Role of water and phase transfer catalysts in the kinetics of condensation of diaryl ketones with acetonitrile initiated by solid potassium hydroxide †

T. William Bentley,*[,a] Ray V. H. Jones,[b] Annette H. Larder[a] and Stephen J. Lock[a]

[a] *Department of Chemistry, University of Wales Swansea, Singleton Park, Swansea, UK SA2 8PP*
[b] *ZENECA Process Technology, Earls Rd. Grangemouth, UK FK3 8XG*

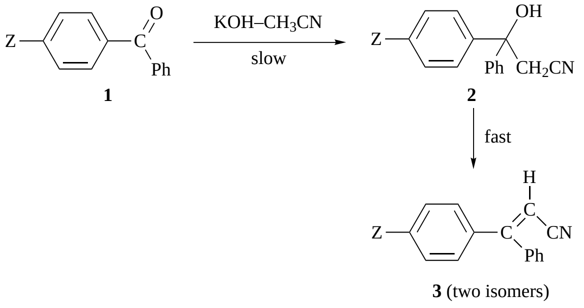
The kinetics of reactions of benzophenone and substituted derivatives with acetonitrile in the presence of excess solid potassium hydroxide (KOH) to give 2,2-diarylacrylonitriles are reported. Reaction rates are strongly temperature dependent, and water, other cosolvents and quaternary ammonium salts all accelerate the reaction; also variation in substituents at one of the *para*-positions (from H to Cl, F and Me) gives a significant rate effect (ρ = 1.9). In contrast, variations in the amount of solid KOH pellets, the presence of crushed KOH, or an increase in the speed of stirring of the refluxing solution do not have significant kinetic effects. The results are consistent with a mechanism in which the anion $[CH_2CN]^-$ is transported from the KOH surface before it reacts with the ketone. The rate of disappearance of benzophenone during most of the reactions is predominantly zero order, but variation in the initial concentrations of benzophenone shows that the initial rate is first order in benzophenone; water formed during the reaction does not remain in the acetonitrile (Karl Fischer titration), and the increasingly moist KOH further catalyses the reaction, so the observation of zero order kinetics is fortuitous. The role of solvents as phase transfer catalysts is discussed.

Reactions initiated by solid bases such as potassium carbonate[1] and potassium hydroxide (KOH)[2] are of increasing interest in preparative reactions, which may be carried out in the absence of added solvents and which may be aided by microwave heating[3] or by ultrasound.[4,5] Our interest in this area has arisen from observations leading to the proposal that solvents or traces of water may act as phase transfer catalysts (PTC) in reactions initiated by solid bases.[6] We now report the kinetics of condensations of diaryl ketones with acetonitrile initiated by solid KOH, in the presence of quaternary ammonium salts and cosolvents acting as phase transfer catalysts. In the many alkylations involving PTC, the kinetics are often complicated by anion exchange during the reaction, whereas rates of condensations may be affected by the water produced.

The role of water in the kinetics of solid–liquid phase transfer catalysis (SLPTC) is known to be complex. As with liquid–liquid PTC, traces of water in the organic phase affect the distribution of catalysts, and hydrogen bonding reduces the reactivity of anions.[7] Also, traces of water may activate the surface of the solid by creating a third phase (an omega phase,[8] a coating or a thin film of aqueous salt[5,9]). In contrast, the driest state PTC reactions may sometimes be the fastest.[9c] We now report evidence that water, formed during the condensations of diaryl ketones with acetonitrile, is absorbed by the solid KOH, and both increases the rate and changes the kinetic order of the reaction.

Results

The reaction of diaryl ketones (**1**) with acetonitrile, initiated by solid KOH, gives good yields of the substituted acrylonitriles (**3**),[2] and the alcohol (**2**) is rapidly dehydrated under the reaction conditions[2] (Scheme 1); we detected only traces of **2**, Z = H during analyses of quenched aliquots of crude reaction mixtures by high performance liquid chromatography (HPLC), and of crude products from preparative-scale reactions by ^{1}H NMR. Initial concentrations of ketones were typically *ca.* 0.5 M, similar to those for preparative-scale procedures (*ca.* 0.5–1 M),[2] and a sufficiently large volume of acetonitrile (usually 40 ml) was present, so that the withdrawal of small aliquots (*ca.* 20 × 50 μl) of solution during sampling did not significantly affect the composition of the heterogeneous reaction mixture.



Scheme 1

Following earlier reports[10] that small amounts of water activated the KOH, water (usually 0.1 ml) was added to the acetonitrile. An excess of KOH, initially present as pellets containing 15% water, became finer particles as the reaction proceeded; although reactions were carried out under reflux (82 °C), magnetic stirring was used to agitate the solution further, but from visual comparisons stirring did not appear to be sufficiently vigorous to cause significant additional crushing of the KOH. As the reaction proceeded, the mixture became yellow within about 10 min and was brown at the end of the reaction, and solid (presumably KOH) formed on the side of the reaction vessel.

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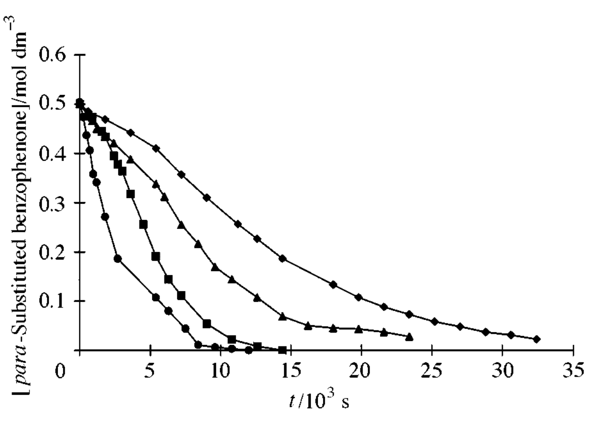


Fig. 1 Plot of ketone concentrations *vs.* time for reaction of ketones [**1**, Z = Me (◆), H (▲), Cl (■), and F (●), 0.02 mol], solid KOH (0.04 mol) in refluxing acetonitrile (40 ml) containing added water (0.1 ml); zero order rate constants were calculated from the linear region (r > 0.99) for >55% reaction

Table 1 Effect of temperature and speed of stirring on the zero order rate constants for production of the nitrile (**3**, Z = H) from benzophenone[a]

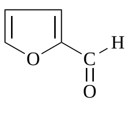
	Rate constant at T °C/10^{-5} M s^{-1}		
Stirring/rpm	60.0	74.8	82.2[b]
0			1.78 ± 0.05
100	0.25 ± 0.02		3.00 ± 0.09
400	0.28 ± 0.03[c]	1.36 ± 0.07	3.13 ± 0.07[d]
900			3.42 ± 0.06

[a] Standard conditions were benzophenone (0.02 mol), HPLC grade acetonitrile (40 ml) containing 0.03 ml of water, added water (0.1 ml) and pelleted KOH (0.04 mol) containing 0.34 ml of water; rate constants were determined by HPLC analysis of the molar concentration of benzophenone; plots of concentration *vs.* time were linear (r > 0.98) for 10–15 data points over extents of reaction varying from at least 30% for slower reactions to >60% for faster reactions. [b] Reflux temperature. [c] Duplicate measurement of rate constant; the error quoted is the average deviation. [d] Average of five experiments repeated periodically throughout the time period of the whole investigation.

Typical plots (Fig. 1) of ketone concentration *vs.* time are approximately linear over a large extent of reaction, and tabulated rate data are expressed as zero order rate constants calculated from the slope of a least squares fit to the linear part of the concentration/time plots. The kinetic effects of substituents (**1**, Z = Me < H < Cl < F) span over five-fold in rate (corresponding to a ρ value of 1.9, significantly larger than the ρ value of 0.36 for the reaction of methylmagnesium bromide with a series of benzophenones[11]) and are consistent with a reaction involving nucleophilic attack by $[CH_2CN]^-$ on the ketone.[2]

More detailed kinetic studies were made on reactions of benzophenone, and all of the remaining experiments on ketones (described below) were carried out using benzophenone. Reactions stirred very slowly (100 rpm) under reflux were slightly faster than unstirred reactions (Table 1), suggesting that the magnetic stirrer may cause some minor physical changes to the KOH. However, there were only minor rate differences between vigorously-stirred solutions (900 rpm) and the very slowly-stirred solutions (Table 1), so as a standard, a mid-range setting of 400 rpm was chosen for this work.

In parallel work on the reaction of furfural (**4**),[12] repeated in part over two years later, formation of nitrile (**6**) occurred with a rate constant of 1.0 ± 0.1 × 10^{-3} M s^{-1}, under conditions closely comparable with those for **1**, Z = H at 60 °C (Table 1); again only traces of hydroxynitrile (**5**) and small amounts (<4%) of Cannizzaro products were detected. Hence furfural (**4**) is over 300 times more reactive than **1**, Z = H, confirming previous semi-quantitative observations that aldehydes are significantly more reactive than ketones under the reaction conditions.[2]



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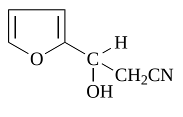

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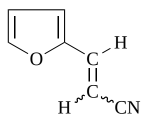

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Table 2 Effect of phase transfer catalysts (10 mol%) on the zero order rate constants for production of the nitrile (**3**, Z = H) from benzophenone[a]

Phase transfer catalyst (0.05 M)	Rate constant/ 10^{-5} M s^{-1}	Extent of reaction (%)	Correlation coefficient
None	3.13 ± 0.07[b]	86	0.994
Bu^n_4NI	4.94 ± 0.15	71	0.998
$PhCH_2Et_3NCl$	11.4 ± 1.4	55	0.993
$CH_3(CH_2)_{15}N(CH_3)_3Br$[c]	14.1 ± 1.2	70	0.982
Bu^n_4NBr	15.5 ± 2.0	74	0.992
$Bu^n_4NHSO_4$	54 ± 20	65	0.95[d]
$CH_3N[(CH_2)_7CH_3]_3Cl$[e]	103 ± 16	50	0.988

[a] As for Table 1, except that the extent of zero order reaction and correlation coefficient (r) are tabulated, and as few as three data points were obtained for the faster reactions. [b] From Table 1; the reaction was heated under reflux and stirred at 400 rpm. [c] Cetavlon. [d] A satisfactory fit to first order kinetics was obtained for over 80% reaction. [e] Aliquat 336.

Table 3 Non-linear effect of concentration of tetrabutylammonium bromide (TBAB) as phase transfer catalyst on the zero order rate constants for production of the nitrile (**3**, Z = H) from benzophenone[a]

Concentration of TBAB/M	Rate constant/ 10^{-5} M s^{-1}	Extent of reaction (%)	Correlation coefficient
None	3.13 ± 0.07[b]	86	0.994
0.01	7.1 ± 0.3	66	0.990
0.05	15.5 ± 2.0[b]	74	0.992
0.25	30.3 ± 1.0	69	0.993

[a] As for Table 1, except that the extent of zero order reaction and correlation coefficient (r) are tabulated; all results except for 0.05 M TBAB are calculated from at least ten data points. [b] As for Table 2.

There is a 10-fold increase in rates between 60 and 82 °C (Table 1), corresponding to a high value of $\Delta H^\ddagger$ (*ca.* 27 kcal mol^{-1}). Differences in reactivity between aldehydes and ketones,[2] substituent effects (Fig. 1), and high activation energies are all consistent with a significant chemical activation barrier in these reactions. Relative rates will also be affected by temperature-dependent changes in the concentration of the reactive anion $[CH_2CN]^-$ in the organic phase, so the value of $\Delta H^\ddagger$ probably overestimates the barrier to the chemical activation step(s). Using conventional titrimetric procedures (sensitive to *ca.* 10^{-3} M), it was not possible to detect the presence of base in acetonitrile, but conductimetric studies showed the presence of *ca.* 10^{-4} M ions at 60 °C and a three-fold increase between 60 and 82 °C.[13]

In order to try to increase the concentrations of the reactive anion $[CH_2CN]^-$ in the organic phase, catalytic amounts (10 mol%) of quaternary ammonium salts (Q^+X^-) were added (Table 2). The effect of varying the concentration of catalyst was determined for tetrabutylammonium bromide (Table 3), and the effect of replacing the added water by other cosolvents is shown in Table 4.

Although all of the reactions (Tables 1–4) were close to zero order for substantial extents of reaction, the observed zero order rate constants were found to be proportional to the initial concentration of benzophenone, under standard reaction conditions (Fig. 2). Hence, this evidence indicates that the kinetic order in benzophenone is one, and the discrepancy in the kinetic order was resolved by more detailed studies of the role of water (see below).

Table 4 Effect of small amounts of cosolvents as phase transfer catalysts on the zero order rate constants for production of the nitrile (**3**, Z = H) from benzophenone[a]

Cosolvent (0.138 M)[b]	pK_a[c]	Rate constant/ 10^{-5} M s^{-1}	Extent of reaction (%)	Correlation coefficient
None		1.66 ± 0.14	>40	0.972
Water	31.2	3.13 ± 0.07	86	0.994
Bu^{t}OH	32.2	1.87 ± 0.16	48	0.967
DMSO	35.0	2.07 ± 0.15	50	0.980
MeOH[d]	29.0	3.34 ± 0.15	80	0.990
PEG 200[e]		*ca.* 10	50	0.93[f]
PEG 6000		31.7 ± 2.3	68	0.98

[a] As for Table 1, except that the extent of zero order reaction and correlation coefficient (*r*) are tabulated. [b] Equivalent to the molar concentration of water added to the acetonitrile in the standard reaction. [c] Data in DMSO from ref. 14. [d] About half the amount of cosolvent (0.063 M) gave a rate constant of 2.76 ± 0.17 (75% reaction, $r = 0.985$). [e] Much less cosolvent (0.014 M) gave a rate constant of 3.30 ± 0.16 (65% reaction, $r = 0.991$). [f] Rates fitted better to first order kinetics up to 95% reaction.

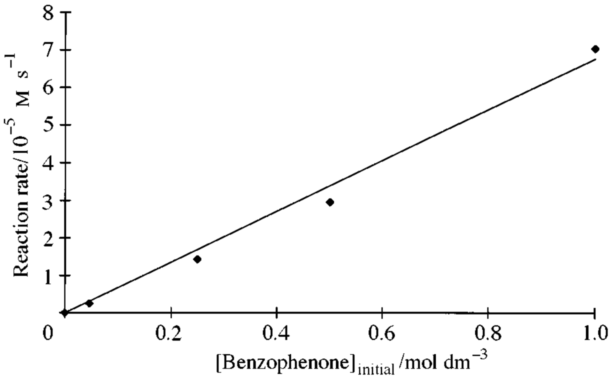

Fig. 2 Plot of zero order rate constants *vs.* concentration of benzophenone (**1**) under standard conditions (as legend to Fig. 1); slope: 7.0 ± 0.4 × 10^{-5} M s^{-1} ($r = 0.996$); zero order rate constants were obtained from a linear region ($r > 0.99$) for >55% reaction (detailed results are given for 0.5 M benzophenone in Table 2)

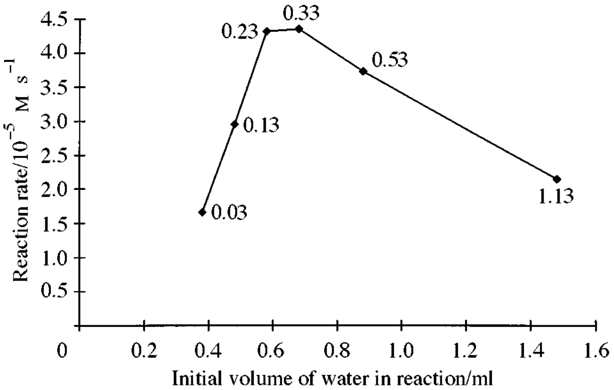

Fig. 3 Plot of zero order rate constants *vs.* amount of water initially present in or added to the acetonitrile; the graph is offset because 0.34 ml water is present in the reagent grade KOH pellets and 0.03 ml is present in the acetonitrile; data refer to benzophenone (**1**) under standard conditions (as legend to Fig. 1, except for added water); zero order rate constants were obtained from a linear region ($r > 0.99$) for >55% reaction (except for the two slowest reactions, where $r > 0.97$ for >30% reaction); detailed results are given for zero added water in Table 4 and for 0.1 ml of added water in Table 2

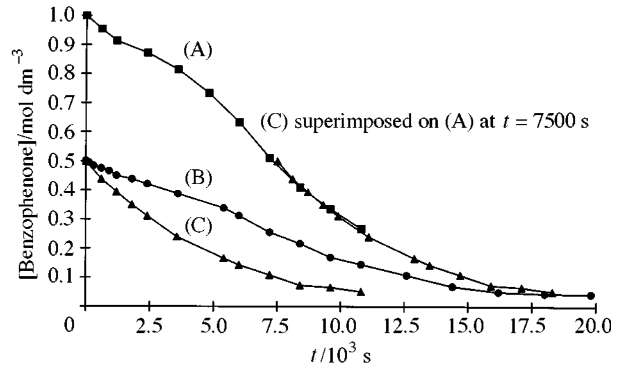

Fig. 4 Plots of ketone concentrations *vs.* time for reaction of benzophenone (**1**, Z = H), solid KOH (0.04 mol) in refluxing acetonitrile (40 ml) containing added water; the experiments differ in the amounts of benzophenone (see *Y* axis) and the amounts of water added; plots (A) and (B) refer to standard conditions (0.1 ml of added water with the KOH added last); plot (C) refers to 'conditioned' KOH (0.36 ml of water in acetonitrile was heated under reflux with the KOH for 7500 s prior to addition of benzophenone), and the experiment was carried out at a stirrer speed of 400 rpm (standard conditions, $k = 7.1 \pm 0.4 \times 10^{-5}$ M s^{-1}) and was repeated at 100 rpm giving a slightly lower rate constant of 5.7 ± 0.3 × 10^{-5} M s^{-1}

Varying the amount of added water from the standard amount of 0.1 ml down to zero and up to 1.1 ml shows a rate maximum at about 0.2 ml added water (Fig. 3), which corresponds to a 50% increase in rate for the addition of an extra 0.1 ml of water over and above that already present in the KOH pellets (0.34 ml), the HPLC grade acetonitrile (0.03 ml) and the 0.1 ml usually added in the standard reaction. Monitoring the standard reaction by simultaneous Karl Fischer titration and HPLC showed that, despite the production of one equivalent of water during the reaction, the amount of water in the acetonitrile decreased as the reaction occurred; after two hours the amount of water in the acetonitrile had returned to its original value of 0.03 ml, whereas 0.30 ml was expected (50% reaction had occurred so 0.17 ml of water must have been produced by the condensation, 0.1 ml was added and 0.03 was present in the acetonitrile). In an independent experiment, under the standard reaction conditions, but in the absence of ketone, a small amount of the acetonitrile solvent was converted to acetamide (0.01 mol) after 6 h;[13,15] *i.e.* up to half of the water produced in the condensation of **1** may react with acetonitrile to give acetamide, but the remainder appears to be absorbed by the KOH pellets.

The above results indicated that a possible autocatalytic role for water was to enhance the reactivity of the KOH as the reaction occurred, and so the following confirmatory experiments were performed (Fig. 4). The decrease in benzophenone concentrations for a reaction carried out using twice the normal amount (0.04 mol, 1.0 M) of benzophenone (Fig. 4) shows satisfactory zero order kinetics ($r = 0.994$ for 73% reaction), and the rate constant ($k = 7.0 \pm 0.3 \times 10^{-5}$ M s^{-1}) is about twice as large as that for the standard 0.5 M reaction ($k = 3.13 \pm 0.07 \times 10^{-5}$ M s^{-1}—see also Fig. 2). The 1.0 M reaction is 50% completed in 7500 s (2.1 h), and at this stage 0.02 mol (0.36 ml) of extra water will have been produced; this stage of the reaction was simulated by heating under reflux ('conditioning') the KOH with water (0.36 ml) for 7500 s, before adding 0.02 mol (0.5 M) benzophenone and monitoring as usual; the results give $k = 7.1 \pm 0.4 \times 10^{-5}$ M s^{-1} and when the data points are offset by 7500 s, they are almost exactly superimposable on the later part of the 1.0 M reaction (Fig. 4). The 'conditioning' process destroyed the KOH pellets, and it appears that the finer, hydrated particles of KOH are (slightly) the more effective catalyst.

For all of the experiments described so far, the amount of KOH was held constant, 0.04 mol pellets in 40 ml of acetonitrile. The small effect of a 20-fold variation in the amount of added base (Table 5) confirms the catalytic role of base and shows that base which accumulates on the side of the stirred reaction vessel will not greatly affect the reproduciblity of the kinetic results. The effect of phase transfer catalysts on reactions with $\frac{1}{8}$ the amount of base are shown in Table 6.

Table 5 Effect of amount of KOH pellets as base catalyst on the zero order rate constants for production of the nitrile (**3**, Z = H) from benzophenone[a]

Amount of base/mol	Rate constant/ 10^{-5} M s^{-1}	Extent of reaction (%)	Correlation coefficient
0.005	2.26 ± 0.06	52	0.997
0.01	3.08 ± 0.10	70	0.996
0.02	3.05 ± 0.10	67	0.997
0.04[b,c]	3.13 ± 0.07	86	0.994
0.1	4.35 ± 0.34	78	0.982

[a] As for Table 1, except that the amount of base was varied and the extent of zero order reaction and correlation coefficient (*r*) are tabulated; all results are calculated from at least ten data points. [b] Amount of base added under the standard reaction conditions. [c] Crushed KOH pellets gave a rate constant of 3.31 ± 0.07, and it was established that the rapid crushing procedure did not lead to an increase in weight (*i.e.* the KOH did not absorb significant amounts of water).

Table 6 Effect of phase transfer catalysts in the presence of $\frac{1}{8}$ of the typical amount of KOH (0.005 mol) on the zero order rate constants for production of the nitrile (**3**, Z = H) from benzophenone[a]

Phase transfer catalyst (0.05 M)[b]	Rate constant/ 10^{-5} M s^{-1}	Extent of reaction (%)	Correlation coefficient
None	2.26 ± 0.06[c]	52	0.997
$\mathrm{Bu^n_4NI}$	2.97 ± 0.12	63	0.994
$\mathrm{PhCH_2Et_3NCl}$	12.5 ± 0.7	45[e]	0.994
$\mathrm{CH_3(CH_2)_{15}N(CH_3)_3Br}$[d]	8.5 ± 0.6	59[e]	0.998
$\mathrm{Bu^n_4NBr}$	10.1 ± 0.4	48	0.996
$\mathrm{Bu^n_4NF}$	47 ± 4	55[e]	0.997
$\mathrm{Bu^n_4NHSO_4}$	14.6 ± 0.7[f]	60[e]	0.982
$\mathrm{CH_3N[(CH_2)_7CH_3]_3Cl}$[g]	32.3 ± 2.4[h]	57[e]	0.987

[a] As for Tables 1 and 2, except that only 0.005 mol of KOH pellets were added and the extent of zero order reaction and correlation coefficient (*r*) are tabulated; at least six data points were obtained for the zero order part of each reaction, except for $\mathrm{Bu^n_4NF}$, for which only three data points were obtained. [b] Catalysts are listed in the order of increasing reactivity observed for 0.04 mol KOH as in Table 2. [c] From Table 5. [d] Cetavlon. [e] Negligible extent of further reaction after 2–3 h (50–80%) conversion of starting material. [f] Duplicated data—the rate constant shown is that obtained after an induction period of 100 ± 20 min during which only 5 ± 2% reaction occurred. [g] Aliquat 336. [h] Rate constant duplicated; error shown is average deviation.

Under these conditions, an induction period of 100 min was observed for tetrabutylammonium hydrogen sulfate; when the reaction mixture was heated under reflux for 60 min before the benzophenone was added, the induction period was reduced to 25 min, and the same zero order rate constant was obtained ($14.2 \pm 0.8 \times 10^{-5}$ M s^{-1}). Presumably, the hydrogen sulfate ion is converted to sulfate, which may form a resistant coating on the base.

Alternative bases were also investigated briefly. Sodium hydroxide was about 10-fold less reactive than KOH, but catalysis by PEG 200, Aliquat 336, or tetrabutylammonium hydrogen sulfate increased the rate constants to within a factor of three of those observed for the corresponding reactions of KOH (Tables 2 and 4). Potassium and sodium carbonates were unreactive, but both gave detectable extents of reaction in the presence of tetrabutylammonium hydrogen sulfate with potassium carbonate being significantly faster. Powdered KOH has previously been found to be the most effective of a series of solid and aqueous hydroxides and carbonates for the butylation of benzamide, catalysed by tetrabutylammonium hydrogen sulfate.[16]

Discussion

The mechanism of the reaction is expected to involve attack by $[\mathrm{CH_2CN}]^-$ on the ketone (**1**) to give an adduct which abstracts a proton from a suitable base (*e.g.* water or acetonitrile) to give **2**, so only catalytic amounts of base are required in theory. In practice, the amount of base exerts only a small effect on rates (Table 5), and the presence of crushed base (Table 5, footnote *c*) also exerts only a small additional effect. Hence, the surface area of the base does not appear to be an important kinetic parameter for these reactions. As the speed of stirring is also unimportant (Table 1), it appears that mass transfer from the KOH surface has only a minor influence on the rate of reaction.

The concentration of $[\mathrm{CH_2CN}]^-$ in the KOH–acetonitrile is low ($<10^{-3}$ M, see above), and it would be kept constant by the excess of base and acetonitrile, and by the base generated in the formation of **2**. Hence, as shown in Fig. 2, the reaction is first order in benzophenone. Quaternary ammonium salts ($\mathrm{Q^+X^-}$), acting as phase transfer catalysts, should help to increase the concentration of $[\mathrm{CH_2CN}]^-$ and so increase rates (Table 2). Lipophilic counteranions are known to interfere with phase transfer catalysis of less lipophilic anions (*e.g.* $\mathrm{HO^-}$, $[\mathrm{CH_2CN}]^-$) and the expected order of efficiencies of the catalysts ($\mathrm{F^-} > \mathrm{Br^-} > \mathrm{I^-}$)[17] is observed for tetrabutylammonium salts (Table 6). Fluoride may also act as a base.[17] Iodide is the least effective counteranion, but it does not inhibit the reaction.[18] The effect of the structure of $\mathrm{Q^+}$ can be seen for two bromides and two chlorides (Tables 2 and 6), and the least organophilic cation $\mathrm{PhCH_2Et_3N^+}$ is the least effective.

Results for condensations of **1** can be compared with a detailed kinetic study of the alkylation of pyrrolidin-2-one by benzyl chloride in the presence of solid potassium carbonate in toluene at 80 °C.[17] Both alkylation and condensation show similar trends in rates for variations in added water and the catalyst's counteranion, and both show a non-linear effect of catalyst concentration on rate (Table 3) typical of PTC.[17] In contrast the alkylation does not proceed at a significant rate in the absence of catalyst, the rate is strongly dependent on the amount of potassium carbonate present (*cf.* Table 5) and on the stirring rate, the kinetic order in electrophile is reported to be zero (supporting data not given), and the activation energy is low (12.4 kcal mol^{-1}).[17]

The following three step mechanism was proposed[17] for the alkylation: (i) a reversible interfacial deprotonation of the pyrrolidin-2-one substrate; (ii) a reversible extraction of the anion by the catalyst; (iii) an irreversible substitution reaction in the bulk of the organic phase. Step (ii) was proposed to be the rate determining step, so the observed rate depends on rates and/or equilibria for steps (i) and (ii), and the mechanism is 'interfacial'.[17,18] Applying this potentially general mechanism to condensations of **1**, the rate determining step appears to be the equivalent of step (iii), attack by $[\mathrm{CH_2CN}]^-$ on **1**; consequently, rates and/or equilibria for all three steps contribute to the observed reaction rate, and the reaction is first order in **1** (Fig. 2). Also step (ii) does not require $\mathrm{Q^+}$ (presumably $\mathrm{K^+}$ is also effective).

The solubility of potassium salts may be increased by polyethylene glycols (PEGs), which are known to be effective in PTC.[19–22] Diols may act as cocatalysts in PTC by increasing the amount of base available in the organic phase: *e.g.* for eliminations using solid KOH in the presence of quaternary ammonium salts.[23] A wide range of alcohols can be extracted, almost exclusively as alkoxide,[24] into chlorobenzene from 50% aq. NaOH if a suitable $\mathrm{Q^+}$ is present [*e.g.* (tetra-*n*-octyl)ammonium ion], and diols are extracted to a greater extent; extraction of base was not detectable in the absence of $\mathrm{Q^+}$;[25] in contrast PEG 600 alone was readily extracted and the concentration of base did not increase when $\mathrm{Q^+}$ was present.[25] Our results (Table 4) show catalysis by various alcohols in the absence of $\mathrm{Q^+}$, so these alcohols (including PEG 600[25]) may be acting as phase transfer catalysts.[6]

Dimethyl sulfoxide (DMSO) is a well known solvent for alkylations using solid KOH,[26,27] and catalysis by DMSO (Table 4) may involve formation of the dimsyl anion followed by transport to the organic phase (pK_a data in DMSO indicate that

DMSO is only slightly less acidic than water—see Table 4). In DMSO, acetonitrile has a pK_a of 31.3, compared with the value of 31.2 for water,[14] and the $[CH_2CN]^-$ anion is the likely nucleophile in condensations of **1** with acetonitrile; hence, this anion may be the source of base in other reactions (*e.g.* epoxidation using sulfonium salts in acetonitrile[10,15]). Consequently, DMSO and acetonitrile also have potential as phase transfer catalysts transporting base from KOH to an organic medium.[6]

Conclusions

The effectiveness of KOH pellets as base catalysts is increased by the addition of small amounts of water (Fig. 3) to give 'feebly-hydrated'[10,15] KOH. In condensations such as formation of nitriles (**3**) from ketones (**1**) in acetonitrile, a significant fraction of the water produced during the reaction is absorbed by the solid KOH, and water acts as an autocatalyst; the kinetic order of the reaction changes from the expected first order (Fig. 2) to approximately zero order. As expected, the reaction is catalysed by quaternary ammonium salts, and our results (Tables 2 and 6) are not complicated by anion exchange which occurs in PTC alkylations. Catalysis by cosolvent/cocatalysts (Table 4) illustrate the potential role of solvents such as water, acetonitrile, DMSO and PEG 200 as phase transfer catalysts in reactions involving solid bases.[6]

Experimental

Materials

Ketones (**1**, Z = H, Lancaster) and (**1**, Z = Me, Cl and F, Aldrich) were used as supplied to synthesise the nitriles (**3**, Z = Me, Cl and F) from acetonitrile and KOH;[2] after column chromatography and characterisation by ^{1}H NMR spectroscopy, **3**, Z = H was recrystallised from 1:6 diethyl ether–hexane, mp 46–47 °C (lit.,[2,28] 47–48 °C), **3**, Z = Me was distilled to give a yellow liquid, bp 210 °C (lit.,[29] 204–207 °C), **3**, Z = Cl was recrystallised from diethyl ether–hexane to give yellow crystals, mp 53.5–55 °C (lit.,[30] 53 °C) and **3**, Z = F was distilled to give a yellow liquid. The hydroxynitrile (**2**, Z = H), obtained by reacting **1**, Z = H, with Bu^{n}Li–acetonitrile in THF at −78 °C,[31] was recrystallised from ethanol, mp 142–144 °C (lit.,[31] 141.5–143 °C). Furfural (**4**) was distilled under reduced pressure and condensed with acetonitrile to give the hydroxynitrile (**5**)[31] and the acrylonitrile (**6**),[2] as described elsewhere.

HPLC grade acetonitrile (Fisons) contained 0.1% water; acetonitrile was dried by distillation from phosphorus pentoxide and then contained 0.015% water. Pelleted KOH (15.3% water), sodium hydroxide (3.0% water) and potassium carbonate (0.1% water) from Fisons were used as supplied.

Quaternary ammonium salts (Aldrich) were also used as supplied, so probably contained traces of water. Methanol and acetonitrile (Fisons HPLC grade), *tert*-butyl alcohol and dimethyl sulfoxide, PEG 200 and PEG 6000 were used without further purification.

Analytical methods

HPLC analyses were made on a 15 cm × 0.25″ Spherisorb S5 ODS2 stainless steel column, eluted with 55% methanol–water for analyses of **1**–**3** (λ set to 225 nm) and with 30% acetonitrile–water for analyses of **4** and the (clearly separated) *E*–*Z* mixture **6** (λ set to 275 nm); to complete analyses within 10 min under our isocratic conditions, flow rates (LDC Milton Roy Constametric 3200 pump) of 2 ml min^{-1} for **1**–**3** and of 1ml min^{-1} for **4** and **6** were required; the absorbance range was usually set to 0.2 (Cecil CE2112 monitor). Samples were injected in 10 µl aliquots using a Perkin Elmer ISS 101 autosampler, and integration was done using a Hewlett Packard 3395 integrator plotter. A range of standard solutions of pure samples in acetonitrile (*ca.* 10^{-3} M) were used to obtain linear response/concentration plots for each compound of interest.

Karl Fischer titrations were conducted using a Mettler-Toledo DL 18 titrator and Hydranal 2 composite.

Kinetic methods

To a 100 ml three-necked flask, fitted with a Liebig condenser, was added ketone (**1**, 0.02 mol) acetonitrile (40 ml), and water (usually 0.1 ml), and the mixture was stirred magnetically (usually at a speed of 400 rpm) and was heated to reflux. The first sample of the reaction mixture was removed (see below) before KOH pellets (2.244 g, 0.04 mol) were added, and the reaction was then sampled at regular intervals whilst heating and stirring continued. Sampling involved using a 1 ml syringe with a 3″ needle to transfer of 2 or 3 drops of reaction mixture into a preweighed volumetric flask, which was then reweighed quickly before the reaction mixture was quenched with two drops of water, diluted to 10 ml with acetonitrile, and stored at <5 °C until duplicate HPLC analyses were made within 24 h.

Control experiments showed that rates were unaffected by a CO_2 trap, or by a drying tube fitted to the top of the condenser. For 'simultaneous' HPLC and water analyses, water and benzophenone were added to a refluxing mixture of acetonitrile and KOH, and the Karl Fischer titrations were carried out without significant delays. In reactions described using 'conditioned' KOH pellets, reaction mixtures were heated for predetermined times with KOH and added water present but in the absence of ketone, the ketone was then added, and monitoring was begun. Experiments with furfural (**4**) were conducted as described above, except at 60 ± 1 °C.

The concentration of carbonyl compound in each sample could be calculated from the weight of each sample and the average area of carbonyl signal, but the precision of the results was improved by also taking into account the area of the nitrile peak.[32] From a plot of concentration of carbonyl compound *vs.* time (*e.g.* Fig. 1), the appropriate linear region was selected, from which zero order rate constants were obtained by least squares analysis using Microsoft Excel.

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