Reductive etherification of substituted cyclohexanones with secondary alcohols catalysed by zeolite H-MCM-22

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Zeolite MCM-22 is an active and regenerable catalyst for a remarkably shape selective reductive etherification of cyclohexanones with bulky substituents at the 4-position, employing secondary alcohols as reductants.

Zeolite MCM-22 has recently been introduced as a unique biporous zeolite.[1] It has been shown that it contains two independent pore systems,[2,3] one defined by sinusoidal 10-membered ring channels extended in two dimensions, and the other by large 12-membered ring supercages (7.1 × 7.1 × 18.1 Å) connected by 10-membered ring channels. The material has a high thermal stability, a BET surface area of $> 400\ m^2\ g^{-1}$ and a sorption capacity of $0.16\ ml\ g^{-1}$,[4,5] which make it very interesting for catalysis. MCM-22 in its acidic form has already been claimed to be active in, for example, the conversion of lower alkenes to heavier hydrocarbons, and of aliphatic hydrocarbons to aromatics, the disproportionation of toluene and the alkylation of benzene.[6]

Here we report on the use of H-MCM-22 as a bifunctional catalyst in the reductive etherification of cyclohexanones having bulky substituents at the 4-position, using secondary alcohols as reductants. The zeolite appears to be active for both acid-catalysed conversion of the ketones to (hemi)acetals and consecutive Meerwein–Ponndorf–Verley (MPV)-type hydride transfer to yield ethers. Until now two catalysts were always required to achieve this, *i.e.* a strong acid for the acetalisation and a transition metal for the reduction step.[7,8] Various solid catalysts including zeolites have been applied in acid-catalysed acetal fomation[9] and the MPV reaction.[10,11] However, the combination of both properties in a single zeolite, enabling the direct synthesis of ethers from ketones, is novel.

MCM-22 with a Si/Al ratio of 15 was synthesized following a literature procedure,[12] dried at 60 °C *in vacuo* and subsequently calcined in a flow of air at 540 °C for 12 h. The acidic form was obtained by four-fold ion-exchange with 1 M aqueous ammonium nitrate at 80 °C for 12 h, followed by calcination as described above. X-Ray diffraction studies and the NMR (^{29}Si and ^{27}Al) spectra of the resulting material were in agreement with literature data.[13] The ^{27}Al NMR spectra indicated the presence of some extra-framework aluminium (δ −1.0). Transmission electron microscopy measurements showed the material to consist of small disk-like particles (130 × 130 × 15 nm), in agreement with scanning electron microscopy data.[2]

Reactions were conducted by refluxing ketone (9 mmol), catalyst (1 g) and 1,3,5-tri-*tert*-butylbenzene (1.6 mmol) as internal standard in Pr^iOH or Bu^sOH (70 ml). The reactions were monitored by GC (CP wax 52 CB column).

H-MCM-22 proved to be active and selective in the reductive etherification of 4-*tert*-butylcyclohexanone with the above mentioned alcohols, giving the corresponding ethers with a *cis*:*trans* ratio of 60:40 (Table 1). Only trace amounts (< 5%) of 4-*tert*-butylcyclohexanol, formed by direct MPV reduction, were observed. Continuous removal of water from the reflux by a bed of zeolite Na-A significantly increased both the conversion and the selectivity to the ether (Table 1). The catalyst could be re-used, following regeneration at 450 °C for 12 h in air, without any loss in activity or crystallinity.

The size and the shape of the ketone substrate appears to be decisive for the course of the reaction. For example, 4-phenylcyclohexanone and 4-methylcyclohexanone could be etherified, although with poor conversions and selectivity. On the other hand, 4-trimethylsilylcyclohexanone, with a similar size and shape to 4-*tert*-butylcyclohexanone, reacted smoothly.

Secondary alcohols are found to be required as hydride donors. With MeOH only acetal formation occurred. Acid sites appear to be essential, since with Na-MCM-22 as catalyst in the etherification of 4-*tert*-butylcyclohexanone only a 5% yield was obtained after 24 h. The reductive etherification is irreversible. Starting from the ether, water and acetone in Pr^iOH in the presence of zeolite H-MCM-22, no reaction occurred.

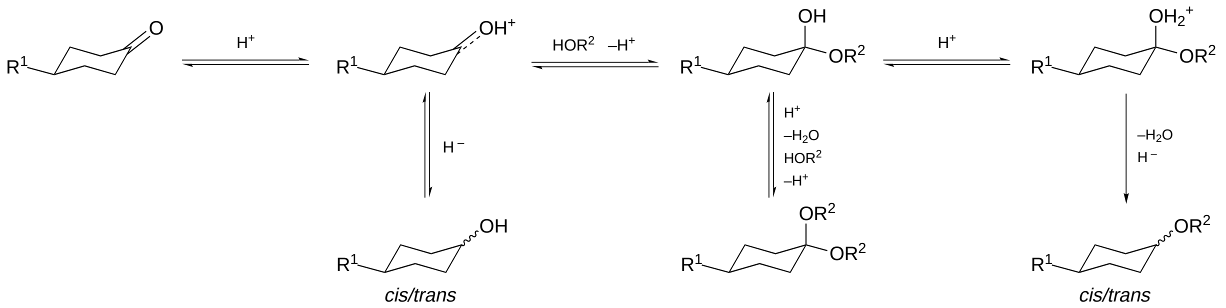
Some zeolites, especially zeolite Beta, perform well in MPV reductions.[14] However, a mechanism involving MPV reduction of the cyclohexanone, followed by acid-catalysed etherification by the solvent, can be excluded, since no reaction occurred on starting from 4-*tert*-butylcyclohexanol under similar reaction conditions. It seems more likely that the reaction proceeds *via* Brønsted acid-catalysed formation of a hemiacetal followed by a Lewis acid-catalysed, MPV-like hydride transfer to yield the ether (see Scheme 1).

The involvement of (hemi)acetals is supported by the fact that when the reaction of 4-*tert*-butylcyclohexanone was performed with a mixture of MeOH and Pr^iOH (1:1 mixture) both the dimethyl and the mixed methyl isopropyl acetals were formed almost instantaneously. These acetals were slowly converted into the isopropyl and methyl ethers. With 4-phenyl- and 4-methyl-cyclohexanones, dissolved in a 1:1 mixture of MeOH and Pr^iOH in the presence of zeolite H-MCM-22, acetal formation also occurred; however, only trace amounts of ether were formed together with some cyclohexene derivatives. The

Table 1 Reductive etherification of various 4-substituted cyclohexanones with secondary alcohols and H-MCM-22 as the catalysts[a]

Substrate	Conversion (%)	Selectivity (%) Ether	Alcohol	TON[b]
4-*tert*-butylcyclohexanone[c]	22	19	35	1.6
4-*tert*-butylcyclohexanone	100	78	6	7.3
4-*tert*-butylcyclohexanone[d]	96	93	6	7.0
4-*tert*-butylcyclohexanone[e]	98	87	9	8.2
4-*tert*-butylcyclohexanone[f]	6	65	29	0.3
4-phenylcyclohexanone[g]	15	20	0	1.1
4-phenylcyclohexanone[d,g]	15	20	0	1.2
4-methylcyclohexanone[g]	15	0	0	1.5
4-methylcyclohexanone[d,g]	12	60	0	1.3
4-trimethylsilylcyclohexanone	> 95	60	< 5	4.8

[a] Reaction conditions: ketone (9 mmol), catalyst (1 g) and 1,3,5-tri-*tert*-butylbenzene (1.6 mmol) as an internal standard, in Pr^iOH (70 ml) under reflux and stirring. Water abstraction from the vapour phase by a Soxhlet apparatus filled with zeolite NaA. [b] Based on the total number of aluminium sites present in 1 g of catalyst. [c] Without removal of water. [d] Reaction with Bu^sOH. [e] Regenerated catalyst. [f] Reaction with Na-MCM-22 as catalyst. [g] Conversions are corrected for the amount of substrate in the vapour phase and the amount adsorbed by the catalyst.



R^1 = Bu^t, Ph, Me, $SiMe_3$
R^2 = Pr^i, Bu^s
H^+ = zeolite OH
H^- = activated H of Al-coordinated secondary alcohol

Scheme 1

diisopropyl acetal was not observed in any reaction although this acetal can easily be prepared homogeneously.[9] Steric strain might prevent its formation. It cannot be excluded, however, that formation of the diisopropyl acetal occurs in the zeolite supercages, from where it cannot escape.

The role of Pr^iOH as hydride donor was demonstrated by a reaction in Pr^iOD (25% labelling). GC–MS and ^2H NMR of the reaction product showed that the C(1)-position of the cyclohexane ring and the secondary carbon of the isopropoxy group were 25% deuterated.

It remains unclear why H-MCM-22 shows this unusual behaviour, while various other solid acids yield only the MPV reduction products.[14] Possibly the number of Brønsted acid sites in H-MCM- 22 greatly exceeds the number of sites capable of catalysing the MPV reduction, resulting in the fast formation of (hemi)acetals followed by a slow conversion to the ethers. An explanation for the remarkable shape selectivity of the reaction may be that it takes place in the zeolite supercages (see Fig. 1).

The aluminium site in MCM-22, required for the hydride transfer, is assumed to be located mostly at the positions marked with an arrow.[15] When 4-*tert*-butyl- (and 4-trimethylsilyl)-cyclohexanone is adsorbed into the zeolite cage, it is forced into an orientation which brings the carbonyl group into close proximity to that site. In this tentative mechanism the aluminium atom plays a three-fold role: activation of the ketone, hydride transfer and stabilisation of the carbocation intermediate formed after water elimination. In contrast, the 4-methyl- and 4-phenyl-cyclohexanones are not forced to adopt this specific orientation.

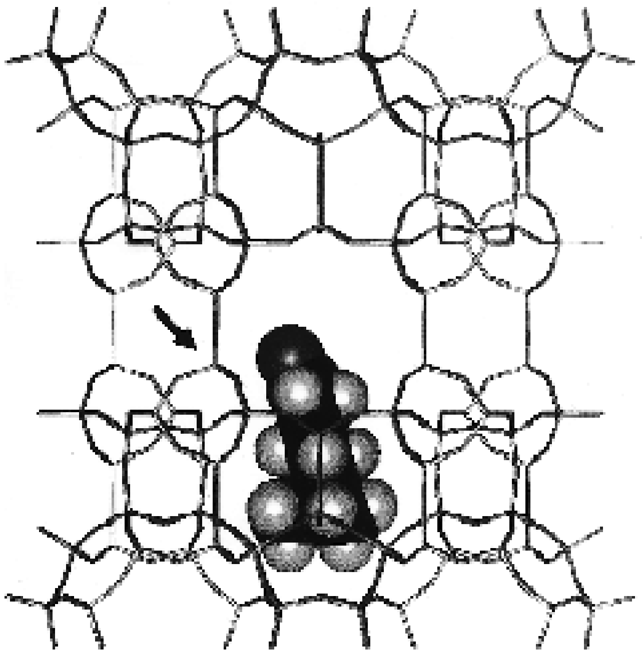


Fig. 1 4-*tert*-Butylcyclohexanone in an MCM-22 supercage

In conclusion, H-MCM-22 is an active catalyst in the reductive etherification of substituted cyclohexanones. The mechanism is proposed to proceed *via* the formation of a hemiacetal followed by an MPV-like reduction.

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