroneously negative will result in an erroneously low reaction enthalpy (erroneously positive). Heats of formation estimated using Benson groups are generally very accurate, within 10 kJ/mol.[15,16] Several compilations of experimentally determined formation heats, including error analysis, are available.[11–14] Literature sources outside of these compilations should be used with caution. It is always a good idea to cross-check literature values against an estimation technique to check for consistency. Large inconsistencies should be investigated further.

Since the accuracy of an estimation is centered around an accurate knowledge of the balanced equation, errors or inaccuracies in the knowledge of the chemistry that is taking place can cause large errors in the estimation. Closely related to this concept is that of unknown side reactions. Obviously if an exothermic side reaction is not accounted for in the estimation, the predicted reaction heat will be too low.

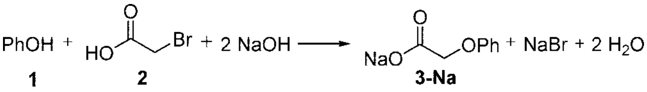
Finally, unknown physical interactions such as exothermic heats of mixing, coordination, complexation, or crystallization can cause an estimation to be too low. Examples of all of these errors will be discussed in some detail.

Examples of Errors in Heat Estimation. The 50 examples presented in Table 1 and Figure 1 represent our current competency with heat of reaction estimation. The exercise of comparing estimation to measurement forced us to scrutinize both techniques very carefully, and resulted in greater accuracy in the values obtained from both methods. It is instructive to look at some of our early estimations to see where errors were made. In fact, the checklist of factors that lead to an accurate heat estimation (vide supra) were derived from mistakes that we made in our early days of practicing estimation. Hopefully, these examples will keep beginners from making the same mistakes.

***Scheme 1.* Original balanced equation used to estimate entry 34, Table 1**



***Scheme 2.* Actual chemistry that is occurring in entry 34, Table 1**



The first example, entry 34 from Table 1, provides a good argument for knowing the balanced equation and knowing when the heat is evolved. The chemistry involves nucleophilic substitution of bromoacetic acid, **2**, with a phenol, **1**, to give the desired carboxylic acid, **3**. The balanced chemical equation used for our original estimation is shown in Scheme 1. Our original estimation gave a $\Delta H_{\mathrm{rxn}} = -62.7$ kJ/(mol of the phenol), and the original measurement was quoted as −98.2 kJ/mol, a difference of 35.5 kJ/mol, or +36.2% error.

Upon closer inspection of the balanced equation, we realized that an error was made. Because the reaction used 2.1 equiv of NaOH (aq), the product would be present as the Na salt, **3**-Na, not the carboxylic acid, **3**. Therefore, we had missed the heat of this acid–base reaction. The correct balanced equation is shown in Scheme 2 above. Since the heat of formation for **3**-Na is not readily available, we added the deprotonation of acetic acid with NaOH (aq) to give sodium acetate and water to model the reaction. The new estimation gave a $\Delta H_{\mathrm{rxn}} = -118.5$ kJ/(mol of the phenol), an error of −20.7% compared to the original measurement that was quoted.

A closer look at the RC1 experiment reveals that the process involves addition of the phenol to excess 2 M NaOH (aq) followed by addition of the bromoacetic acid. The heat for generation of the sodium phenolate by addition of the phenol was measured to be −11.2 kJ/(mol of phenol) and the heat for addition of the bromoacetic acid was −98.2 kJ/mol, so the heat for the overall reaction heat from the measurement is actually −109.4 kJ/mol, a difference of only 8.3% verses the estimation. This example demonstrates the importance of having the correct balanced equation and knowing when the heat is released. Even though the heat evolved with formation of the sodium phenolate is quite small, it could have potentially given a much larger ATR under reaction conditions in which the heat sink were smaller.

The second example, entry 40 from Table 1, highlights the importance of being aware of off-gassing and identifying physical phenomena that produce heat. The chemistry is generation of an acid chloride by treatment of a carboxylic acid with thionyl chloride and pyridine in acetonitrile. Our original estimation gave a $\Delta H_{\mathrm{rxn}} = -38.1$ kJ/(mol of the carboxylic acid), and the measurement was −136.2 kJ/mol, a difference of 98.0 kJ/mol, or +72% error! It is important to note that no off-gassing was observed in the measurement and 3.5 equiv of pyridine was used. The original estimation used the gas phase heat of formation for SO_2, −296.83 kJ/mol. Use of the liquid

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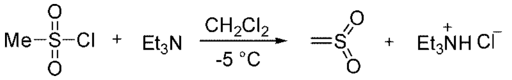
(21) Hoffmann, W.; Kang, Y.; Mitchell, J. C.; Snowden, M. J. *Org. Process Res. Dev.* **2007**, *11*, 25.

Scheme 3. **Side-reaction of methanesulfonyl chloride with triethylamine**



phase heat of formation, −320.5 kJ/mol, provides an estimation of −61.8 kJ/mol, a difference of 74.4 kJ/mol, or +55% error. Since no off-gassing was observed in the measurement, the use of the liquid phase number is more accurate. As stated earlier, as a general rule, we now use the more conservative number if the fate of the off-gas is unknown. The second adjustment to our estimation is related to heat from two physical events. There is a significant heat of complexation between pyridine and SO_2, −48.6 kJ/mol, and a smaller heat of solution of $SOCl_2$ in pyridine, −10.2 kJ/mol.[22,23] Adding these heats to the estimation we get a value of −120.6 kJ/mol, a difference of 15.6 kJ/mol, or +12% error. Great care must be taken when considering off-gassing and in identifying all secondary sources of heat such as complexation and solution. As shown in this example, the effect on the estimation is dramatic. It is interesting to note that even with this large error the safety scenario did not change, but that the level of error was only a result of our inexperience with estimation.

The next example, entry 23 from Table 1, highlights the importance of knowing the fate of excess reagents. The chemistry is mesylation of an alcohol with 1.2 equiv of methanesulfonyl chloride and 1.6 equiv of triethylamine at −5 °C in methylene chloride. The original estimation gave a $\Delta H_{\rm rxn} = -169.4$ kJ/(mol of the alcohol) and the measurement gave −218.8 kJ/mol, a difference of 49.4 kJ/mol, or +23% error. We began to suspect that the excess methanesulfonyl chloride may react with the triethylamine, and a literature search confirmed our suspicion. Methanesulfonyl chloride reacts with triethylamine to give a highly reactive sulfene, as shown in Scheme 3.[24]

We measured the heat of reaction in a SuperCRC calorimeter by charging methanesulfonyl chloride to a solution of triethylamine in methylene chloride at −5 °C. This gave a heat of reaction of −112 kJ/(mol of methanesulfonyl chloride). Considering the 0.2 equivalent excess of methanesulfonyl chloride used in the alcohol mesylation experiment, −25.0 kJ/(mol of alcohol) can be expected from the side reaction. Therefore, adding this correction to the original estimation gives −194.4 kJ/(mol of the alcohol), a difference of 24.4 kJ/mol, or 11% error. Again, the safety scenario did not change between the original estimation and the improved estimation, but it is easy to see that a process involving a smaller heat sink and/or a large excess of methanesulfonyl chloride in the presence of a base could lead to a dangerous under-estimation if the exothermic side reaction is not taken into account. How do you know to consider a side reaction if you do not know it exists? You do not, but when significant excesses are present, you should search the literature for known side reactions, or search compatability hazards databases such as NOAA.[25] Obviously, lack of a literature reference does not mean that a reaction does not exist, but due diligence is important. A relatively quick experiment in the SuperCRC or other screening calorimeter is also a viable option, since the data can be used for future estimations.

The last example, entries 10 and 43 from Table 1, highlights the importance of identifying equilibrium reactions. Treatment of methyl alcohol with potassium *tert*-butoxide generates potassium methoxide. The aromatic fluoride is then added to the methoxide, and fluoride displacement gives the desired phenyl methyl ether. The original estimation for step 1, the formation of methoxide, gave a $\Delta H_{\rm rxn} = -155.3$ kJ/(mol of methanol) and the measurement gave −58.0 kJ/mol, a difference of −97.3 kJ/mol, or −202% error, meaning that the estimation is much more conservative than the measurement. It is important to realize that this is an equilibrium reaction, and therefore only a portion of the heat is observed in the measurement, whereas the estimation assumes 100% conversion. The estimation for step 2, fluoride displacement, gave a $\Delta H_{\rm rxn} = -96.7$ kJ/(mol of the fluoride) and the measurement gave −139.0 kJ/mol, a difference of 42.3 kJ/mol, or +30% error, meaning that the measurement is more conservative than the estimation. Since the formation of the methoxide is an equilibrium, the heat left to drive that equilibrium to completion (by consumption through reaction with the fluorobenzene) will also be evolved along with the heat of the displacement. An estimate of the heat left in the equilibrium is $-155.3 - (-58.0) = -97.3$ kJ/(mol of the fluorobenzene). Therefore, adding this heat to the original estimate for step 2 gives an updated estimate, −194.0 kJ/mol, a difference of 55.0 kJ/mol, or −40% error. Normally the heat left in an equilibrium will not be known, and therefore in situations like this we recommend adding the estimated heat from step 1 to the estimated heat for step 2 in order to arrive at a conservative value for step 2.

Heat Estimation Database. In order to maximize the efficiency gain and to ensure accuracy in our estimations, we have created a heat estimation database that allows for (1) rapid archival/retrieval of model compounds, (2) automatic calculation of reaction heat and adiabatic temperature rise, and (3) reporting/documentation of the results. A significant amount of work goes into finding reliable heat of formation data for the more complex model compounds. Therefore, it makes sense to capture the data in a format that is easy to locate for future use, and our database contains structure, keyword, and reaction searching to meet this need. In order to ensure accuracy, we are in the process of cross-checking all of the literature $\Delta_f H$ values against Benson group estimations. Significant discrepancies lead to further investigation. To further enhance accuracy, the database uses the $\Delta_f H$ information and the process recipe to automatically calculate the heat of reaction and the adiabatic temperature rise, respectively. Finally, all the information is documented using a unique session code, and an easy to read report can be generated at the push of a button. More information regarding this database will be published in a future article.

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(22) Benoit, R. L.; Milanova, E. *Can. J. Chem.* **1979**, *57*, 1319.

(23) Kanonerov, V. P.; Tsvetkov, V. G.; Lelekov, V. E.; Biryukova, T. G. *Russ. J. Gen. Chem.* **1997**, *67* (7), 1088.

(24) March, J.; Smith, M. B. *March's Advanced Organic Chemistry*, 5th ed.; Wiley-Interscience: New York, 2001, p 1338. The reactive sulfene probably goes on to react with other components of the mixture, but the heat from these further side reactions is not included in the estimation.

(25) National Oceanic and Atmospheric Administration; download the Free Chemical Reactivity Worksheet at http://response.restoration.noaa.gov/chemaids/react.html.

Future Plans and Conclusions. Predictive techniques have a very important place in the reactive chemicals evaluation process, and the use of estimation techniques based on $\Delta_f H$ for calculation of reaction heats has been shown to be a valid technique for a number of chemistries. The benefit of predictive techniques is that their judicious and knowledgeable use can save valuable time in today's global arena where the timelines to scale-up are compressed. Efficiency, without compromising on safety, can be achieved by allowing process safety professionals to make sound scientific judgment on how and when estimation can be used.

Experimental testing and estimation techniques are complimentary in the sense that agreement between experiment and theory adds to the reliability of, and hence one's confidence in, the hazard assessment prior to scale-up. Any disparity between experiment and prediction should lead to further analysis, testing, or calculations. However, only in a few number of cases are we likely to determine the reaction heat by both estimation and measurement. Therefore, this paper outlines our strategy for the independent use of either technique, when appropriate, to assess process hazards within Pfizer. In fact, in many cases, estimation can have distinct advantages over measurement techniques. In addition, estimation can be used to give heat values for reactions where measurement is not practical or safe. The use of predictive techniques will also help to focus the efforts of the hazard evaluation specialist on the most appropriate reactive chemical testing.

We will continue to grow our knowledge, experience, and confidence as we explore future reactions. The estimations presented herein have been performed by using $\Delta_f H$ thermochemical data. Future work will make more use of analogous chemistry that has been measured, both as an estimation technique and as comparative data for estimation calculations. When measurements are undertaken on such interactions as heats of mixing/solution and heats of coordination/complexation, the results of these experiments will help form a database that will serve to further enhance the scope and accuracy of heat estimation. We will also be working on the development and applicability of T_r–T_j data (pseudo measurement) from appropriate laboratory instruments to support scale-up into our production facilities.

Supporting Information Available

An example of heat estimation. This material is available free of charge via the Internet at http://pubs.acs.org.

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