Formaldehyde Encapsulated in Zeolite: A Long-Lived, Highly Activated One-Carbon Electrophile to Carbonyl-Ene Reactions

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Traces of formaldehyde are found everywhere in nature; they can be in the air, rain, streamwater, coal, or even wood smoke. However, when formaldehyde is present in the atmosphere at ppm levels, it can cause serious side effects such as sore throat, headache, nausea, dizziness, atopic dermatitis, and other sick-house syndromes.

From the viewpoint of organic synthesis, formaldehyde is a versatile one-carbon electrophile.[1−3] However, its synthetic utility is often limited by its intractableness because of a low boiling point of −19.5 °C as well as its intrinsic instability because of a tendency to rapidly polymerize to a solid paraformaldehyde. Therefore, formaldehyde is generally obtained by the depolymerization of paraformaldehyde or trioxane with thermal or Lewis acid treatment, just prior to use.

In 1990, Yamamoto et al. reported the generation of a stable formaldehyde−bulky organoaluminum complex.[3] The complex enabled not only the carbonyl-ene reaction[4] with olefins but the addition of various nucleophiles in high yields. However, the complex was not stable for a long time at 0 °C.[3a] Thus, it was recognized that formaldehyde is difficult to preserve in a pure monomer form under ambient conditions.

Here, we report the successful storage of formaldehyde using zeolite, which suppresses self-polymerization and decomposition without losing the reactivity of formaldehyde toward nucleophiles. The zeolite-encapsulated formaldehyde (HCHO@zeolite) can now be used as a highly reactive C_1-electrophile in carbonyl-ene reactions.

We selected commercially available X- and Y-type faujasite zeolites (abbreviated as NaX and NaY, respectively) out of various types of zeolites as a vessel for formaldehyde. NaX (Si/Al = 1.5) and NaY (Si/Al = 2.7) zeolites, which have the same crystalline structure and only differ in their ratio of Si and Al atoms, have the following features: (i) they have interconnected supercages of 1.3 nm in diameter with pore windows of 0.74 nm in diameter, which are large enough to let in various organic compounds; (ii) they enable accelerated organic reactions due to the intrinsic acidity and basicity of NaX and NaY, which are dependent on the ratio of Si and Al atoms in the zeolite framework;[5] and (iii) they specifically react with reactants and products of select shape or select transition states due to the uniform, three-dimensional structure of the zeolite supercage in which the organic reactions proceed.[6]

HCHO@NaX and HCHO@NaY were easily prepared. Powdery NaX or NaY zeolite was placed in a flask, and gaseous formaldehyde generated by the thermal depolymerization of paraformaldehyde (or 99% ^{13}C-enriched paraformaldehyde, Cambridge Isotopes) was passed over the zeolite at 0 °C. Maximum adsorption of HCHO was observed with equivalent units of HCHO one-half that of sodium cations in the zeolite (about 72 mg of HCHO per g of NaX or NaY). This corresponded to three to four HCHO molecules per supercage.[7]
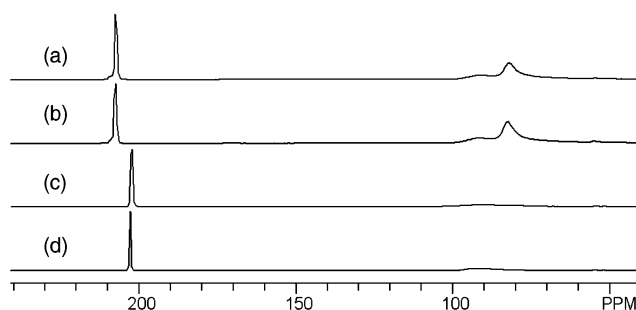

Figure 1. ^{13}C MAS NMR spectra acquired at 25 °C after the adsorption of formaldehyde-^{13}C on NaX and NaY: (a) HCHO-[13]C@ NaX, (b) HCHO-[13]C@ NaX after storage in a refrigerator at 5 °C for 50 days, (c) HCHO-[13]C@ NaY, (d) HCHO-[13]C@ NaY after storage in a refrigerator at 5 °C for 50 days.

At first, we investigated ^{13}C-labeled formaldehyde encapsulated in NaX and NaY by ^{13}C MAS NMR (75 MHz) at 25 °C. In the ^{13}C MAS NMR spectra of HCHO-[13]C@NaX (Figure 1a), we observed a sharp single peak at 207 ppm which was identified as that of a formyl carbon.[8a] Two small broad peaks at 91 and 81 ppm were observed and assigned as those of a paraformaldehyde and formaldehyde hydrate ($CH_2(OH)_2$) moiety, respectively.[8] The chemical shift (207 ppm) of formaldehyde adsorbed on NaX, which was previously reported,[8a] was that of formaldehyde in the presence of excess paraformaldehyde, but that shown in Figure 1a demonstrates the example of formaldehyde exclusively adsorbed to NaX.

The formyl carbon of HCHO-[13]C@NaY appeared at 202 ppm, and other related compounds such as paraformaldehyde, formaldehyde hydrate, methanol, and formic acid were scarcely detected on NaY (Figure 1c).

Surprisingly, the signal patterns of HCHO@NaX and HCHO@NaY remained unchanged after storage in a refrigerator at 5 °C for 50 days (Figure 1b and d). This result demonstrates the high stability of formaldehyde in the supercages of NaX and NaY and the tendency not to polymerize or disproportionate.

Formaldehyde incorporated in NaX and NaY shows slightly different chemical shifts at 207 and 202 ppm, respectively, which presages a difference in their reactivity to nucleophiles. We examined the carbonyl-ene reactions of various olefins with HCHO@zeolite to evaluate its reactivity (eq 1 and Table 1).

$$(1)$$
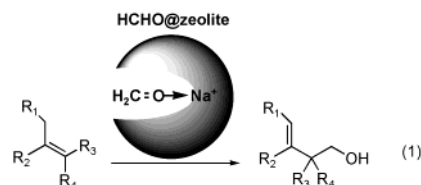
The carbonyl-ene reaction of α-methylstyrenes using HCHO@NaY proceeded smoothly and in excellent yields (entries 1 and 5), which

Table 1. Carbonyl-Ene Reactions Using HCHO@NaY[a]

| Entry	Substrate	Reaction temp. (°C)	Isolated yield (%)	Selectivity	
1[b,e]		20	94		**only**
2[b,e]		20	92		
3[b,f]		20	32		
4[b,g]		20	0		
5[b]		20	99		**only**
6[c]		0	90		**only**
7[c]		0	76	(50 : 50)	
8[d]	**1**			**2** + **3** + **4** + **5**	
	HCHO @ NaY	-20	92	(**2** : **3** : **4** : **5** = 20 : 13 : 67 : 0)	
	(HCHO)n, Me₂AlCl[h]	25	89	(**2** : **3** : **4** : **5** = 42 : 2 : 0 : 56)	
	trioxane, MAPH[h]	-78	97	(**2** : **3** : **4** : **5** = 72 : 28 : 0 : 0)	

[a] HCHO@NaY (HCHO content 2.4 mmol/g). [b] Solvent: cyclohexane. [c] Solvent: cyclohexane/hexane = 9/1. [d] Solvent: hexane. [e] Use of HCHO@NaY stored at room temperature for 30 days. [f] Use of HCHO@NaX (HCHO content 2.4 mmol/g). [g] Reacted with gaseous HCHO without zeolite. [h] See ref 3b.

had been difficult to achieve efficiently by using typical Lewis acids.[2] More interestingly, the reaction with HCHO@NaY, which had been kept at room temperature for 30 days, afforded a comparable yield (entry 2). This proves that active HCHO can survive in NaY even at room temperature for at least 30 days without any loss of reactivity. In contrast, HCHO@NaX was much less reactive in the same reaction even though monomeric form-aldehyde was similarly incorporated in supercages of NaX (entry 3).[9] We suppose that this is due to the lower acidity of NaX as compared to that of NaY. It was also confirmed that a simple treatment of olefin with gaseous formaldehyde without NaY gave no ene adducts (entry 4). This result strongly supports the fact that formaldehyde in HCHO@NaY is stabilized and simultaneously activated inside the zeolite supercages, which increases its elec-trophilicity.

The reaction of trisubstituted and cyclic olefins with HCHO@NaY afforded the corresponding ene products in good yields (entries 6−8), but unfortunately with low selectivity (entry 7). In the case of limonene, there was a large difference in selectivity between HCHO activated by Lewis acids and HCHO@NaY (entry 8). Dimethylaluminum chloride and a much bulkier organoaluminum reagent, MAPH (methylaluminum bis(2,6-diphenylphenoxide)), induced the reaction preferentially at the olefinic site on the side chain of limonene.[3b] On the other hand, the reaction of limonene with HCHO@NaY predominantly gave ene adduct **4** with good selectivity and in high yield. This selectivity seems to be derived from the particular affinity of a NaY supercage to a cyclic hydrocarbon over a linear one.[10]

Carbonyl-ene product **6** was able to be transformed to a chiral epoxide **7** in 93% yield with 89% ee by a combination of Zr(Ot-Bu)₄/diisopropyl tartrate/cumene hydroperoxide/molecular sieves, which was a key intermeditate for the synthesis of Tachykinin receptor antagonists (**8**).[11]

8   Tachykinin receptor antagonists
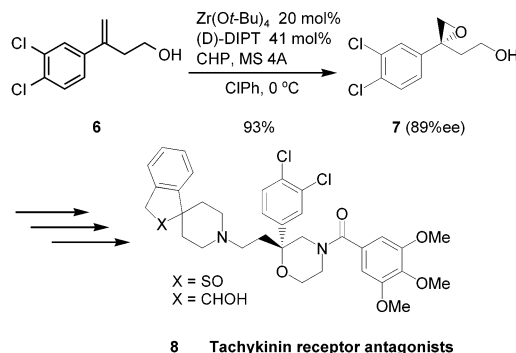
In summary, we demonstrated that ubiquitous faujasite zeolite, NaY, which forms uniform supercages of nanosize, can preserve labile formaldehyde in a monomeric form for a long period of time at ambient temperatures and can also activate the formaldehyde sufficiently enough to react with various olefins. The application of HCHO@zeolite to other nonionic nucleophiles is underway.[12]

Supporting Information Available: Experimental procedures and spectroscopic data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) By using HCHO@CaA and HCHO@Na-mordenite, no carbonyl-ene adducts were obtained.

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(12) Ionic reagents such as RMgX are not proper as a nucleophile toward HCHO@zeolite because the aluminosilicate framework of zeolites with a high Al content such as NaX and NaY is fragile under such strongly basic conditions.

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