Green Chemistry

Cite this: *Green Chem.*, 2012, **14**, 90

www.rsc.org/greenchem

COMMUNICATION

A quantitative comparison between conventional and bio-derived solvents from citrus waste in esterification and amidation kinetic studies

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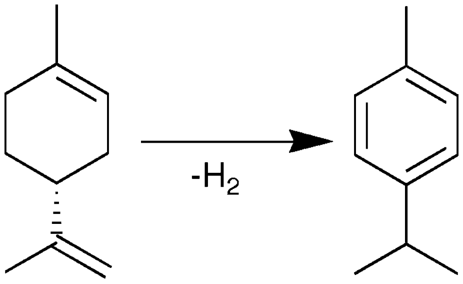
Received 18th October 2011, Accepted 7th November 2011
DOI: 10.1039/c1gc16299c

(*R*)-(+)-Limonene, which is available in large quantities from citrus waste, and its close derivative *p*-cymene are shown herein to be viable yet sustainable solvents for amidation and esterification reactions.

Citrus waste provides an opportunity to obtain useful and valuable chemicals.[1] Fifteen million tons of citrus waste accumulates annually as a result of the food and drink processing industry and other minor contributors.[2] Often simply disposed of or incorporated into animal feed,[3,4] this huge and naturally occurring resource is not being fully taken advantage of although the means to do so have been successfully demonstrated.[1,5,6]

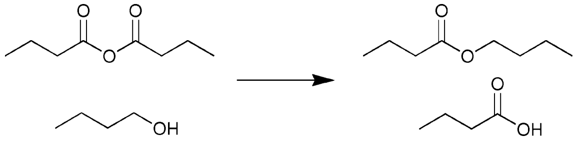
(*R*)-(+)-Limonene, referred to hereafter simply as limonene, is the major component of the essential oil in oranges, which can be extracted by steam distillation,[7] or supercritical fluid extraction in yields of up to 5% based on the dry weight of the citrus waste.[8] Potential applications for limonene and its derivatives are not insignificant. Limonene is a common component in cleaning and degreasing products,[9] and has also been used as a solvent for synthesis. The reactivity of the limonene terminal double bond and its chirality have been exploited in both ring opening polymerisations and the construction of optically active polymers respectively.[10,11] The sequential isomerisation and dehydrogenation of limonene to the aromatic compound *p*-cymene provides a route to a more robust solvent (Scheme 1). This procedure is well documented in the literature, and is attainable in quantitative yield under microwave irradiation using either a mixed silica–alumina catalyst or clay supported metals.[12,13]

The established bio-solvents are all of high polarity, exemplified by 2-MeTHF and glycerol.[14,15] The introduction of limonene and *p*-cymene, both hydrocarbon solvents, broadens the range of available bio-derived media for organic synthesis. Despite bio-derived organic solvents possessing the same VOC issues as petrosolvents, using a renewable solvent goes a long way towards satisfying growing consumer and legislative demands with regards to sustainability. This is because the majority of material input required for a chemical synthesis is usually the solvent.[16] Although the feedstock is limited by the regionality and seasonality of the crop, utilisation of citrus waste to give limonene as a solvent and platform molecule does not compete with food production.



Scheme 1 Synthesis of *p*-cymene from limonene.

In this work both limonene and *p*-cymene are shown for the first time to be viable reaction media for the conversion of butanoic anhydride and 1-butanol into butyl butanoate (Scheme 2). Secondly the synthesis of *N*-benzyl-4-phenylbutanamide from 4-phenylbutanoic acid and benzylamine is also found to proceed favourably in the citrus waste derived solvents (Scheme 3). Uncatalysed reactions were chosen to establish the fundamental nature of any solvent effects without the added complication of competing interactions with the catalyst. The performance of limonene and *p*-cymene in these case studies was established by conducting both reactions in a variety of additional solvents and monitoring the progress of each reaction by ^{1}H-NMR spectroscopy in the same manner as previously demonstrated by Welton and co-workers.[17] No normalisation of the NMR signal integrals was found to be necessary.



Scheme 2 Reaction A: the synthesis of butyl butanoate.

The control that solvent polarity exerts over the rate of chemical reactions can only be understood if polarity is correctly defined and separated into its unique modes of expression. For this purpose, the triple parameter Kamlet–Taft solvatochromic

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Table 1 Solvent polarity parameters and second order rate constants

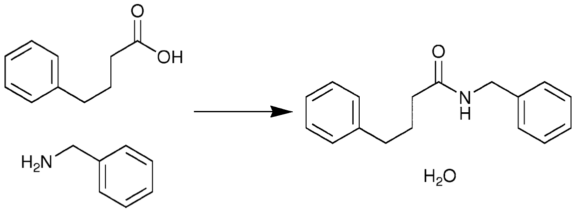
Solvent	α	β	π^*	δ_H	$k_2/10^{-6}$ dm^3 mol^{-1} s^{-1} Reaction A[a]	Reaction B[b]
Acetonitrile	0.35[c]	0.37[c]	0.80[c]	24.2[d]	7.42	—
Butanone	0.00[e]	0.51[f]	0.68[f]	19.0[d]	10.6	—
Chlorobenzene	0.00	0.06	0.65	19.4[d]	59.7	27.2
Chloroform	0.20[g]	0.10[g]	0.58[g]	18.9[d]	54.9	—
Cyclohexanone	0.00[e]	0.58	0.71	20.2[d]	—	15.7
p-Cymene	0.00	0.13	0.39	17.4[h]	84.1	24.5
DMF	0.00[e]	0.71[f]	0.88[f]	24.0[d]	3.24	12.4
DMSO	0.00[e]	0.74[f]	1.00[f]	26.6[d]	—	11.0
1,4-Dioxane	0.00[e]	0.38[f]	0.53[f]	20.5[d]	18.8	17.2
Limonene	0.00	0.00	0.16	15.1[i]	106	27.6
Toluene	0.00	0.12	0.50	18.2[d]	62.6	23.6
p-Xylene	0.00	0.14	0.47	18.0[d]	—	24.1

[a] Conducted at 50 °C; 1.1 M acid anhydride concentration, 1.0 M alcohol concentration. [b] Conducted at 100 °C; 0.50 M acid concentration, 0.55 M amine concentration. [c] Ref. 23 [d] Ref. 24. [e] Based on the spectral data of Reichardt's dye (Ref. 25). [f] Ref. 20. [g] Average of several dye sets (Ref. 26). [h] Calculated from the literature ΔH_{vap} value (Ref. 27). [i] Calculated from the literature ΔH_{vap} value (Ref. 28).

Table 2 LSER coefficients according to eqn (1), taken to 3 significant figures. Key: LSER 1. Rate of Reaction A without considering δ_H (Fig. 2); LSER 2. Rate of Reaction A when also considering δ_H; LSER 3. Rate of Reaction B; LSER 4. Enthalpy of activation (Reaction B, units of kJ mol^{-1}); LSER 5. Entropy of activation (Reaction B, units of J mol^{-1} K^{-1})

LSER	XYZ	XYZ$_0$	*a*	*b*	*s*	$h/10^{-3}$	R^2
1	$\ln(k_2)$	−9.18	0.00	−4.97	0.00	—	0.917
2	$\ln(k_2)$	−8.06	0.00	−3.47	0.00	−3.89	0.979
3	$\ln(k_2)$	−10.5	—[a]	−1.18	0.00	0.00	0.979
4	$\Delta H^{\ddagger}$	104	—[a]	−63.8	0.00	0.00	0.982
5	$\Delta S^{\ddagger}$	−55.9	—[a]	−181	0.00	0.00	0.982

[a] No hydrogen bond donating solvents were used in Reaction B due to the possibility of competing side reactions.



Scheme 3 Reaction B: the synthesis of *N*-benzyl-4-phenylbutanamide.

scale divides solvent polarity into hydrogen bond donating ability (α), hydrogen bond accepting ability (β), and a combination of dipolarity and polarisability (π^*).[18] Solvent parameters and rate constants relevant to this study are presented in Table 1. Reaction A and Reaction B were conducted in nine solvents each. The Kamlet–Taft parameters of limonene, *p*-cymene, and the other solvents present in this study were derived from the UV-Vis spectroscopic absorbances of Nile Red, Reichardt's dye, 4-nitroaniline and *N*,*N*-diethyl-4-nitroaniline in accordance with literature precedent.[19–22] Existing parameter values from the literature were used to complete the data set where possible.

The three Kamlet–Taft parameters have been sufficient to explain a wide range of solvent induced phenomena when utilised in the form of a linear solvation energy relationship (LSER).[29] A generalised LSER is given in eqn (1), where XYZ is a variable term proportional to free energy.[30] In this work the natural logarithm of bimolecular rate constants, enthalpy of activation, and entropy of activation are applied in this role. Not all solvent polarity parameters will necessarily be statistically relevant in every relationship. Conversely in certain instances further parameters may be required to account for all experimental observations. The square of the Hildebrand solubility parameter (δ_H^2) provides a measure of cohesive energy and is used to describe solvent effects resulting from a change in the size of the cavity that a substrate resides in during the course of a reaction. Table 2 presents the LSER coefficients for various correlations based on the kinetics of Reaction A and Reaction B.

$$\mathrm{XYZ} = \mathrm{XYZ}_0 + a\alpha + b\beta + s\pi^* + h\delta_H^2 \qquad (1)$$

When considering the three Kamlet–Taft parameters as the only independent variables, the rate of Reaction A was found to be dictated by β (Fig. 1). The remaining parameters (α and π^*) were found not to be statistically significant. However, it was noticeable that acetonitrile did not appear to follow this trend. The discrepancy is overcome by introducing δ_H^2 into the LSER treatment. Fig. 1 shows the strong predictive element when β and δ_H^2 are used in combination to account for the rate of Reaction A. This implies that the activated complex of Reaction A occupies a larger cavity within the solvent than the reactants require. As such, strongly associating solvents resist the progression of the reaction in an attempt to maintain their intermolecular bonding to a greater degree than expected based only on their hydrogen bond basicity. The greatest rate constants were achieved in limonene and *p*-cymene.

The kinetics of Reaction B follow a comparable trend to Reaction A, except that β is adequate on its own to account

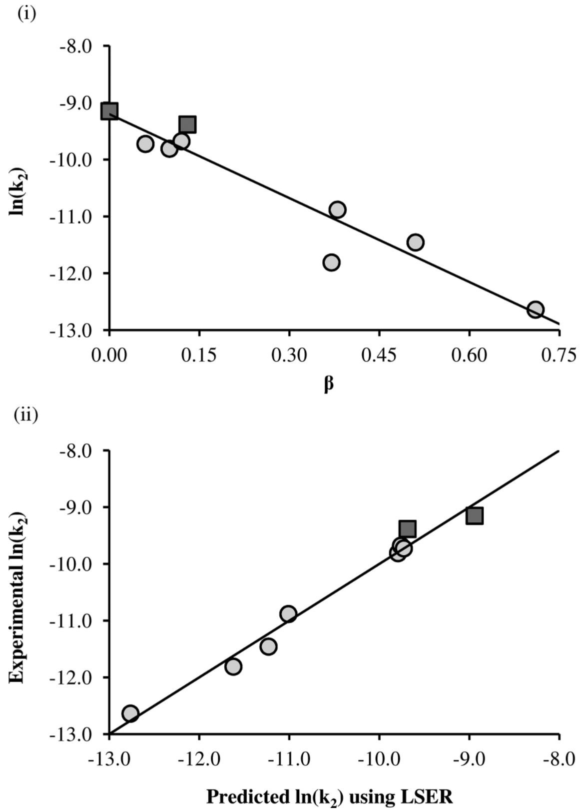


Fig. 1 (i) LSER describing Reaction A without accounting for the cohesive energy of the solvent (see Table 2, entry 1). (ii) Comparison between predicted and experimental ln(k_2) values for Reaction A when both β and δ_H^2 are used in the construction of the LSER (see Table 2, entry 2). Key: squares indicate citrus waste derived solvents; circles indicate conventional solvents.

for the observed reaction rates of the amidation (Fig. 2). This similarity is not unexpected given that the two reactions are mechanistically related, both proceeding as a result of a nucleophilic attack on a carbonyl group. Investigating further, Reaction B was performed at different temperatures as a means to separate the enthalpy and entropy of activation from the observed rate constants by means of manipulating the Eyring equation.[31] Again only β is required to predict the enthalpy ($\Delta H^‡$) and entropy of activation ($\Delta S^‡$) for Reaction B in a given solvent. For example, using the coefficients listed in Table 2, $\Delta H^‡$ for Reaction B can be calculated at 95.7 kJ mol^{-1} in *p*-cymene but only 56.8 kJ mol^{-1} in DMSO. This observation, in general terms, states that $\Delta H^‡$ is reduced with increasing β of the solvent. Such a relationship would be expected to produce enhanced rates of reaction in hydrogen bond accepting solvents. In Fig. 2 the opposite is demonstrated to occur because polar solvents introduce a large entropic penalty during the formation of the activated complex. So although hydrogen bonding stabilises the activated complex of the reaction, the molecular organisation within the reaction medium required to do so is ultimately a hindrance at the high temperatures required for the reaction to proceed in the absence of coupling agents or a catalyst (Scheme 4).

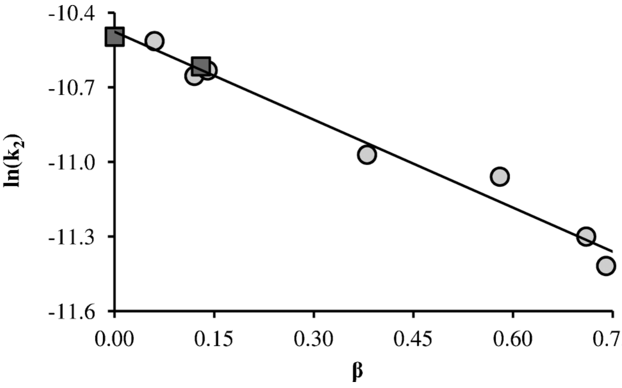
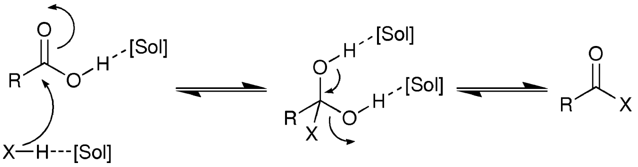


Fig. 2 LSER describing Reaction B at 100 °C (see Table 2, entry 3). Key: see Fig. 1.



Scheme 4 Proposed transition state stabilisation for a nucleophilic attack on a carboxylic acid where [Sol] indicates a solvent molecule capable of accepting hydrogen bonds.

The solvent influence controlling the rates of Reaction A and Reaction B mirrors a previously reported acid catalysed Fischer esterification and the condensation of carboxylic acids with dicyclohexylcarbodiimide.[17,32] All of these reactions are tied by the common theme of a nucleophilic attack upon a carbonyl moiety. Although varied reasons have been proposed for the kinetic dependence of these reactions on the β solvent polarity parameter, ultimately entropic control is not incompatible with any of these chemistries. In conclusion, the low hydrogen bond basicity of limonene and *p*-cymene has been shown to provide an effective medium for the synthesis of esters and amides. Readily obtainable from abundant citrus waste feedstocks, these low polarity solvents complement the existing array of hydrogen bonding bio-derived solvents. Because it is common for the solvent to have a profound effect on the kinetics and thermodynamics of a reaction,[31] developing a range of sustainable solvents with varied attributes is of some merit. Given its resemblance to toluene, *p*-cymene would seem to be an ideal drop-in replacement with the added benefit of a straightforward synthesis from waste biomass.

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