Double-aberration corrected TEM/STEM of solid acid nanocatalysts in the development of pharmaceutical NSAIDS

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Abstract. We report nanostructural and physico-chemical studies in the development of an efficient low temperature heterogeneous catalytic process for nonsteroidal anti-inflammatory drugs (NSAIDS) such as N-acetyl-p-aminophenol (paracetamol or acetaminophen) on tungstated zirconia nanocatalysts. Using a double-aberration corrected TEM/STEM, modified in-house for in-situ studies at the sub-Angstrom level, we directly observed in real-time, the dynamic precursor transformation to the active catalyst. We quantified the observations with catalytic activity studies for the NSAIDS. The studies have provided the direct evidence for single tungsten promoter atoms and surface WOₓ species of ≤ 0.35 nm, with nanoclusters of WOₓ (0.6 to 1nm), located at grain boundaries on the surface of the zirconia nanoparticles. The correlation between the nanostructure and catalytic activity indicates that the species create Brønsted acid sites highly active for the low temperature process. The results open up opportunities for developing green heterogeneous methods for pharmaceuticals.

1. Introduction
Catalysts with strong acidic properties are of interest in key catalytic processes including isomerisation of butanes and pentanes and in acylation [1,2]. The rearrangement of ketoximes to amides or lactams in the presence of acid catalysts is known as Beckmann rearrangement. N-acetyl-p-aminophenol (paracetamol or acetaminophen) is one of important non-steroidal anti-inflammatory drugs (NSAIDS) commonly used by humans because of its analgesic properties. Conventionally it is prepared by acetylation of p-aminophenol with acetic anhydride via homogeneous catalysis. The preparation of N-acetyl-p-aminophenol involves reacting 4-hydroxyacetophenone to obtain the ketoxime (4-hydroxyacetophenone oxime) followed by the Beckmann rearrangement in the presence of an acid catalyst, including fuming sulphuric acid [1,2]. This process however produces unwanted wastes. The use of solid acid catalysts can offer significant advantages over homogeneous acid catalysts for the synthesis of amides/lactams of pharmaceutical importance as in the case of caprolactam synthesis [3]. In this study, we have investigated tungstated zirconia solid acid nanocatalysts to catalyse the Beckmann rearrangement of 4-hydroxyacetophenone oxime to N-acetyl-p-aminophenol at low temperatures. The schematic of the process is shown in Figure 1.
2. Experimental Procedures
We synthesised two sets of samples with different W loadings including 5, 10 and 15 wt% W. The first series of samples (referred to as WZA) were prepared using zirconium oxohydroxide solution and infusing with ammonium metatungstate, followed by drying and calcination. In the second series of samples (WZB) reported in the literature, zirconium oxohydroxide was pre-calcined and then used with ammonium metatungstate, followed by drying and calcinations procedures similar to those used for the WZA series of samples. The two sets of samples exhibited different zirconia grain sizes and locations for active species. The oximes were synthesized from the corresponding ketones by reaction with hydroxylamine hydrochloride in a mixture of ethanol and pyridine at 358 K, by the general method reported in the literature. We used NH$_3$ adsorption microcalorimetry to estimate the acid strengths of the WZA catalysts as a function W surface density.

![Beckmann rearrangement of 4-hydroxyacetophenone oxime to N-acetyl-p-aminophenol.](image)

The development of atomic resolution environmental TEM (atomic resolution-ETEM) [4,5] for the direct visualisation of dynamic gas-solid reactions under controlled reaction conditions of gas pressures (with flowing gas) and temperatures at the atomic level has demonstrated that it is possible to study dynamic catalytic reactions at the atomic scale. In the present study in-situ electron microscopy studies at the sub-Angstrom level were performed using our in-house development of a modified double-spherical aberration corrected JEOL 2200 FS TEM/STEM, operating at 200 kV [6,7]. We modified the instrument with a larger gap (HRP) objective lens polepiece and gas tolerant pumping system [6,7] in the Nanocentre at the University of York, to directly witness live precursor transformation. The in-situ AC TEM studies were complemented by in-situ HAADF STEM. The development enables sample heating using a standard heating holder under controlled conditions and tilting of the sample for alignment into the correct crystal zone axis orientation. The instrument is fitted with an EDX detector for composition analysis at the sub-nm scale. A combination of AC HAADF-STEM and AC-TEM was employed to further analyse the species.

3. Results and Discussion
In WZA sample with 15 wt% tungsten loading (15WZA), W single atoms and surface WO$_x$ species with sizes of ≤0.35 nm to slightly larger species of ~0.375 nm were primarily observed using negative defocus imaging, co-existing with nanoclusters and WO$_3$ nanoparticles (with sizes of up to 0.6 nm to 1 nm), on the surface of nano-zirconia. The single atoms and WO$_x$ species coexisting with nanoclusters are shown in Figure 2 and Figure 3, respectively. The structure and the composition of the nanoparticles were confirmed by measurements of lattice spacings and by sub-nm EDX. Average size of such ZrO$_2$ crystallites (nanocrystals) in WZA samples was estimated to be 2.6 nm (with sample variance $\sigma^2=0.334$ nm$^2$). Catalytic activity measurements were performed to correlate the nanostructure of the catalysts containing these active sites, with selectivity and activity to N-acetyl-p-aminophenol at low temperatures [8]. The measurements show very high selectivity and activity of more than 94% and 97%, respectively, for the catalysts at 403K as shown in Figure 4.

Our comparative experiments have elucidated that WZB samples prepared using procedures reported in the literature have larger grains sizes of ≥ 30 nm-50 nm. WZB samples and post preparation procedures that deliberately increase the surface density of active species by coimpregnation of ZrO$_2$ and WO$_3$ on zirconia catalysts do not anchor active sites at grain boundaries of zirconia.
Figure 2. AC-HAADF STEM image indicating the presence of W single atoms from the rectangular area marked by an arrow on the figure. Intensity profile taken from the area is shown on the right. Arrowed peak corresponds to single atom. (Surface WO$_x$ species are indicated by a white circle).

Figure 3. Negative defocus imaging revealing uniformly distributed surface tungsten oxide species (<0.3 nm e.g. at S) and nanocusters anchored at grain boundaries of nano-zirconia (indicated by white arrows).

Figure 4. Conversion of 4-hydroxy acetophenone oxime and selectivity of paracetamol as a function of low reaction temperatures. Solvent = Benzonitrile; time= 12 h ; Oxime = 0.9 mmol; Catalyst = 20 mg. Excellent selectivity and activity were observed at 403K.
Figure 5(a) and (b) illustrate the grain size difference between the WZA and WZB preparations, respectively. The direct observation of 15WZA nanocatalysts clearly illustrates the segregation of surface species and clusters to grain boundaries on the nano-zirconia surface as illustrated in Figure 5(a). When 15WZB catalyst was examined in a similar way, a number of differences were apparent in the size and morphology of the catalyst particles compared to 15WZA. The most striking differences were the lack of tungsten oxide species at grain boundaries of zirconia particles and larger grain sizes of zirconia particles in 15WZB sample (Fig.5b). Our observations have shown that the lack of anchoring of active species at grain boundaries of catalysts results in the migration and sintering of the species and the subsequent deactivation of the catalysts. The observations are consistent with much lower selectivity and activity observed for the WZB samples.

Figure 5. AC-TEM images of: (a) WZA catalyst and (b) WZB catalysts illustrating the difference in zirconia grain sizes. In our preparation (a), zirconia grains are only a few nms compared to about 50 nm in the conventional catalysts. In (b), W-oxide clusters (e.g. arrowed) sintered faster in the conventional catalyst, growing to about 5 nms in about 2.5 hours and many nms after several hours.

4. Conclusions
The results demonstrate the nature and the role of active sites and high activity of tungstated zirconia nanocatalysts in the NSAID reaction. They further provide an environmentally clean alternative to the current homogeneous process.

Acknowledgements
We thank the University of York, JEOL and Yorkshire Forward / European Regional Development fund (ERDF) for sponsoring the York JEOL Nanocentre; Japan Society for Promotion of Science (JSPS) and Japan Fine Ceramic Center (JFCC) for a fellowship (KY) and University of Huddersfield for a fellowship (NS).

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