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Increasing the life expectancy of carbanions by zeolite inclusion

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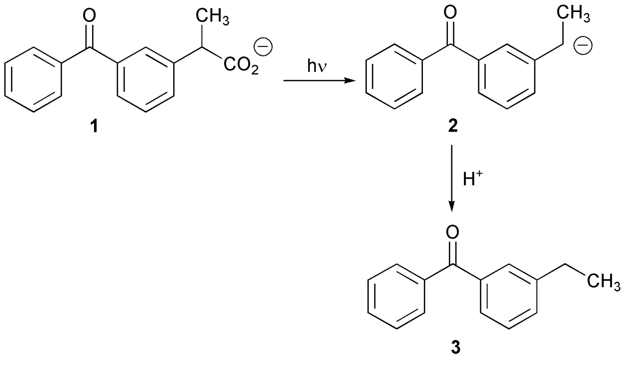
Carbanions have been detected for the first time in zeolite cavities where their lifetime is more than ten times longer than in solution; included carbanions show Grignard-like behaviour.

Zeolites have been widely employed as hosts in supramolecular systems and encapsulation frequently results in lifetime enhancements for otherwise short lived reaction intermediates, including triplet states,[1] free radicals,[2,3] and carbocations.[4,5] Sometimes these effects are simply the result of isolation or restriction of molecular motions, while in other cases they take advantage of the acid–base or redox properties of the microenvironment. In this communication we report the first example of the enhancement of a carbanion lifetime, thus opening the door for novel nucleophilic substitution processes.

The photochemistry of ketoprofen (**1**), a non-steroidal anti-inflammatory drug (NSAID) has been the subject of recent interest,[6] in part, because the beneficial effects of this drug can be offset by adverse effects, such as phototoxic reactions.[7–9] In addition to interesting pH-dependent photochemistry,[10–14] ketoprofen has been suggested as an unusual example of singlet state benzophenone photochemistry,[15,16] although the question of precursor multiplicity is still a matter of study. In aqueous solution the carbanion (**2**) forms rapidly, following irradiation, from the carboxylate of **1** and decays with a lifetime of about 200 ns, that approximately doubles in dry dimethylsulfoxide; **2** has a strong absorption at ~580 nm (Scheme 1).

In this work we have included **1** in the cages of zeolite NaY, a faujasite with cages of approximately 13 Å in diameter. Ketoprofenate was included by treatment of the acid with sodium methoxide in methanol, followed by incorporation into dehydrated zeolite from the methanol solution. Surprisingly, given the negative zeolite framework, the carboxylate includes readily and efficiently using this simple technique. After inclusion residual methanol was removed by drying under vacuum (50 mtorr) resulting in a dehydrated and solvent free sample, **1**@Y. The sample was then exposed to the pulses from a 308 or 266 nm excimer laser and the signals recorded using standard time-resolved diffuse reflectance techniques.[17–19] The transient observed is much longer lived than in solution and its decay is no longer monoexponential. The encapsulated carbanion now decays with complex kinetics and lifetime distribution analysis reveals at least three separate modes of decay. The longest lifetime component represents an increase of about a factor of fifty, as compared to buffered solution, and is experienced by more than half of the transients generated. These values are somewhat variable depending on unavoidable exposure to ambient humidity but are reproducible within ±100 ns for the short-lived components and ±2 μs for the longer lifetime.



Scheme 1

The multi-exponential behaviour described above suggests that carbanion **2** senses more than one environment in the cavities of the zeolite. This is not an uncommon situation in zeolites, where a distribution of sites frequently leads to multimode behaviour. In this case, while all the supercages in zeolite NaY have the same structure, the water content or number of acid sites may differ. Presumably, the short lifetimes reflect locations where protonation is easy and does not require extensive migration of the carbanion. Fig. 1 illustrates the carbanion spectra and Fig. 2 the distribution analysis mentioned

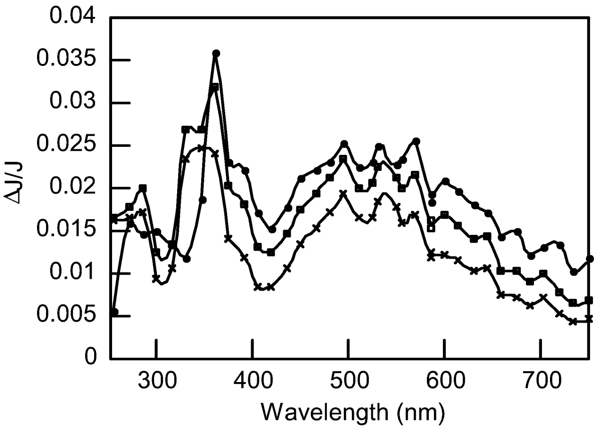


Fig. 1 Transient diffuse-reflectance spectra recorded 1.36 μs (●), 4.72 μs (□), and 14.5 μs (×) after 266 nm laser excitation.

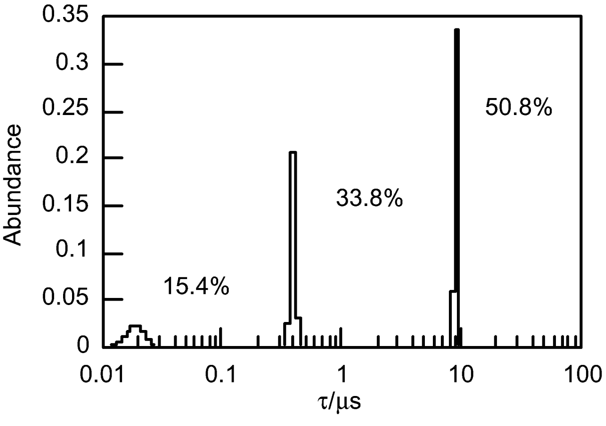


Fig. 2 Lifetime distribution analysis compiled from kinetic data acquired at 600 nm at various times after the 266 nm laser pulse.

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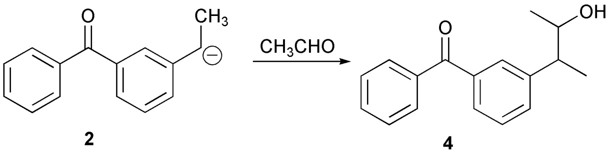
above. The remarkably narrow distributions (see Fig. 2) suggest the presence of discrete, well defined sites.

The lifetime enhancement observed opens exciting possibilities for novel nucleophilic substitution chemistry; essentially Grignard-type chemistry, triggered photochemically in supramolecular systems.

Product studies were performed in perfluorohexane slurries. Irradiation of zeolite inclusion complexes in slurries is common practice; however, these experiments run the risk that actual light exposure occurs when the substrate is in the liquid phase. Use of fluorous solvents, where most organic molecules are insoluble, readily eliminates this concern. Irradiation of **1** at 254 nm in the absence of added quencher reveals 3-ethylbenzophenone (**3**) as the main reaction product, as has been observed in solution. Addition of typical nucleophilic scavengers leads to observable lifetime reductions. For example, exposure of the zeolite to small quantities of water reduces the lifetime of the long-lived component by two to three times. The reduced lifetime is still an order of magnitude longer than what is observed in aqueous solution but this is reasonable considering the reduced mobility and concentration as compared to solution.

Similar lifetime reductions were observed using acetaldehyde and bromoalkanes as quenchers. In both cases preparative experiments were also conducted by loading **1**@Y with the desired quencher by vapour diffusion and irradiating the resulting solid as a perfluorohexane slurry (dry conditions). Acetaldehyde was absorbed to a loading of ≥ 15 molecules per supercage. Bromoethane was absorbed to a much lesser extent resulting in a loading of only ~ 2 molecules per supercage. In both cases we detected the peak characteristic for the product of S_N2 reaction (Scheme 2) by GCMS following Sohxlet extraction of the zeolite with ethyl acetate, however, the S_N2 reaction on bromoethane was inefficient while in the case of acetaldehyde the alcohol product **4** was obtained in 82% yield and with excellent conversion (MS m/z 254 (M^+), 209, 177, 105, 77). Protonation to give **3** was largely suppressed in the presence of acetaldehyde, accounting for about 8–9% of the products. The remainder ($<10\%$) corresponded to a chromatographic peak that was tentatively assigned to the dimer of the radical produced by electron loss from **2**; the presence of electron acceptor sites in the zeolites is well established.[20,21]



Scheme 2

The product from reaction with bromoethane was only obtained as a minor component in the photolysis of **1**@Y, the protonated compound, *i.e.* 3-ethylbenzophenone, was the major product; this contrasts with the efficiency of the acetaldehyde reaction and may be a combined consequence of the lower loading and the increased reactivity of typical Grignard-type intermediates towards carbonyls as compared to halogenated alkanes. By analogy to metal alkyls and Grignard reagents, the species within the zeolite is probably Na^+**2**; this is consistent with the reactivity – and increased lifetime – observed. Conceivably, interaction between the cations and the carbonyl may assist this reaction. Use of Mg^{2+} as a counterion may be interesting and is the subject of current studies.

From a mechanistic point of view these results are quite important since they demonstrate the potential of zeolites to host carbanion mediated reactions. Further, in the last decade many new zeolitic materials have been synthesised and characterized, including a range of mesoporous materials with large cages (such as MCM-41). In addition, a variety of methodologies have been developed to ″tune″ the acid–base and redox properties of zeolite supercages. We believe that the implementation of these methodologies and the use of new materials with reduced acidity will lead to improved synthetic applications in the future. Our current research is exploring some of these possibilities.

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