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A New Autocatalytic Thioacetate-Enal Addition Reaction: A Michael Addition or Not?

Gennadiy Ilyashenko,[a] Andrew Whiting,[a,*] and Allen Wright[b]

[a] Department of Chemistry, Durham University, Science Laboratories, South Road, Durham DH1 3LE, U.K.
Fax: (+44)-(0)191-384-4737; phone: (+44)-(0)191-334-2081; e-mail: andy.whiting@durham.ac.uk
[b] Department of Chemical Engineering, Newcastle University, Newcastle upon Tyne, NE1 7RU, U.K.

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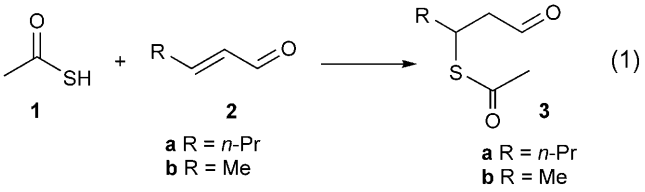
Abstract: Rather than proceeding through a Michael-type or 1,4-addition, thioacetic acid adds across unsaturated aldehydes in an autocatalytic manner and involving a double exotherm, as demonstrated by both adiabatic and reaction calorimetry. NMR studies show that an intermediate acylthio-hemiacetal is involved and that the product continues to react competitively with thioacetic acid.

Keywords: aldehydes; autocatalysis; Michael addition; sulfur

The Michael addition is one of the oldest[1,2] and most widely used organic reactions.[3–5] The accepted mechanism involves a direct addition of a nucleophile to the remote carbon of the conjugated C=O, or related system[6,7] and this view has changed little since its discovery. The utility of the Michael addition is due to its broad applicability in terms of both electrophile and nucleophile, with hetero-Michael reactions[8,9] being heavily investigated and exploited for accessing β-oxy-, aza- and thiocarbonyl compounds from unsaturated carbonyl derivatives. In particular, the hetero-Michael addition reaction between thioacetic acid **1** and *trans*-2-hexenal **2a** to derive adduct **3a** [Eq. (1)] is of interest because it occurs under both general acid- and base-catalysed conditions,[10,11] however, it has yet to succumb to asymmetric catalysis.[12] Herein, we report that the formal Michael addition outlined in Eq. (1) does not proceed as a simple bimolecular addition reaction as might be expected based on literature precedents.[6,7] Indeed, the reaction is multi-stage, involves at least two intermediates and is autocatalytic, hence, these unexpected results suggest that a reinterpretation of this, and perhaps other hetero-Michael additions, may be required.



(1)

Initially, adiabatic calorimetry[13] was employed for monitoring the progress[14,15] of the reaction shown in Eq. (1) using hexenal **2a** in order to correlate with the expected mechanism,[16,17] and to carry out process modelling and kinetic fitting[18] as a prelude to developing an asymmetric catalytic entry to the β-thioaldehyde **3a**[19] which is used as a fragrance/flavour compound.[10]

Adiabatic calorimetry, commonly used for thermochemical safety studies,[13] was applied using a simple Dewar flask and a PC-data high-frequency logging thermocouple to obtain adiabatic temperature profiles (Figure 1) for the reaction of **1** with **2a** in different solvents [Eq. (1)]. Unexpectedly, for several solvents, the reaction clearly exhibited a two-stage temperature rise, indicating a two-stage reaction process (Figure 1). An adiabatic temperature rise normally exhibits self-acceleration due to positive feedback of temperature with Arrhenius kinetics. The presence of a distinct second adiabatic temperature rise is usually caused by the primary reaction raising the system temperature to a sufficient level that a secondary reaction is initiated. However, closer examination of some of the experiments revealed that this was not the case.

In all the Dewar experiments (Figure 1) there was a small deviation from ideal adiabatic reactor behaviour due to heat loss, with gradual cooling of the system as the reaction proceeded to completion. As a result of this cooling, the temperature derivative, dT/dt, is re-

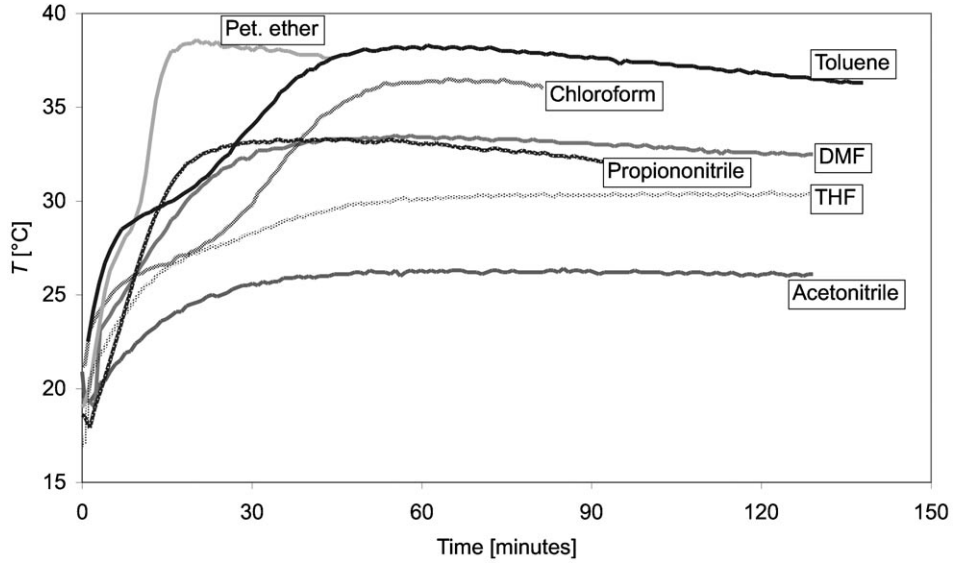


Figure 1. Temperature *versus* time for the reaction shown in Eq. (1) in different solvents (Note: DMSO was omitted because of safety concerns[20]).

duced between the first and second transients. With higher levels of heat loss the derivative tends to zero or even becomes negative (see Supporting Information for the example of this effect in the case of toluene). This is an important observation: if $dT/dt \leq 0$, positive feedback of temperature to produce self-acceleration cannot occur, hence, the second temperature rise is not an onset Arrhenius effect. This self-accelerating reaction suggests that the inherent reaction mechanism is in some way autocatalytic.

In order to demonstrate this effect more clearly, additional isothermal experiments were carried out using an HEL SIMULAR™ reaction calorimeter using power compensation[20] to measure the reaction exotherm, Qr (W). Precise temperature control was achieved using an external cooling system together with regulated electrical heating inside the vessel. Changes in the heater base load (power compensation) were monitored to obtain a direct measurement of Qr. The reaction mixture was also sampled during these runs and analysed with respect to hexenal. When thioacetic acid **1** was first added to a solution of *trans*-2-hexenal **2a** in toluene the reaction produced a double exotherm. Once this reaction was completed, additional *trans*-2-hexenal **2a** and thioacetic acid were added. This time, only a single exotherm was observed (Figure 2, a). For the second addition, only two-thirds the quantities of **1** and **2a** were added in order that the power compensation could cope with the sudden large exotherm. The total energy released for each addition was calculated from the integral of the Qr curves (Figure 2, a) and showed that the overall heat of reaction was approximately the same for each addition. Figure 2, b compares the chemical conversion of hexenal with the corresponding thermal conversion, θt, calculated as θt = (heat evolved up to time t)/(total heat evolved to reaction completion) [Eq. (2)].

$$\Theta_t = \frac{\int_0^t Qr}{\int_0^{end} Qr} \quad (2)$$

The fact that the chemical conversion curves for hexenal **2a** do not match the overall reaction thermal conversion is not surprising and supports the view that more than one reaction is taking place, each with a different heat of reaction.

These mergers of the double peaks of the Qr signal for the first addition into a single immediate exotherm following the second addition strongly supports the concept of autocatalytic behaviour as suggested by the adiabatic calorimetry. The challenge, therefore, was to elucidate a suitable reaction mechanism that could account for this observed behaviour.

In order to provide an insight into the possible reaction pathways and to explain the observations shown in Figure 1 and Figure 2, dynamic (time resolved) NMR spectroscopy experiments were undertaken. *trans*-2-Hexenal **2a** and crotonaldehyde **2b** both exhibit the same adiabatic behaviour, therefore, the latter was selected as substrate of choice for NMR studies, thus simplifying NMR spectra interpretations. The results from the $CDCl_3$-based reactions revealed the presence of two new species (**A** and **B**), in addition to starting materials and product (see Supporting Information). Indeed, after careful examina-

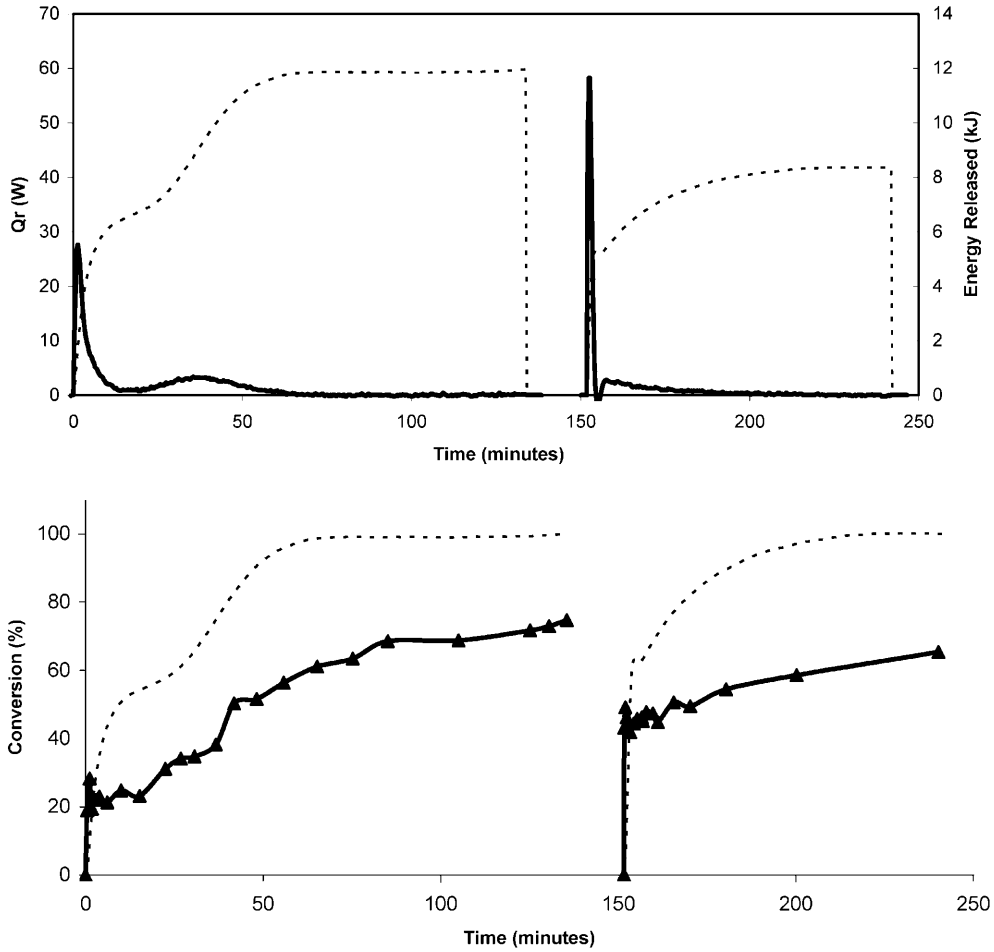
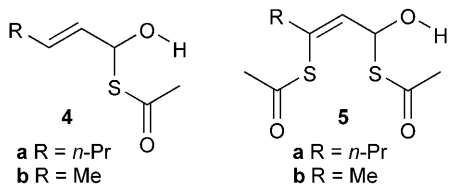


Figure 2. a (*top*) Exotherm (Qr, shown as a continuous line) and total energy released during isothermal calorimetry experiment (shown as a broken line). **b** (*bottom*) Thermal conversion (shown as a broken line) and chemical conversion (shown as triangles). Note, the second addition of reagents was made at 150 min.

tion of each of the ^{1}H NMR spectra, it was possible to postulate that species **A** and **B** correspond to structures **4b** and **5b**, respectively.



A further examination of the time-resolved NMR spectroscopic studies on crotonaldehyde **2b** showed that both the appearance and disappearance of two species **A** and **B** (i.e., **4b** and **5b**, respectively) could be followed over time in both toluene-d_8 and $CDCl_3$, although due to space constraints the focus is on results obtained from reactions carried out in $CDCl_3$ only (Figure 3).

Running this reaction using *trans*-2-hexenal **2a** in place of crotonaldehyde **2b** with thioacetic acid **1** produced the same results (see Figure S1 and Table S2 in Supporting Information) and, despite peak overlap, it was possible to decipher sufficient characteristic NMR signals to show that this reaction proceeded with two species equivalent to **A** and **B** being involved and proposed to have structures **4a** and **5a**, respectively. The fact that the reaction is autocatalytic was also unequivocally confirmed by adding 10 mol% of adduct **3b** to the reaction of **1** with **2b** prior to the initiation of the reaction, which resulted in a dramatic acceleration of the product formation and reduction in the formation of species **4b** and **5b**. We postulated that it might be the non-conjugated aldehyde function in the product **3** that was responsible for autocatalysis. In order to probe this, the thio-Michael addition was carried out in the presence of both 4-nitrobenzaldehyde (10 mol%) and propionaldehyde (10 mol%) as models of **3**. In both cases, the reactions were slower than in the uncatalysed reaction (Figure 4, d and e). It

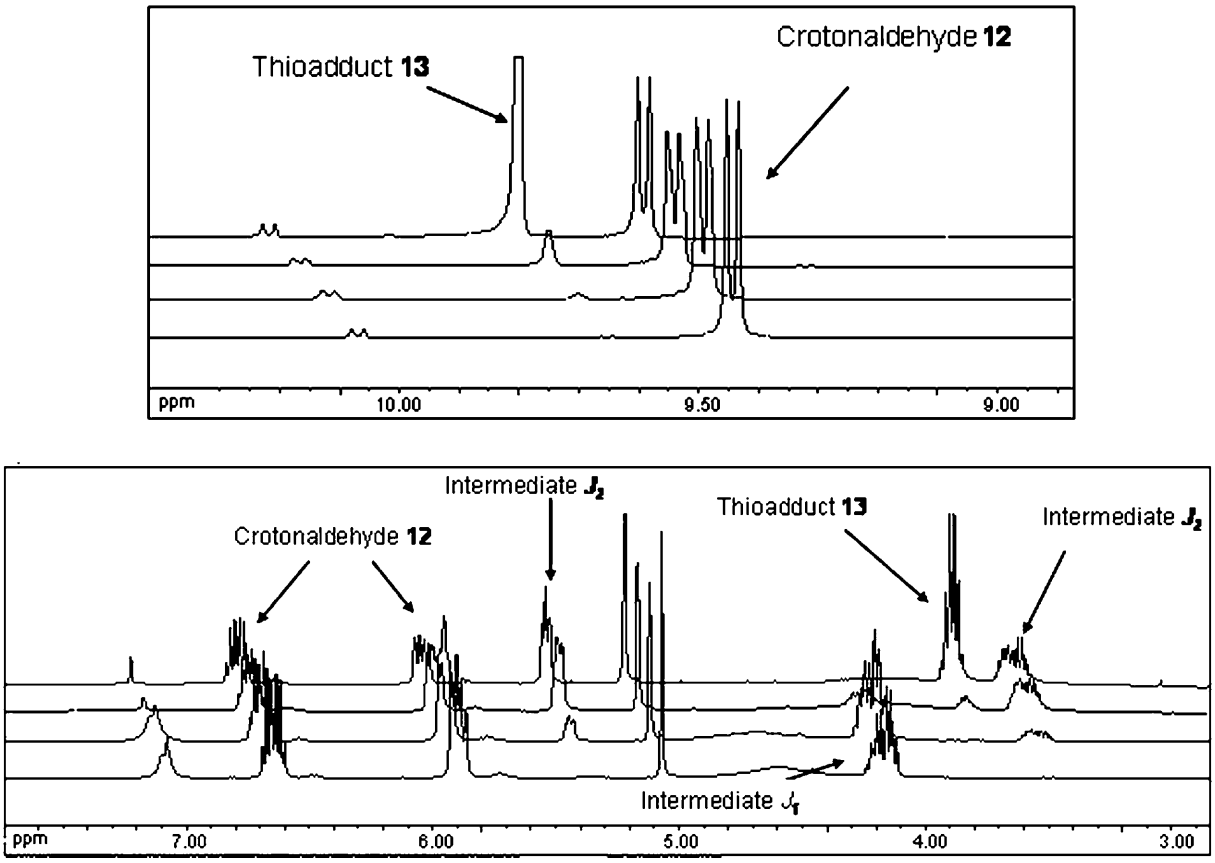


Figure 3. Representative data for ^{1}H NMR spectroscopy studies of the reaction between thioacetic acid **1** and crotonaldehyde **2b** in $CDCl_3$: changes in the aldehyde region (appearance of the product) and changes in the alkene region (appearance and disappearance of intermediates), time at which spectrum was collected (from front to back): $t_1 = 7$ min, $t_2 = 14$ min, $t_3 = 26$ min, $t_4 = 160$ min; (For the complete summary of ^{1}H NMR characterisation data of reactants **1** and **2b**, species **A** and **B**, and product **3b** see Supporting Information) and structures of species **A** and **B**.

appears that both 4-nitrobenzaldehyde and propionaldehyde compete with crotonaldehyde **2b** for the initial addition of thioacetic acid **1** presumably forming thioacyl hemiacetal species, hence, removing available acid from the reaction mixture. Since the thioacyl hemiacetal species exist in equilibrium with the aldehyde, thioacetic acid **1** is released slowly during the reaction when its concentration is decreased sufficiently enough to shift the equilibrium. As expected, an electron-withdrawing nitro group favours the formation of thioacyl hemiacetal, hence, 4-nitrobenzaldehyde decreases the rate of the thio-Michael reaction more than propionaldehyde. Although these observations do not explain the nature of the autocatalytic process, they eliminate the possibility of simple catalysis by either an aldehyde or its thioacyl hemiacetal derivative.

The finding that these addition reactions are two-stage (Figure 1 and Figure 2), involve two species (*vide supra*) and are autocatalytic indicates that the reaction is unlikely to involve a simple Michael-like 1,4-addition of thioacetic acid to the unsaturated aldehydes. Indeed, the reaction proceeds with a 1,2-addition of the thioacetic acid to the aldehyde, which could either be followed by a 1,3-sulfur rearrangement[22] or this could simply compete with the slower direct 1,4-addition (Michael) process. Although it is known that allylic phenyl sulfides[23] undergo thermal and acid-catalysed rearrangements (of the proposed mechanisms,[24–26] an associative process is supported by kinetic isotope effects[25,26]), to the best of our knowledge, this particular rearrangement is unknown. Associative mechanisms have been proposed, but only in the Michael addition of amines.[28] Therefore, in order to probe how this rearrangement might proceed, crotonaldehyde diethyl acetal **6** was reacted with 1 equivalent of thioacetic acid **1** (Scheme 1), which surprisingly derived the olefin addition product **8**. At first glance, this looks like a general acid-catalysed direct addition of thioacetic acid to the alkene of **6**, however, following the reaction by NMR spectroscopy clearly revealed that the reaction proceeded quickly and cleanly to give mixed thioacyl hemiacetal **7**, which slowly rearranged to the product **8**. Importantly, the vinyl ether **11** was not observed, which suggests that the expected intermediate oxonium ion **10**

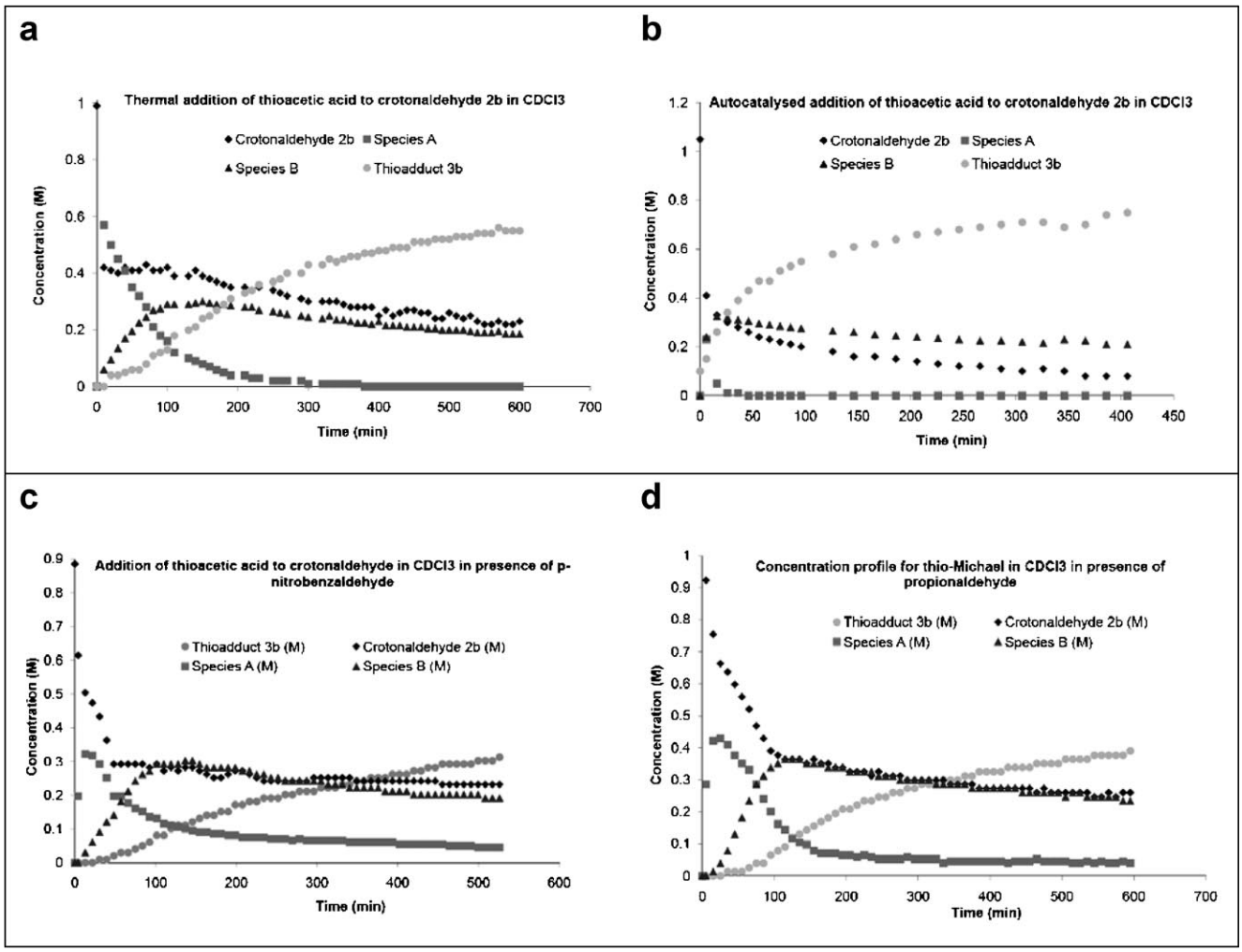
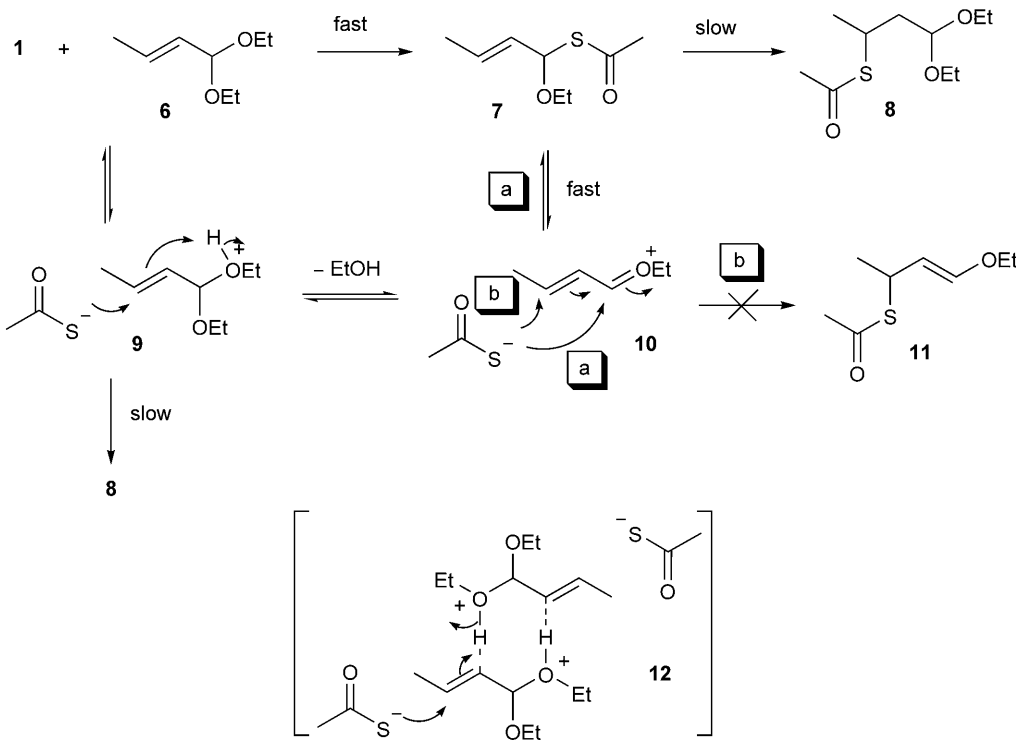


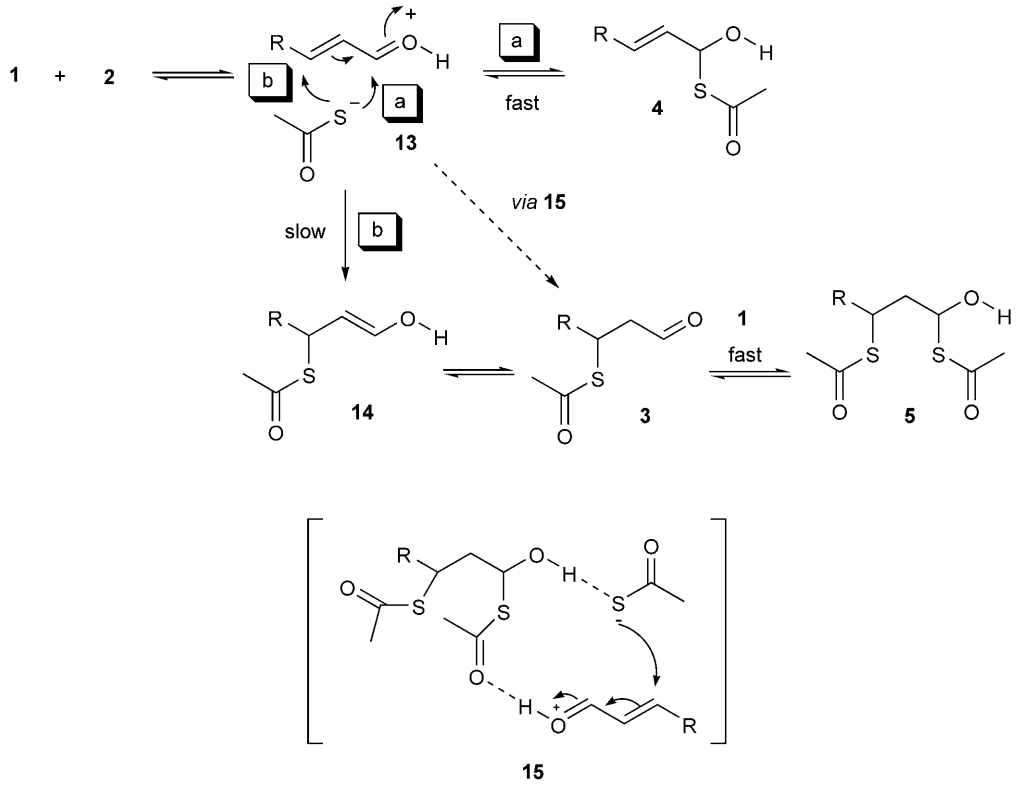
Figure 4. Representative data for ^{1}H NMR spectroscopy studies of the reaction between thioacetic acid **1** and crotonaldehyde **2b** in $CDCl_3$: **a**) concentration profile for the thermal addition of thioacetic acid; **b**) concentration profile for the catalysed addition of thioacetic acid (10 mol% of product was added prior to the start of the reaction); **c**) concentration profile for the addition of thioacetic acid in the presence of 4-nitrobenzaldehyde (10 mol%); **d**) concentration profile for the addition of thioacetic acid in the presence of propionaldehyde (10 mol%).

formed from protonation (*via* **9**) of **6** can only account for the appearance of acetal adduct **9** *via* path b (Scheme 1). The formation of **7** must involve a relatively fast equilibrium process to account for both its formation, and its subsequent reaction, back through oxonium ion **10**, addition of ethanol to give **9**, followed by direct irreversible addition of thioacetate to the proton activated olefin. However, since this amounts to a symmetry disallowed 1,3-H-shift, the protonated acetal **9** could exist as a dimeric H-bonded species (such as **12**) to which the addition of thioacetate derives **8**.

Elucidation of the reaction of thioacetic acid **1** with crotonaldehyde dimethyl acetal (Scheme 1) may also clarify the mechanism operating in the apparent Michael addition [Eq. (1)], i.e., as outlined in Scheme 2. Hence, reversible protonation of the unsaturated aldehydes **2** derives **13**, which undergoes rapid addition of thioacetate to give the observed intermediate acyl hemiacetal **4**. This type of species can also undergo fragmentation back to **13** and recombination *via* a slower irreversible addition of thioacetate to derive enol **14** and hence aldehyde **3** *via* keto-enol tautomerisation. The formation of dithioacetate adduct **5** can then compete for thioacetic acid in a further fast reversible addition reaction. Enol **14** is not observed, not surprisingly, since enol derivatives of aldehydes neither exhibit stability nor high enol concentrations due to rapid keto-enol equilibration favouring the aldehyde form.[28] It is likely that the conversion of **13** to product **3** does not solely proceed through the enol from addition path b (Scheme 2), rather, species **13** could transform directly to adduct **3** in a manner not unrelated to that proposed in the acetal system (see Scheme 1), i.e., *via* a species such as **15**. Indeed, this seems to explain the origin of the autocatalytic effect



Scheme 1. Proposed mechanism for the reaction of thioacetic acid **1** with crotonaldehyde diethyl acetal **8**.



Scheme 2. Proposed mechanism for the reaction of thioacetic acid **1** with aldehydes **2**.

since it involves the dithioacetate adduct **5** acting as the autocatalytic species *via* hydrogen bonding to ion pair **13**. This results in a fast, intramolecular delivery of thioacetate to the activated oxonium ion and this explanation fits the observed results.

In summary, the addition of thioacetic acid **1** to unsaturated aldehydes clearly does not proceed through a simple, direct addition mechanism involving a thio-Michael addition and as revealed by both adiabatic and reaction calorimetry, it appears to be a two-step, autocatalytic process. Whilst in Figure 1, two-step behaviour is clearly visible for toluene and chloroform, close examination of the transients for petroleum ether, DMF and THF also show an inflection in the curve, although to a lesser extent. Propionitrile, however, shows a single linear response during its temperature rise and acetonitrile shows only a single curve achieving a considerably lower final temperature. Indeed, it is clear that the system under study forms a complex network of reactions each of which may well proceed at different rates depending on the solvent. If the rates involved in the first step in the reaction are reduced by these solvents, only a single curve would result.

Examination of the corresponding addition reaction of thioacetic acid to an allylic acetal system uncovers an intriguing rapid acetal exchange process, which precedes a slower addition to the olefin. Using this as a model, a mechanistic model as outlined in Scheme 2 can be proposed to explain the observed addition compounds, and the important finding that aldehyde addition precedes a formal thio-Michael addition reaction to derive adduct **3**. The exact basis of how the formal Michael addition proceeds, i.e., *via* a direct slow, 1,4-addition or a fragmentation–recombination is not clear, however, the fact that there is an autocatalytic process associated with dithioacetate adduct **5** strongly indicates an assisted process such as described by **15**. It is likely that these observations will not only have repercussions upon asymmetric SH additions[5] since the conversion of species **4** or **6** to **3** does not appear to be a simple process, but may also have an impact on the development of new catalytic asymmetric Michael additions in general. Indeed, it may be that other types of Michael reactions also proceed through similar mechanisms. Further studies to elucidate the mechanistic, kinetic and autocatalytic details of these processes are underway and will be reported in due course.

Experimental Section

Synthesis of 3-Acetylthiohexenal (3a)

A mixture of chloroform (15 mL), and *trans*-2-hexenal **2a** (1.64 mL, 0.014 mol) was treated with thioacetic acid 1 (1 mL, 0.014 mol). After 12 h, the mixture was evaporated and purified by silica gel chromatography (hexane:ethyl acetate, 9:1, as eluent) to give **3a** as a yellow oil; yield: 2.19 g (90%). All spectroscopic and analytical data were identical to those reported.[29]

General Procedure for the Addition Reactions Carried Out in the Thermos Flask

All adiabatic reactions were carried out using a Thermos Model 32-34-50 flask, Filler 32-50F with a 0.5 L capacity and equipped with magnetic stirring. All temperature readings were made using a Testo 946 digital thermometer with a Testo Type T temperature probe linked to a PC *via* an RS232/USB connector. Data were logged every 2 seconds and stored directly on the PC using the Testo Comfort software and exported to MS Excel for data processing. The Dewar flask, fitted with its temperature probe was closed with a cotton wool plug to reduce evaporative heat loss.

Solvent Screening

Solvent (100 mL), *trans*-2-hexenal **2a** (11.0 mL, 0.094 mol) and thioacetic acid **1** (6.6 mL, 0.094 mol) were added to the Thermos flask and the temperature change was recorded over time. Solvents employed were: 1) petroleum ether (80/100); 2) THF; 3) chloroform; 4) toluene; 5) DMF; 6) propiononitrile; 7) acetonitrile (see Figure 1).

General Experimental Procedure for the Reaction of Thioacetic Acid 1 with Crotonaldehyde 2b

A solution of crotonaldehyde **2b** (62 μL, 0.75 mmol) and DCM (48 μL, 0.75 mmol) in toluene-d_8 (586 μL) was prepared and analysed by ^{1}H NMR spectroscopy. Thioacetic acid **1** (54 μL, 0.75 mmol) was then added to the reaction solution and sample was monitored by ^{1}H NMR spectroscopy for up to 9.5 h. Once the data were assigned to corresponding species, the reaction concentration profiles were obtained.

Reaction of Thioacetic Acid 1 with *trans*-2-Butenal Diethyl Acetal 6

A solution of *trans*-2-butenal diethyl acetal **6** (20 μL, 0.14 mmol) in toluene-d_8 (550 μL) was prepared and analysed by ^{1}H NMR spectroscopy. Thioacetic acid **1** (10 μL, 0.14 mmol) was then added to the reaction solution and sample was monitored by ^{1}H NMR spectroscopy initially for a period of 12 h. During that time all of the starting material **6** was converted to intermediate **7** (as assigned by ^{1}H NMR spectroscopy). The reaction was left for a further 48 h during which all of the intermediate **7** was converted to product **8**. The mixture was then diluted with toluene (3 mL), washed with saturated solution of K_2CO_3 (2×5 mL), dried over $MgSO_4$ and concentrated under vacuum to give the product as pale yellow oil; yield: 17 mg (57%). The final product contained traces of residual toluene and thioadduct **3b** which arises from slow decomposition of **8**.

Acknowledgements

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