Continuous Tubular Flow Reactor for XAFS Studies of Organometallic Reactions: Possibilities and Limitations for Studies of the Soai Reaction

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Abstract. A computer-controlled continuous tubular flow reactor system has been commissioned that permits time-resolved in situ XAFS measurements of organometallic reactions. The system was commissioned by Zn K-edge measurements of products formed during the Soai reaction. XANES data are shown that illustrate the quality of the data that can be achieved. The XANES spectra are compatible with the presence of dimer, trimer or other oligomeric alkoxide species in the Soai process. It is shown how heterogeneity in the Soai reaction system leads to considerable complications with the measurements due to the formation of floating particles of the aldehyde/iPr₂Zn adduct formed in the reaction; additionally, decomposition of iPr₂Zn with residual air and moisture leads to deposits on cell walls.

1. Introduction
Alkylations of pyrimidyl aldehydes (Scheme 1) by diisopropylzinc have over the last two decades received considerable attention because they represent an amplifying asymmetric autocatalytic reaction mechanism that can, in principle, achieve homochiral products in an essentially non-chiral environment.¹ The reaction has initially been developed by Soai and co-workers²-⁵ and is therefore often referred to as the ‘Soai’ reaction. A pyrimidyl aldehyde ¹ reacts with diisopropylzinc ² to an organozinc complex ³, from which the pyrimidyl alcohol (product ⁴) can be obtained by hydrolysis. Chiral amplification in this reaction occurs because the chiral product ³ transfers the unreacted isopropyl group enantioselectively, forming the pyrimidyl alcohol ⁴, which can then react with further diisopropylzinc ² to form the same product. In other words, ⁴ is both the product of the alkylation and the chiral auxiliary, so the overall process is autocatalytic and strong amplification of chirality can be achieved.

Elucidating the structural nature of the intermediate(s) involved in the decisive autocatalytic step of the reaction will be crucial for a deep understanding of the chiral amplification process. Mechanistic details of the reaction have until now been derived only from computational studies of possible intermediates, NMR-studies of the relevant species in solution, and by calorimetric studies of
Scheme 1. An example of a Soai autocatalytic reaction.

the reaction kinetics.\textsuperscript{6-10} Organometallic zinc complexes that are monomeric, dimeric, trimeric or even tetrameric have been proposed as possible candidates for the chiral intermediate that achieves the autocatalytic selection of only one product enantiomer. We have now undertaken the first studies of the reaction by X-ray Absorption Fine Structure (XAFS) spectroscopy at the Zn K-edge, to obtain structural information about the local environment of zinc in the reaction media.

2. Experimental

The \textit{in situ} flow XAFS measurements at the Zn K-edge were performed at station 9.3 of the SRS, UK, and at 12ID-B\textsuperscript{11} of the Advanced Photon Source (APS) at Argonne National Laboratory (USA). Supporting work with non-flowing solutions was performed using sealed Eppendorf microcentrifuge tubes\textsuperscript{13} at BM29 of the ESRF, Grenoble, France. Solutions were loaded into the microcentrifuge tubes in a glove bag continuously purged with dry N\textsubscript{2}. All reactions were performed at room temperature. At all three beamlines simultaneous measurements in transmission mode with gas ionization chambers and by fluorescence-yield (FY) detection with multielement Ge detectors were performed. Reactants and dry toluene solvent were obtained from Aldrich.

Figure 1. Schematic arrangement of the PTFE tubular flow reactor mounted on a heatable Al frame; also shown are representative \textit{in situ} Zn K-edge FY XANES data taken at positions A1, D2 and C4 during the Soai reaction with a 1:1 volume mixture of 0.1 mol L\textsuperscript{-1} diisopropylzinc and pyrimidyl aldehyde solutions.
The flow reactor was based on PTFE tubing (1/8 inch outer diameter) attached to an aluminium support frame that had 16 holes in a regular 4×4 pattern machined out of it (see schematic sketch in figure 1). At the positions of these holes in situ monitoring of the reaction progress along the tube was possible by combined transmission and fluorescence-yield detection. For our studies of the Soai reaction the pyrimidyl aldehyde and diisopropylzinc were mixed at the tube inlet by joining the two solution streams in a PTFE ‘T’-piece (Omnifit). The solution streams were provided by syringe pumps (Versa 6, Kloehn) fitted with 1 mL syringes and non-distribution valves; they were controlled remotely via a serial interface with a LabVIEW (National Instruments) GUI. A pair of syringe pumps was used for each of the two reactants (0.1 mol L⁻¹ diisopropylzinc and pyrimidyl aldehyde solutions). Handshaking operation synchronised the pump pairs: while one pump was dispensing the other was aspirating in preparation for subsequent dosing. As mentioned above, due to the oxygen and moisture sensitivity of this iPr₂Zn solution a nitrogen atmosphere was needed to keep the environment inert within the pump pairs and flow cell apparatus. This was achieved by including a nitrogen feed on the multiport pump-head and purging before introduction of iPr₂Zn solution. The reactant solutions were also prepared and stored under nitrogen. By varying the flow rate from the dosing pumps it is possible to tune the flow rate in the reactor to obtain information about the nature of metal species as a function of reaction time. Positioning in the X-ray beam was achieved by using a computer controlled XYZ stage calibrated to the dimensions of the reactor system. FY XANES data obtained at the APS during the reaction in a solution containing 0.1 mol L⁻¹ of pyrimidyl aldehyde and 0.1 mol L⁻¹ diisopropylzinc are included in figure 1. A photograph of the completely assembled system at station 9.3 of the SRS is shown in figure 2.

3. Results and Discussion

3.1 Flow Experiments

The XANES data from figure 1 indicate that under the chosen flow conditions the reaction had progressed almost to completion at the initial measurement point, A1. Only minor spectral changes
occur as the reaction progresses towards positions D2 and C4. The appearance of occasional ‘spikes’ in the XANES data shown in figure 1 was traced to the formation of small floating particles of a precipitate formed by the Soai process. We found that particles moving into and out of the X-ray beam would cause such distortions of the spectra, which were especially strong in transmission mode. In fact, several runs of experiments were rendered uninterpretable by the resulting presence of strong non-random noise.

In addition to the observed formation of a precipitate a strongly adherent wall deposit became apparent during the flow reactor experiments. These stationary deposits additionally influenced the XANES spectra. They form because the velocity of the flowing solution near the walls is lower than in the inner volume of the tube. The extent to which wall deposits can grow quickly is illustrated by electron microscopic images in figure 3. The lower of the two images shows that after running the Soai reaction for 50 min the deposit had a thickness of 5 µm. Ex situ energy-dispersive X-ray (EDX) analysis (figure 3) confirmed that the deposit contains ZnO and organozinc material. It seems likely that the formation of such wall deposits can only be suppressed if the reactor design is modified to maintain a high space velocity of the reaction medium, for example through strong turbulent flow or shear, near the wall where the XAFS measurements take place. Abrupt changes of flow direction or introduction of constricted regions on the tube may achieve this objective.

The XANES data included in figure 1 are reminiscent of the Zn K-edge XANES of Zn$^{2+}$ species in a tetrahedral environment, such as ZnO$^{12}$. This is illustrated in figure 4, in which the spectrum from position C4 is compared to a previously published$^{12}$ spectrum of solid crystalline ZnO. It can be seen that the energetic positions of the shoulder at ~9664 eV, the main resonance at ~9669 eV and the broad resonance around ~9682 eV coincide. Note however that the amplitudes of the XANES resonances of the Soai product, and especially the features in the EXAFS region (e.g., at ~9717 eV), are strongly reduced, indicating disorder relative to crystalline ZnO on one hand and the presence of a significant self-absorption effect, likely associated with the formation of the observed solid product on the other. It appears that deposition of a poorly ordered ZnO and/or Zn(OH)$_2$ product

Figure 3. Electron microscopy and EDX analysis of the organozinc wall deposit on the inside of the PTFE reactor tube.
takes place on the wall of the reactor tube and dominates the observed XAFS spectrum. The most likely origin is the presence of residual water and/or $O_2$ in the reaction system, decomposing diisopropylzinc to $Zn(OH)_2$ and $ZnO$, respectively.

### 3.2 Products of Soai Process under Non-Flow Conditions

Experiments with a sealed static reactor cell (a standard Eppendorf polypropylene microcentrifuge tube) allowed us to minimise the formation of wall deposits and to selectively characterise the precipitate formed by the Soai process. This was achieved by allowing sedimentation of the precipitate at the bottom of the microcentrifuge tube, which also enabled us to separately examine the remaining supernatant solution. Figure 4 contains the resulting transmission XANES spectra of the sedimetrated precipitate (3rd spectrum from top) and of the supernatant solution (2nd spectrum from top) obtained by mixing 0.1 mol L$^{-1}$ aldehyde and 0.1 mol L$^{-1}$ iPr$_2$Zn in toluene in a 1:1 molar ratio. It can be seen by comparison with the spectrum of iPr$_2$Zn in toluene (top spectrum) that any Zn species remaining in the supernatant solution stem from unreacted iPr$_2$Zn. In contrast, the spectrum of the sedimetrated precipitate (second spectrum from top) has no strong white line, indicating that p-like valence states are occupied and that the local bonding and/or coordination geometry are fundamentally different from that in iPr$_2$Zn. For a 1:1 mixture of iPr$_2$Zn and aldehyde one would statistically expect a product mixture containing unreacted iPr$_2$Zn as well as the monomeric species.
(Scheme 1) and some monomeric dialkoxide species 5 (figure 3). To address which of these species was responsible for the observed spectrum we carried out the reaction of iPr₂Zn with a 20-fold excess of aldehyde because this reaction is expected to result in the formation of only the dialkoxide 5. Interestingly, the XANES spectrum of this product (3rd spectrum from bottom in figure 3) is very similar to the spectrum of the precipitate formed in the 1:1 mixture, indicating that the dialkoxide is preferentially formed even when understoichiometric amounts of aldehyde are supplied. What is currently not clear is whether the precipitate contains the monomeric species 5 or whether the previously proposed 6-10 dimers, trimers or oligomers of 5 are formed. In these products the Zn centres would be in a distorted tetrahedral coordination environment,10 which is compatible with the overall appearance of the spectra and especially the absence of the strong white line in the XANES spectra of the observed product.

4. Conclusions
A fully computer-controlled continuous tubular flow reactor system for time-resolved in situ XAFS measurements has been commissioned. Zn K-edge XANES data demonstrate that with 3rd generation synchrotron beam spectra of very good quality can be achieved with Zn concentrations in the 100 μmol region. Heterogeneous processes in the Soai reaction lead to considerable complications with the measurements due to the formation of floating particles of the aldehyde/iPr₂Zn adduct formed in the reaction, while the deposition of solid iPr₂Zn decomposition products on the walls of the flow reactor dominates the spectra after less than an hour of continuous reaction. The Soai precipitate formed in 1:1 iPr₂Zn:aldehyde mixtures appears to be the dialkoxide complex, while the remaining supernatant still contains unreacted iPr₂Zn. The XANES data for the dialkoxide do not exclude the presence of non-monomeric species; that a precipitate is observed supports the notion that the formation of dimers, trimers, tetramers or higher oligomers takes place.

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References
1. Buono, F. G.; Iwamura, H.; Blackmond, D. G., Ang. Chem. - Int. Ed. 2004, 43, 2099.
2. Soai, K.; Kawasaki, T., Chirality 2006, 18, 469.
3. Soai, K.; Shibata, T., J. Synth. Org. Chem. Japan 1997, 55, 994.
4. Soai, K.; Niwa, S., Chem. Rev. 1992, 92, 833.
5. Todd, M. H., Chem. Soc. Rev. 2002, 31, 211.
6. Gridnev, I. D.; Serafimov, J. M.; Quinney, H.; Brown, J. M., Org. Biomol. Chem. 2003, 1, 3811.
7. Islas, J. R.; Lavabre, D.; Grevy, J. M.; Lamoneda, R. H.; Cabrera, H. R.; Micheau, J. C.; Buhse, T., Proc. Nat. Acad. Sci. 2005, 102, 13743.
8. Buhse, T., Tetrahedron-Asymmetry 2003, 14, 1055.
9. Gridnev, I. D.; Serafimov, J. M.; Brown, J. M., Chem. - Int.Ed. 2004, 43, 4884.
10. Klankermayer, J.; Gridnev, I. D.; Brown, J. M., Chem. Commun. 2007, 3151.
11. Beno, M. A.; Jennings, G.; Engbreton, M.; Knapp, G. S.; Kurtz, C.; Zabransky, B.; Linton, J.; Seifert, S.; Wiley, C.; Montano, P.A. Nucl. Instrum. Meth, A 2001, 690, 467.
12. Schroeder, S.L.M.; Moggridge, G.D.; Lambert, R.M.; Rayment, T.; J. Phys. IV, 1996, C7, 91.
13. Meehan, D.J.; Nchari, L.N.; Hembury, G.A.; Beesley, A.M.; Schroeder, S.L.M.; in preparation.