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‘One-pot’ Hammett plots: a general method for the rapid acquisition of relative rate data†Hon Man Yau,^a Anna K. Croft^b and Jason B. Harper^{*a}

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A general ‘one-pot’ method for determining relative rates of reaction in complex mixtures has been established using free energy relationships to demonstrate its utility. Competition experiments involving as many as seven species gave relative rate constants that are in good agreement to those obtained from individual kinetic analyses.

Free-energy relationships, such as the Brønsted relation¹ and the Hammett equation,² have long been used to obtain mechanistic information and predict reaction outcomes. The knowledge of the relative rates of a series of reactions is necessary to establish a free-energy relationship for a given reaction. However, the acquisition of rate constants is not always a trivial exercise when precise control of reaction conditions, as well as temporal considerations in sample handling, repetition, reaction times and data processing, are taken into account.

Binary competition experiments^{3–7} have been used to circumvent some of the problems listed above. That being said, in order to obtain relative rate information for n related species, $n - 1$ experiments are still necessary with the result that some of the time-consuming procedures involved with individual kinetics experiments still exist.

Various strategies have been reported in the literature for the rapid evaluation of absolute and/or relative rate information involving more than two competing species. One such example has been the simultaneous kinetic analyses of the esterification and saponification of eight different isomers of hexanoic acid and methyl hexanoate, respectively.⁸ Whilst the ability to obtain eight rate constants in a single experiment is impressive, the periodic sampling and analysis required in this case is time consuming and the requirement for sample preparation prior to analysis may lead to artifacts in other cases. Further, chromatographic conditions for optimal resolution may not always be readily available.

Another example of note is the use of a high-throughput ‘one-pot’ method in the assessment of Hammett substituent constants.⁹ In this case, an “analytical construct” attached to a

solid support was used initially in the competitive pre-attachment of differently-substituted anilines; the resultant product distribution was determined using ESI⁺-MS after liberation of species made up of the reacted aniline and an MS sensitising moiety (the basis of using the analytical construct). Due to the sensitivity of this analytical method, highly accurate relative rate information was obtained. The use of such an analytical construct with a specific reactive functionality, which is not necessarily trivial to prepare itself,¹⁰ poses several limitations. In particular, the reactions are restricted to those for which conjugation is facilitated by the particular reactive functionality, and sample preparation is still required to remove the species to be analysed from the solid support.

A *general* method that is without the limitations stated above and allows the acquisition of relative rate information for many species in a single competition experiment is therefore highly desirable. Herein, we demonstrate the utility and scope of such a method.

Key to the process described is the relationship shown as eqn (1). Originally derived by Ingold and Shaw,¹¹ it relates the rate constants for the reaction of two competing substrates to the amount of each substance present at the beginning of the reaction and at the time of analysis (see ESI†, Appendix S1).

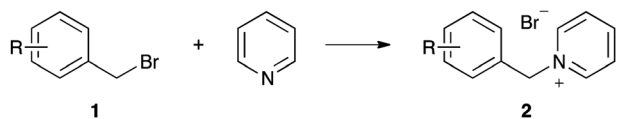
$$\frac{k_x}{k_y} = \frac{\ln\left(\frac{s_x}{s_{x,t=0}}\right)}{\ln\left(\frac{s_y}{s_{y,t=0}}\right)} \quad (1)$$

This equation differs from the expression that is commonly used,^{3–7} which equates the ratio of the products of two competing reactions to the ratio of their rates. The latter only holds when equimolar amounts of competing starting materials are used and the competing starting materials are present in large excess, relative to the common reactant. As such, an immediately apparent advantage of using eqn (1) is that there is no such requirement; in fact, provided the ratio of any two competing substrates is known, the absolute concentrations are not required. Given this, and since the extent of each reaction is also irrelevant (provided none have gone to completion), sub-stoichiometric amounts of the common reagent can be used for fast reactions, whilst super-stoichiometric amounts can be used for slow reactions. All the processes are carried out, by definition, under the same conditions and the number of competing reactions is only limited by the technique used to analyse the mixture;¹²

^a School of Chemistry, University of New South Wales, Sydney, NSW 2052, Australia. E-mail: j.harper@unsw.edu.au; Fax: +61 2 9385 6141; Tel: +61 2 9385 4692

^b School of Chemistry, University of Wales Bangor, Bangor, Gwynedd LL57 2UW, UK

† Electronic supplementary information (ESI) available: General procedures, NMR spectra, Hammett plots and data from all experiments described in the text. See DOI: 10.1039/c2cc34074g



Scheme 1 The Menshutkin reaction between the benzyl bromides **1a–g** and pyridine (**a** R = *p*-OCH₃, **b** R = *p*-CH₃, **c** R = *m*-CH₃, **d** R = H, **e** R = *p*-Br, **f** R = *p*-CO₂CH₃, **g** R = *p*-NO₂).

all that is required is that the extent of reaction in each case can be determined accurately.[‡]

The efficacy of the method is shown by considering the competing Menshutkin reactions between pyridine and the seven benzyl bromides **1a–g** (Scheme 1) and comparing data from competitive experiments with the equivalent results obtained from individual kinetic experiments that we have previously reported.¹³ The resulting Hammett plot has been shown to be non-linear and affords an insight into how the method performs in such a complex case (*cf.* the linear case). ¹H NMR spectroscopy, which allowed the extent of reaction of each of the bromides **1a–g** to be determined without the need for preparation of the reaction mixture, was chosen as the analytical method though other methods which distinguish starting materials **1a–g** and products **2a–g** would also be appropriate.

A sub-stoichiometric amount of pyridine was added to the mixture of the benzyl bromides **1a–g** of known composition to initiate the competition experiment. The extent of reaction in each case was determined using the relative amounts of each of the starting materials **1a–g** and each of the products **2a–g** present, which were in turn deduced from the ¹H NMR integrals corresponding to the resonances of the respective benzylic protons (Fig. 1). It should be noted that although signal overlap was observed between compounds **1a** and **1d**, **1c** and **1e**, **2b** and **2c** and **2d** and **2e**, since the composition of the initial reaction mixture was known, simple relationships between the relative amounts of starting materials and products were used to deduce the relative amounts of all species (see ESI[†] for full details). Using the normalised integrals, relative rate constants were calculated using eqn (1).

The relative rate constants obtained for the Menshutkin reactions using the method presented in this work are in good agreement (see ESI[†]) with those previously reported,¹³ for both the reactions carried out in acetonitrile and in the ionic liquid [bmim][NCF₃SO₂]. The latter case shows that the method can be used with non-traditional solvents. The comparison of individual

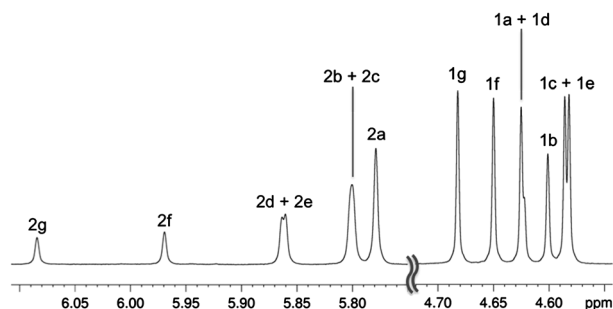


Fig. 1 A representative ¹H NMR spectrum (500 MHz) showing the final distribution of starting materials and products of the competitive Menshutkin reaction between benzyl bromides **1a–g** and pyridine to afford the corresponding pyridinium bromide products **2a–g**.

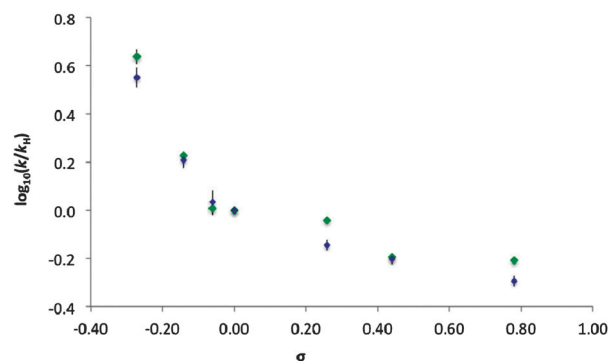
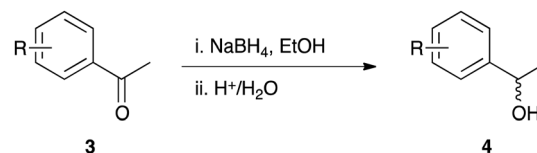


Fig. 2 Hammett plots constructed from the relative rate information obtained for the Menshutkin reactions between benzyl bromides **1a–g** and pyridine, carried out in acetonitrile at 300.7 K. Data shown is from this work (blue) and from that reported previously (green).¹³

and competitive data is illustrated for the acetonitrile case in Hammett plot form as Fig. 2. The smooth nature of the curve likely relates to a key advantage of the competitive case, that being that, by definition, all experiments are carried out under identical conditions. Importantly, using this method, the time taken from sample preparation to the construction of the Hammett plot was no more than one day.

The method is further demonstrated through considering the sodium borohydride reduction of the acetophenones **3a–d** (Scheme 2). As no reliable relative rate data was available in the literature with ethanol as the solvent,¹⁴ binary competition experiments were initially carried out. Subsequently, following the procedure described above, relative rate information for the competitive sodium borohydride reduction of acetophenones **3a–d** in ethanol was obtained; in all cases a sub-stoichiometric amount of reducing agent was used.[§] Along with analysis using ¹H NMR spectroscopy (see ESI[†]), ¹³C NMR spectroscopy utilising the relaxation agent tris(acetylacetonato)chromium(III) was also used (Fig. 3). For many systems, heteronuclear MR spectroscopy is envisaged to circumvent the issues of signal overlap that may occur when using ¹H NMR spectroscopy, due to the wider spectral window. The results from competition



Scheme 2 The reduction of acetophenones **3a–d** using sodium borohydride (**a** R = *p*-OCH₃, **b** R = *p*-CH₃, **c** R = H, **d** R = *p*-Br).

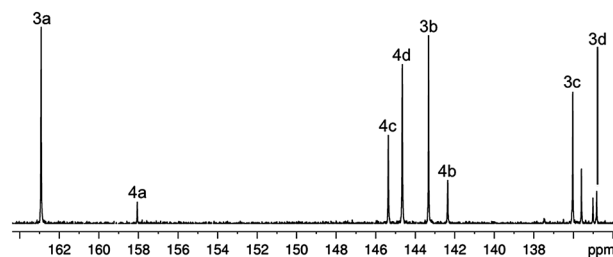


Fig. 3 A representative ¹³C NMR spectrum (150 MHz) showing the signals used to calculate relative rate constants of the competitive sodium borohydride reduction of acetophenones **3a–d**.

Table 1 Relative rate constants for the competitive sodium borohydride reduction, in ethanol at 295 K, of either all four acetophenones **3a–d** simultaneously or binary combinations of the acetophenones **3a–d**

Acetophenone	k/k_H (^1H)	k/k_H (^{13}C)	k/k_H (Binary)
3a	0.19 (0.03)	0.17 (0.04)	0.17 (0.07)
3b	0.44 (0.12)	0.43 (0.03)	0.36 (0.04)
3c	1	1	1
3d	3.62 (0.21)	3.42 (0.21)	3.74 (0.29)

experiments containing all four acetophenones **3a–d** are shown in Table 1 along with those obtained from binary competition experiments carried out under the same conditions.

The relative rate constants obtained from all the competition experiments with either all of the acetophenones **3a–d** or two at a time are the same within the uncertainties of the measurement, irrespective of the analytical method used. Likewise, the Hammett plots constructed from the different data sets have similar ρ values; 2.46 (^1H) and 2.42 (^{13}C) in the presence of all the acetophenones **3a–g** and 2.65 in the binary case.

These results illustrate the ability of this method to afford relative rate information for reactions with lifetimes much shorter than the timescale of the analytical method used; that is, it demonstrates that the absolute values of the rate constants are unimportant to the performance of the method. It is also worth noting the difference in rate between the fastest and the slowest reactions in this case is a factor of 20, demonstrating that such differences can be accurately determined using these analytical techniques. While not necessary in these cases, the range of accessible rates can be extended by increasing the proportion of the slower reacting substrate in the initial mixture.

As a comparison between spectroscopic and chromatographic analytical techniques, analysis of the competitive sodium borohydride reduction of acetophenones **3a–d** was also carried out using reverse phase HPLC. Along with requiring sample treatment prior to analysis, despite much effort being spent on optimising elution conditions, it was not possible to directly observe phenylethanol **4b**, which had to be extrapolated from the known quantities of other species at multiple wavelengths. The errors involved with extrapolation likely result in the significant deviation of the relative rate constant for the acetophenone **3b**–phenylethanol **4b** pair from that obtained using ^1H NMR spectroscopy (see ESI†). Otherwise, the relative rate constants obtained using reverse-phase HPLC are in good agreement with those obtained using NMR spectroscopy. While reverse-phase HPLC (and other chromatographic techniques) can potentially achieve better resolution of signals than NMR spectroscopy, and hence may be used in circumstances where NMR spectroscopy is simply not suitable, it should be noted that the time involved with the former is often substantially more than the latter. Also, NMR spectroscopy does not require pre-analysis work-up, so that quantitation can be performed in the native state of the reaction mixture and, more importantly, does not suffer from matrix effects. For these reasons, it is our opinion that NMR spectroscopy is a

superior technique in that it is more suitable for the rapid accrual of relative rate information where it is applicable.

Whilst stoichiometric processes have been demonstrated here, there is clear application of this method to catalytic systems. For example, relative rates of conversion of a range of substrates by a given catalyst (be it biological, metallic or organic) could be readily determined, although the contribution to the selectivity by binding and reactivity effects would require some deconvolution. While the presence of intermediates may complicate analysis, use of an appropriate analytical technique with sufficient resolution (such as ^{13}C NMR spectroscopy and HPLC – it does not matter what the analytical procedure is as the method itself is general) should overcome this.

In summary, a general method for the rapid assessment of relative rate information from competition experiments involving multiple competing species has been validated. Along with being inherently more flexible than existing methods in terms of the ratio of reagents present, both competing and not, there are clear temporal benefits over existing methodologies. All that is required is an analytical technique through which the extent of reaction can be determined; herein the utility of direct analysis using NMR spectroscopy has been highlighted.

Notes and references

† It is worth noting that such an analysis assumes that there is no reaction between each of the competing substrates, that there is no reaction between any of the substrates and any of the products, and that the competing species do not alter the reactivities of one another. Within these limitations, the method is general.

§ As a sub-stoichiometric amount of sodium borohydride is used, the observed rate constants are a composite of each of the possible reduction steps. However, this does not affect the method of analysis as is demonstrated by agreement between binary and competition experiments.

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