COMMUNICATION

Cooperative nucleophilic–electrophilic organocatalysis by ionic liquids†

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The anionic and the cationic partners of ionic liquids may act cooperatively and independently as nucleophilic and electrophilic catalysts. This ambiphilic propensity was demonstrated by kinetically discriminating the contributions of the anion (nucleophilic catalyst) and of the cation (electrophilic catalyst) to the solvent-free Baylis–Hillman dimerization of cyclohexenone catalysed by ionic liquids.

In the general scheme of catalyzed organic ionic reactions, *i.e.* that involve attack of a nucleophilic species on an electrophilic species, one catalyst (**N**) may trigger the nucleophile (basic catalysis), another catalyst (**E**) may be able to activate the electrophile (acid catalysis). However simultaneous catalysis by **N** and **E** is generally not straightforward, as the two species will tend to annihilate each other. When a cooperative action of both catalysts is sought for, a "spacer" must be interposed between **N** and **E**, such as a "physical spacer",[1] or when they are grafted to a solid support at an appropriate distance (this may be considered a "virtual spacer").[2]

On this basis, ionic liquids are potentially a stable nucleophilic–electrophilic couple, where the anion can activate the nucleophile (either as a true nucleophile or as a base), and the cation the electrophile. Due to their very nature of ionic liquids, they do interact but not destructively.

We have recently reported the green halide-free synthesis of the methylcarbonate phosphonium salt $P_{8,8,8,1}MeOCO_2$ **1** by methylation of trioctyl phosphine with dimethylcarbonate DMC.[3] Anion-exchange in **1** generated an offspring of ionic liquids, such as the hydrogencarbonate salt $P_{8,8,8,1}HOCO_2$ **2** and the bromide salt $P_{8,8,8,1}Br$ **3**.
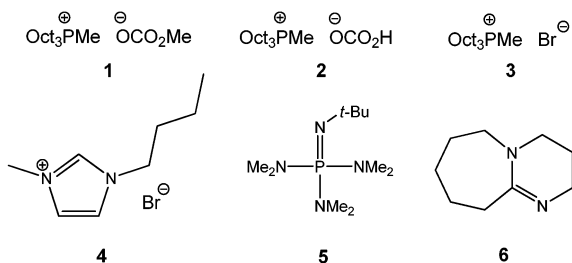
We observed[3] that ionic liquids **1** and **2** acted as unexpectedly strong bases, and were able to catalyse deprotonation of

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† Electronic supplementary information (ESI) available. See DOI: 10.1039/c2cc31099f

nitroethane and its successive Michael addition to cyclohexenone at a rate comparable to P_1–*t*Bu phosphazene **5**, and faster than known strong organic bases such as DBU **6**, DMAP, DABCO. Such strong basicity was unexplainable by the pK_a of the anions of **1** and **2**,[4,5] and seemed to indicate that the cation had a catalytic role as well. Reports exist on other ionic reactions that were boosted by the presence of ionic liquids,[6] and in one case an "electrophile–nucleophile dual activation" was openly invoked.[7] However, until now, unambiguous proof for their enhanced catalysis was never provided. (It should be noted here that any perceived incongruity between nucleophilic and basic catalyses is inconsequential in the present context.)

To probe this kind of ambiphilic nucleophilic–electrophilic catalysis, we have devised to investigate as a case study the Baylis–Hillman (B–H) type dimerisation of cyclohexenone **7** to the dimer **8**,[8] in the presence of catalytic quantities of ionic liquids **1**, **2**, **3**, and butyl–methylimidazolium (BMim) bromide **4**, compared to P_1–*t*Bu **5** and DBU **6**. (Here the term ambiphilic represents an extension of the concept generally used for stoichiometric reagents where the electrophile and nucleophile are present on the same molecular entity.[1])

The reactions were kinetically followed under solventless conditions. Under these conditions of high concentration, the signals of reagents, products and catalysts can be adequately followed by ^{13}C NMR spectroscopy. The experimental procedure for sample preparation was already described,[9] and is detailed in the ESI† section. The measurements are directly carried out in a spectrometer at 60 °C, under the regime of ^1H inverse gated decoupling, in order to minimize NOE effects. The selected peaks (the vinylic carbon at the 3 position of **7** or **8**, and the catalyst peaks indicated in the ESI† section) were fitted into a combination of Gaussian and Lorentzian functions, the analytical integral evaluated and adequately weighed. Because dimerization was the only observed process, and because the peak integrals of the most chemically equivalent 3 positions of **7** and **8** could be assumed to correctly monitor the corresponding substance quantities, the sum of the peak integrals of **7** and **8** (twice) was considered to be constant for the whole kinetic run; the integrals were normalized against it, giving the activities of the involved species **X** in the form of "unitary molar fractions", represented as {**X**}.

The molar amounts of catalysts with respect to **7** were always in the range of 1–6 mol%.

The results for an exemplificative kinetic run are shown in Fig. 1. The complete set is shown in the ESI† section.
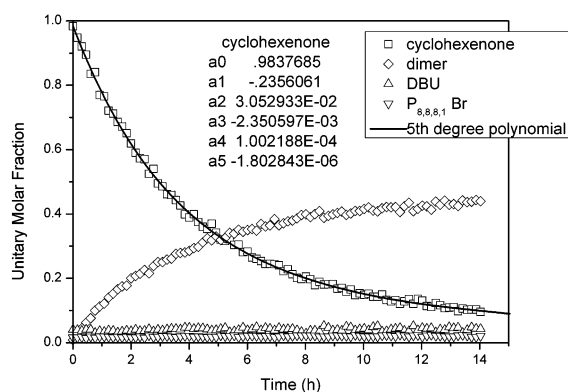
Fig. 1 The conversion (entry 9 in Table 1) of cyclohexenone **7** into the dimer **8** in the cocatalysis of $P_{8,8,8,1}$Br **3** and of DBU **6**. The interpolation of the decrease of **7** into a 5th degree polynomial and the corresponding a_0–a_5 coefficients are shown.

It is well established that the mechanism of B–H type reactions involves a nucleophilic catalysis,[8] as shown in Scheme 1, step (a), where **N** is the nucleophilic catalyst (represented here as an anionic species), and **7N** (in this case study) is the activated nucleophilic complex.

We introduce, and will later demonstrate, the possibility of an electrophilic catalysis, step (b), where **E** is the electrophilic catalyst (represented here as a cationic species) and **7E** is the activated electrophilic complex. A Michael type attack of **7N** follows, either on non-activated "free" cyclohexenone **7** (represented here in the convenient mesomeric structure), step (c), with kinetic constant k_0, or on activated **7E**, step (d), with constant k_1.

As a representative kinetic parameter of this whole set of processes, we selected the normalized initial rate constant $(-d\{7\}_0/dt)/\{7\}_0$. The initial rates are usually determined by the slope of the straight line drawn through a choice of the initial experimental data. As this choice is rather arbitrary, we devised to take advantage of the procedure based on the Newton polynomial interpolation of the experimental measurements.[9] We selected a 5th degree interpolation. The zero order coefficient of the derivative is the first order

coefficient a_1 of the interpolation, and is the only surviving coefficient at zero time. As the temperature of the sample and an acceptable instrumental homogeneity were not attained instantaneously, acquisition of the first value was delayed and the value of $\{7\}_0$ was generally less than unity. Furthermore, the accuracy of $\{7\}_0$, based on a single measurement, was questionable. A better choice was the zero order coefficient a_0, i.e. the intercept of the polynomial. Thus, the best value for $(-d\{7\}_0/dt)/\{7\}_0$ was given by the ratio $-a_1/a_0$.

The inspection of Fig. 1 reveals that the catalysts were regenerated (in agreement with the mechanisms in Scheme 1) and that they were also thermally stable. The average values, over the entire measurement set of the kinetic run, are reported in Table 1. The sample preparation (by weighing) could not assure equal fractions of the nucleophilic catalyst; therefore the kinetic parameters were normalized to $-a_1/(a_0\{N\})$, and the fractions of the electrophilic catalyst to $\{E\}/\{N\}$.

The results for the B–H dimerization of **6** with the described catalysts are collected in Table 1. The anions of the ionic liquids **1**–**4** and the species **5** and **6** were considered as the nucleophilic catalysts **N**. The counter cation $P_{8,8,8,1}$ of **1**–**3** and BMim of **4** were considered as the potential electrophilic catalysts **E**.

A rigorous comparison between rate constants would entail the use of a nucleophilicity scale. However, in the absence of nucleophilicity values for DBU,[10] and since phosphazenes are only qualitatively described as poor nucleophiles,[11] we had to be satisfied with the literature[4,5,12,13] pK_a values listed in Table 1.

The results in Table 1 revealed two striking points. (1) Entries 1, 2, 5 and 6: the basicities (and thus presumably the nucleophilicities) of hydrogencarbonate and of methylcarbonate are far lower than those of phosphazene P_1–tBu **5** or DBU **6**, nevertheless, the dimerization of cyclohexenone was catalyzed by the anions of **1** and **2** with similar or even greater rates. Besides the established catalysis by the nucleophile, it was therefore tempting to attribute some electrophilic catalytic role to the $P_{8,8,8,1}$ cationic partner as well. (2) Entries 3 and 4: in agreement with the very low basicity of the bromide anion,

Scheme 1

Table 1 Initial rates for the conversion of cyclohexenone **7** to the dimer **8**, at 60 °C under solvent-free conditions, in the presence of a series of nucleophilic catalysts **N** and of differing quantities of electrophilic catalysts **E**. {X} means "unitary molar fraction" (see the text)

	N		E		$-a_1$[c]	a_0[c]	$\{E\}/\{N\}$	$-a_1/(a_0\{N\})$
		$\{N\}$[b]		$\{E\}$[b]	h^{-1}			h^{-1}
1	$MeOCO_2^{-a}$	0.027	$P_{8,8,8,1}$	0.027	0.27	0.79	1.00	12.60
2	$HOCO_2^{-a}$	0.028	$P_{8,8,8,1}$	0.028	0.24	0.84	1.00	10.09
3	Br^{-a}	0.015	$P_{8,8,8,1}$	0.015	(0.0)	(1.0)	1.00	0.00
4	Br^{-a}	0.043	BMim	0.043	(0.0)	(1.0)	1.00	0.00
5	P_1–tBu[a]	0.031	—	—	0.28	0.96	—	9.37
6	DBU[a]	0.045	—	—	0.07	0.99	0.00	1.48
7	DBU	0.041	$P_{8,8,8,1}$	0.007	0.14	0.95	0.17	3.62
8	DBU	0.044	$P_{8,8,8,1}$	0.013	0.19	0.96	0.30	4.46
9	DBU	0.041	$P_{8,8,8,1}$	0.020	0.24	0.98	0.48	5.86
10	DBU	0.041	$P_{8,8,8,1}$	0.039	0.29	0.93	0.94	7.48
11	DBU	0.042	$P_{8,8,8,1}$	0.057	0.32	0.95	1.35	8.17
12	DBU	0.053	BMim	0.043	0.50	0.90	0.81	10.48

[a] Indicative pK_a from the literature: $MeOCO_2^- = 5.51$[4], $HOCO_2^- = 6.37$[5], $Br^- = -4.9$[12], P_1–tBu $= 26.98$[13], DBU $= 24.34$[13]. [b] Average of the values measured during the kinetic run. [c] a_0 ($\{7\}_0$), a_1 (d$\{7\}_0$/dt): zero and first order coefficients of the 5th degree polynomial interpolation of the decrease of **7** (except for entries 3 and 4).
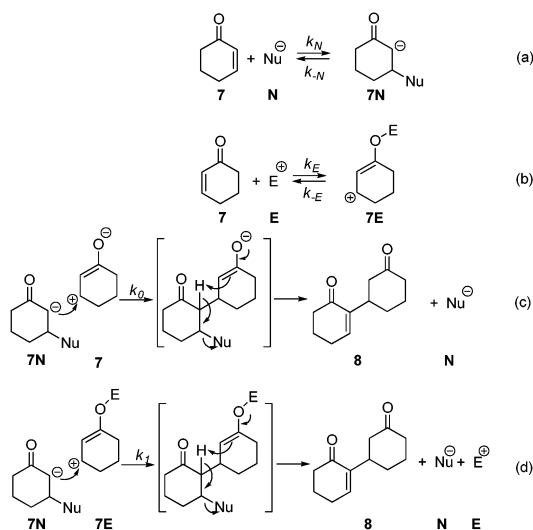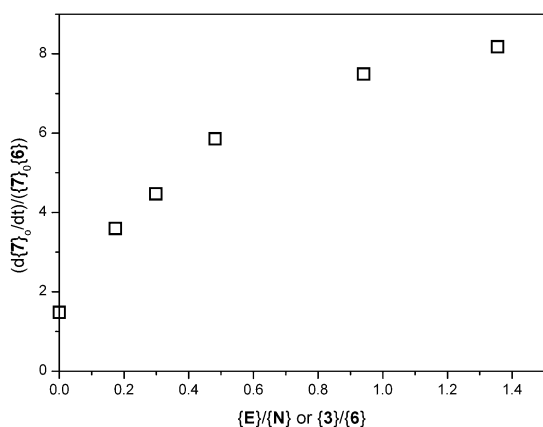
Fig. 2 The solvent free conversion of cyclohexenone **6** into the dimer **7**, cocatalyzed by methyltrioctylphosphonium bromide **3** and DBU **6** (entries 6–11 in Table 1). {**X**} means "unitary molar fraction" of **X**. Initial rate constants, normalized against {**6**}, are plotted *vs.* the ratio {**3**}/{**6**}.

$P_{8,8,8,1}Br$ **3** and BMimBr **4** were totally inactive toward cyclohexenone dimerization, confirming the principle that a strong enough nucleophile was necessary to trigger the B–H reaction, regardless of the role of the cation as a potential electrophile. This circumstance led to devise a strategy to discriminate between the contributions of the nucleophilic **N** and the electrophilic **E** catalysts. A series of five further experiments were run, with a constant amount of DBU **6** as a specific nucleophilic catalyst, and increasing amounts of $P_{8,8,8,1}Br$ **3** as a potential electrophilic co-catalyst. Finally, entry 12 describes a reaction carried out with DBU **6** and BMimBr **4** for comparison. The results are listed in Table 1 and plotted in Fig. 2.

It was readily apparent that the rate of the dimerization reaction increased with increasing amounts of **3**, indicating that the onium ion displayed electrophilic catalysis, as indicated in Scheme 1, steps (b) and (d). These considerations could be safely extended to the enhanced catalytic activity observed for $P_{8,8,8,1}CH_3OCO_2$ **1** and $P_{8,8,8,1}HOCO_2$ **2**, where the nucleophilic and the electrophilic catalysts were the anionic and cationic parts of the same entity. This kind of electrophilic activation of a carbonyl by phosphonium ion had already been proposed.[14]

The phosphorous atom can accommodate a high valence number and also possesses great affinity toward oxygen. The structure **9** can be proposed for the activated complex **7E**, similar to that established for another tetraalkylalkoxyphosphorane.[15]
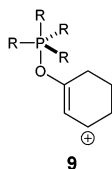
An experiment (entry 4) run using BMim Br **4** alone confirmed that bromide as a nucleophile was inactive. However, when **4** was coupled with DBU **6** (entry 12), the BMim cation was itself able to act as an electrophilic catalyst. This kind of activation finds precedents for imidazolium ionic liquids,[7a] and lends further support to our conclusions.

In summary, this investigation may be regarded as the first clear-cut piece of evidence that ionic liquids can operate synchronously as nucleophilic and as electrophilic catalysts. The ability of other ionic liquids as catalysts has been already noted, but left totally unexplained.[6] In one case, the nucleophilic anion is rather a solvent cage disruptor and the electrophilic cation a leaving group scavenger.[7a] When the basicity or nucleophilicity of a catalyst goes beyond the usual scale, the action is attributed to the presence and the boost of another base or nucleophile.[16] This cannot account for the apparent high nucleophilicity of methyl carbonate in **1** or of hydrogen-carbonate in **2**: no other nucleophile is present. Rather, the ambiphilic abilities of ionic liquids **1** and **2** must be taken into account: they operate cooperatively but independently, without interfering with each other.

Ambiphilic catalysis by ionic liquids rests upon a delicate equilibrium: the ionic liquids must be strong enough nucleophilic and electrophilic catalysts in order to operate, but not too strong in order to avoid reciprocal annihilation. For example, ammonium ionic liquids exist only when the anion is a weak conjugated base, and cannot otherwise survive, because Hofmann elimination takes over.[17]

Notes and references

1 K. Matsui, S. Takizawa and H. Sasai, *J. Am. Chem. Soc.*, 2005, **127**, 3680–3681; C. C. Cárdenas, N. Rabi, P. W. Ayers, C. Morell, P. Jaramillo and P. Fuentealba, *J. Phys. Chem. A*, 2009, **113**, 8660–8667.
2 A. Puglisi, R. Annunziata, M. Benaglia, F. Cozzi, A. Gervasini, V. Bertacche and M. C. Sala, *Adv. Synth. Catal.*, 2009, **351**, 219–229.
3 M. Fabris, V. Lucchini, M. Noè, A. Perosa and M. Selva, *Chem.–Eur. J.*, 2009, **15**, 12273–12282.
4 W. Behrendt and G. Gattow, *Z. Anorg. Allg. Chem.*, 1973, **398**, 198–206.
5 J. Meier and G. Schzwarzenbach, *Helv. Chim. Acta*, 1957, **40**, 907–917.
6 (a) J. McNulty, J. Dick, V. Larichev, A. Capretta and A. J. Robertson, *Lett. Org. Chem.*, 2004, **1**, 137–139; (b) Y.-K. Liu, H. Zheng, D.-Q. Xu, Z.-Y. Xu and Y.-M. Zhang, *J. Zhejiang Univ., Sci., B*, 2006, **7**, 193–197; (c) S. S. Shinde, B. S. Lee and D. Y. Chi, *Org. Lett.*, 2008, **10**, 733–735; (d) L. Zhang, X. Fu and G. Gao, *ChemCatChem*, 2011, **3**, 1359–1364.
7 (a) A. K. Chakraborti and S. R. Roy, *J. Am. Chem. Soc.*, 2009, **131**, 6902–6903; (b) J. W. Lee, J. Y. Shin, Y. S. Chun, H. B. Jang, C. E. Song and S.-G. Lee, *Acc. Chem. Res.*, 2010, **43**, 985–994.
8 (a) I. Uddin, K. Nakano, Y. Ichikawa and H. Kotsuki, *Synlett*, 2008, 1402–1406; (b) D. B. Ramachary and R. Mondal, *Tetrahedron Lett.*, 2006, **47**, 7689–7693.
9 V. Lucchini, M. Fabbri, M. Noè, A. Perosa and M. Selva, *Int. J. Chem. Kinet.*, 2011, **43**, 154–160.
10 M. Baidya and H. Meyr, *Chem. Commun.*, 2008, 1792–1794.
11 O. Legrand, *Synlett*, 2000, 752.
12 A. Kütt, T. Rodima, J. Saame, E. Raamat, V. Maäemets, I. Kaljurand, I. A. Koppel, R. Y. Garlyauskayte, Y. L. Yagupolskii, L. M. Yagupolskii, E. Bernhardt, H. Willner and I. Leito, *J. Org. Chem.*, 2011, **76**, 391–395.
13 I. Kaljurand, A. Kutt, L. Soovali, T. Rodima, V. Maemets, I. Leito and I. A. Koppel, *J. Org. Chem.*, 2005, **70**, 1019–1028.
14 M. Selva, M. Fabris, V. Lucchini, A. Perosa and M. Noè, *Org. Biomol. Chem.*, 2010, **8**, 5187–5198.
15 H. Schmidbaur, W. Buchner and F. H. Köhler, *J. Am. Chem. Soc.*, 1974, **96**, 6208–6210.
16 P. Caubère, *Chem. Rev.*, 1993, **93**, 2317–2334.
17 (a) R. K. Sharma and J. L. Fry, *J. Org. Chem.*, 1983, **48**, 2112–2114; (b) M. Bos, *Tetra-n-butylammonium Hydroxide*, in *Encyclopedia of Reagents for Organic Synthesis*, ed. L. Paquette, J. Wiley & Sons, New York, 2004.