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The Oxidative Spirocyclisation of 2-(ω-Hydroxyalkylfurans) as a Key Step in Natural Product Synthesis – Jeremy Robertson (jeremy.robertson@chem.ox.ac.uk)

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During the devlopment of our synthetic approach to the lituarines1,2,3 (Box 1) we recalled that the oxidation of substituted furans with epoxidizing agents results in ene-diones. Application of this reaction to furans bearing a hydroxyalkyl group at the 2-position was expected to lead to a double cyclisation process resulting in spirocyclic butenolide products. In reducing this idea to practice, we were pleased to find that this proposal worked well using an excess of MCPBA at room temperature. In the context of our lituarine synthesis, this process led to the rapid assembly of a large fragment of the natural products, the C(6)–C(18) tricyclic spiroacetal (Box 2).

Soon afterwards, we discovered that these spirobutenolide intermediates were viable substrates for conjugate addition with S-stablilized organolithium reagents and, at low temperature, addition proceeded kinetically anti-to the oxygen in the tetrahydropyranyl ring; this sense of stereoselectivity matched that required for the methyl group in the lituarines.

Further elaboration of the conjugate adducts allowed introduction of the C(18)–C(19) bond bysilyl enol ether addition to an intermediate spiroacetal oxonium ion, an unprecedented transformation with wide scope for application in natural product synthesis (Box 3).

Collectively, these results constitute a powerful general approach to a variety of natural products based on substituted spiroacetal structures and we have completed a number of these targets and are actively pursuing others.

As specialists in synthetic methodology and natural product synthesis, we are engaged in searching on a daily basis for literature precedent for specific transformations and the reaction datasets hosted by the Chemical Database Service are indispensible. Although these datasets are not comprehensive, the flexibility available in setting up reaction searches is unparalleled which results in the highest quality hits. We greatly value this service and we very much hope that it will remain accessible to the academic community.

1, lituarine A; R¹ = R² = H
2, lituarine B; R¹ = OAc, R² = OH
3, lituarine C; R¹ = R² = OH

Box 1 – the lituarines

(i) 77%

(ii) 57%

(i) MCPBA; TPAP-NMO;
(ii) (MeS)₃CLi; Raney Ni

Box 2 – spirocyclisation and conjugate addition

(i) DIBAL; Ac₂O

(ii) R'C(OTMS)=CH₂, SnBr₄; 53%

Box 3 – Oxonium ion formation and stereoselctive trapping
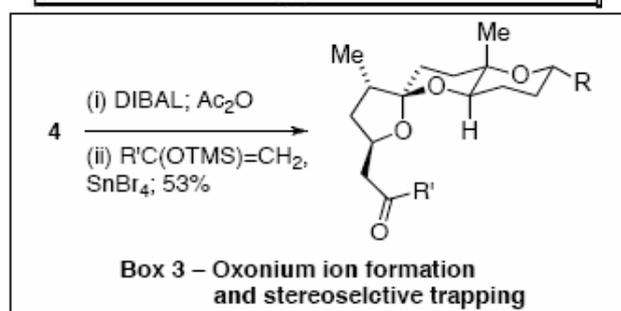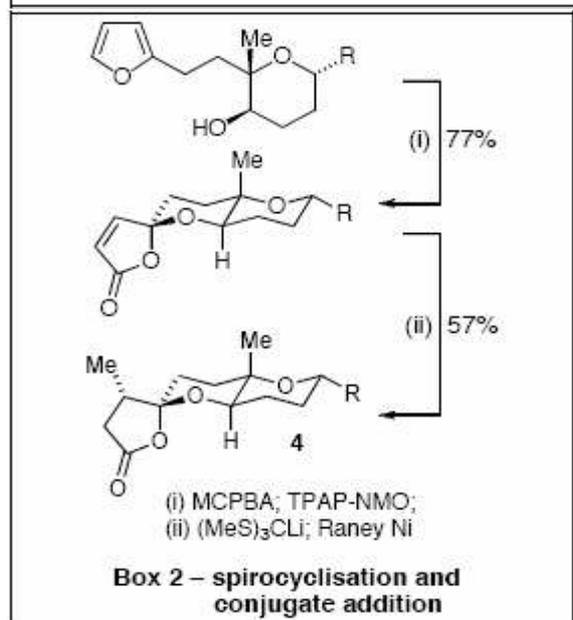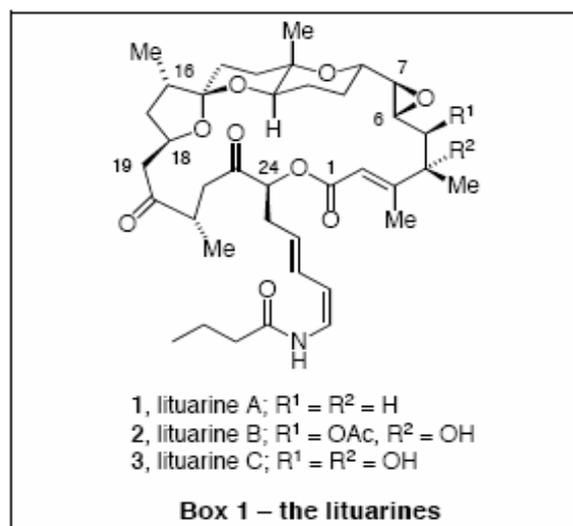
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Organometallic Chemistry: Synthesis, Structure and Reactivity.
Jonathan P Rourke, University of Warwick.

The primary aim of our research is the synthesis of novel organometallic species with a view to understanding their reactivity in a number of subsequent reactions. To this end, we normally require complete characterisation (including an Xray structure) of our materials before we start studying reactivity. Thus the CDS at Daresbury has proved to be an invaluable resource. We make particular use of the CCDC, which we access via Conquest, to compare our solid-state structures with those that have already been published. Exporting bond lengths and angles that we constrained in our searches into Vista allows for an easy statistical analysis of structural data. Other valuable resources provided by the CDS include the Available Chemicals Database (really helps with synthetic shortcuts) and the Reaction Web/ISIS database to determine reaction routes.
Examples are given below:

1) Carbene complexes of platinum.

When we attempted the cyclometallation of certain pyridines with platinum we actually synthesised some unusual carbene structures where comparison of bond lengths in the solid state was crucial in determining the carbene like nature of the complex.[1]

$R = C_7H_{15}$
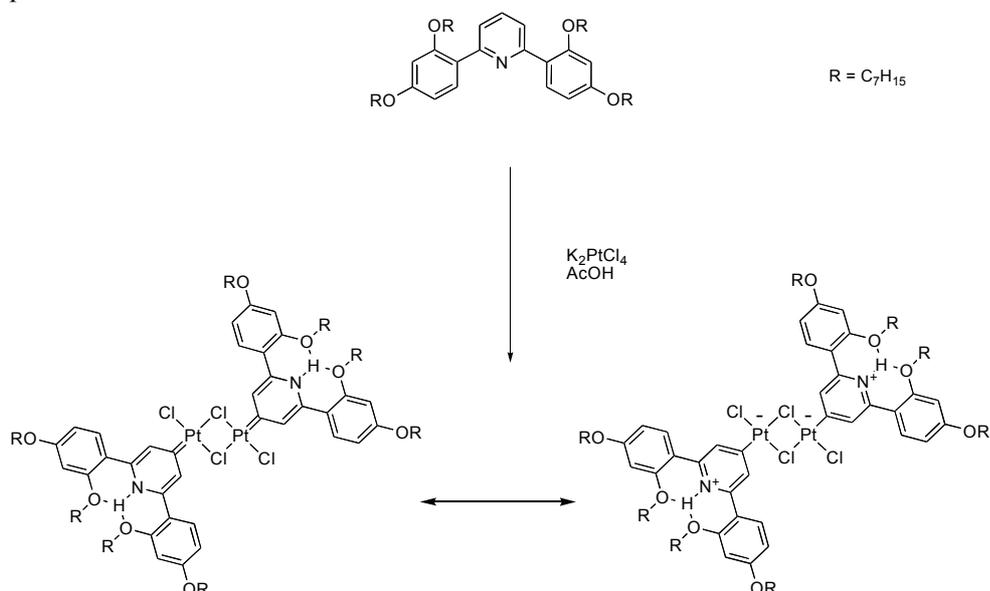
Later work with these complexes, showed how ^{13}C NMR could be used as a tool for determining whether molecules existed in carbene or zwitterion form.[2]

2) C-H Activation induced by water.

In the course of studying cyclometallation reactions we were able to identify a very high yielding route to CNC tridentate complexes of diphenyl pyridines,[3] and subsequently show how it is the elimination of HCl that drives the reaction: an elimination that can be induced with the simple addition of water.[4]


3
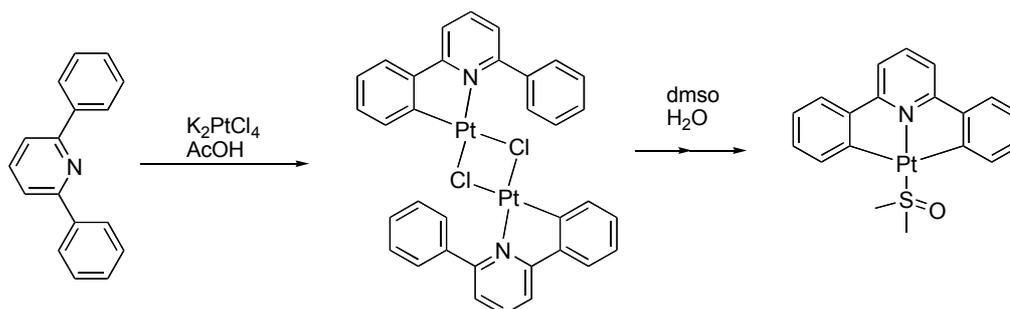
3) Pt-Pt interactions in the solid state.

During the study of a number of different complexes, we have often observed extended three-dimensional structures throughout the solid state of our complexes. The example illustrated below is an example of a dimeric structure held together by Pt-Pt interactions.[5]
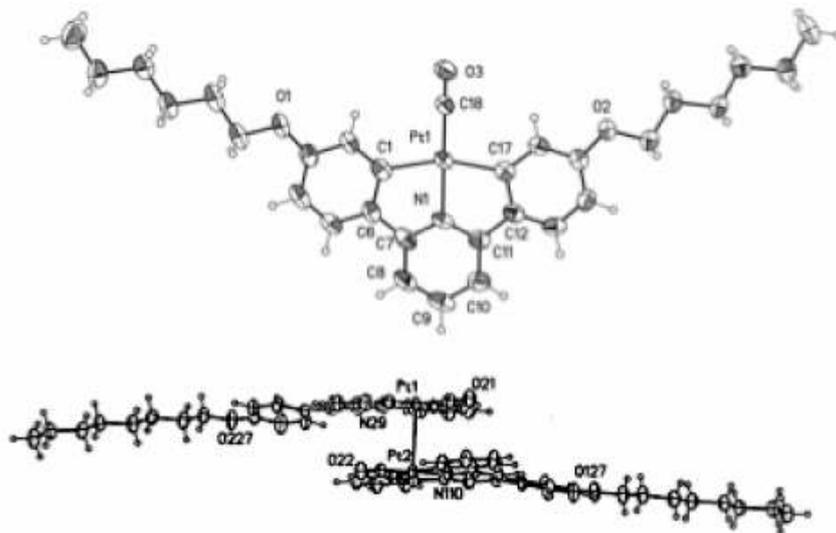
4) Cyclometallated nitrogen heterocycles.

We have also sought to study how the three dimensional structure of molecules affect their physical properties. To this end we investigated the synthetic chemistry that leads to a co-operative double C-H activation of pyridazines,[6] and then investigated the liquid crystalline properties of the molecules.[7, 8]
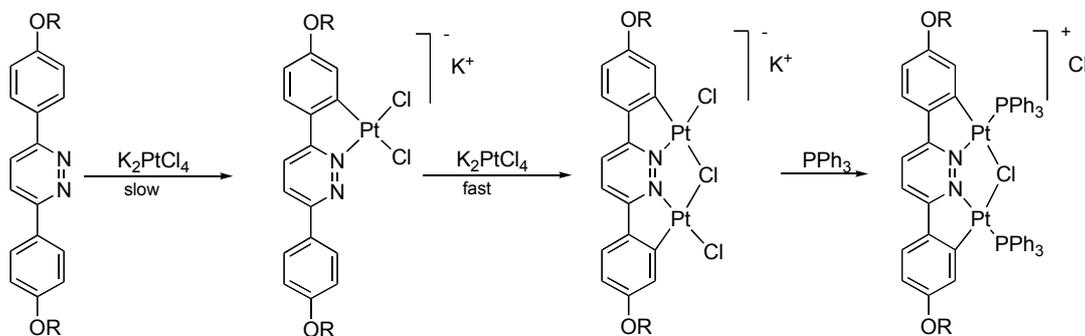
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Motorways and the Mineralogy of Chromium Contaminated Land

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Environmental mineralogy [1, 2] has an important role to play in understanding the solid state speciation and geochemical behaviour of toxic metals in contaminated soils. For example, the implementation of the contaminated land provisions of Part IIA of the UK Environment act [3] now requires an approach based on risk assessment, where it is clear that total

Figure 1. Sampling COPR at Dukes Road, Glasgow.

metal determinations by chemical analysis alone are no longer sufficient. Our group (see references), initially funded under the NERC URGENT program, has applied a variety of mineralogical methods to chromate ore processing residue (COPR) which contaminates land around Glasgow, Scotland (Figure 1).

  These methods are underpinned by use of the Chemical Database Service (CDS) databases in some very simple but important ways. These include calculation of X-ray powder diffraction (XRPD) patterns to aid in phase identification, as a source of structure details for starting models for Rietveld

refinement of XRPD patterns - and/or structure representation to illustrate mineralogical concepts of relevance to metal speciation, as well as a source of other basic crystallographic data.

Approximately 2.5 million tonnes of COPR, produced by a 'high lime process' have been used as fill at a network of sites in and around Glasgow [4]. The COPR is derived from a former chromium works at Rutherglen, which operated between 1830 and 1968. Large areas are heavily contaminated with alkaline (up to pH 12.3) waste, often of granular appearance (Figure 2) containing Cr(VI), a known carcinogen of significant mobility.
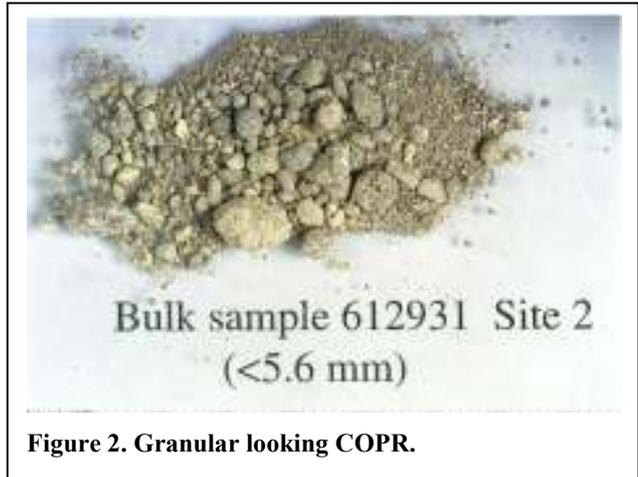
Figure 2. Granular looking COPR.

Using a combination of quantitative mineralogical analysis of XRPD data (Figure 3) by the Rietveld method and phase compositions obtained by electron microprobe analysis, it was shown previously (5) that chromium was present in at least five distinct phases, namely chromite, brownmillerite, etringite, hydrocalumite and hydrogarnet. Along with other crystalline phases in COPR these were rationalised into three categories - 1) unreacted chromite ore, -2) high temperature phases mainly brownmillerite and periclase produced during the high lime roasting process, and -3) low temperature phases, including brucite, calcite, aragonite, ettringite, hydrocalumite and hydrogarnet all produced by hydration and carbonation among other reactions of the COPR over the protracted period that it has been exposed to ambient conditions and to leaching at the disposal sites.

Figure 3. XRPD pattern of COPR with phase identification.
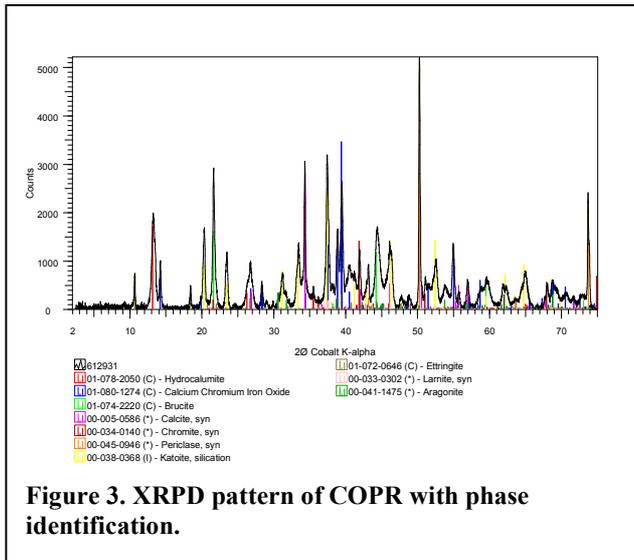
Unreacted chromite accounted for an average of about 6% by weight of COPR and along with brownmillerite which averaged around 14 wt. %, it was demonstrated [5] that these two phases host virtually all the of Cr (III) found in COPR. Hydrocalumite belongs to a group of phases known in the cement literature as AFm.


Figure 4. Back Scattered Electron image of hydrocalumite type phase (platy hexagonal habit) in COPR
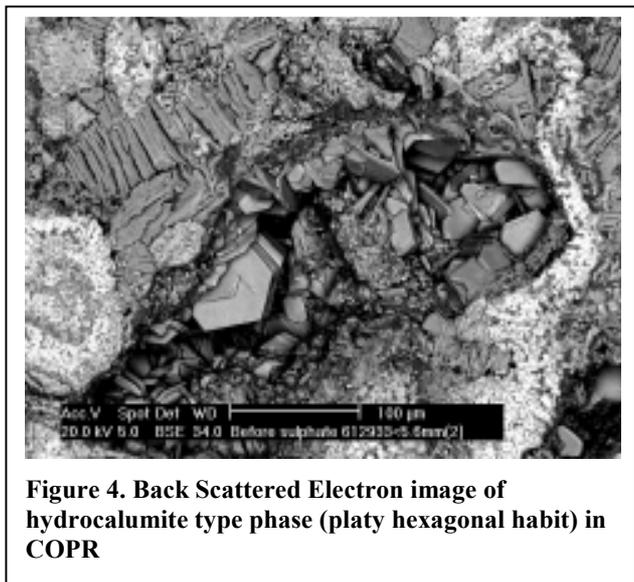
The basic structure of these phases consists of layers of composition $[Ca_2(Al,Fe)(OH)_6 \bullet 2H_2O]+$ the positive charge from which is balanced by interlayer anions; and they may occur in a range of hydration states. In COPR it was found that hydrocalumite is an important host for approximately half of its Cr(VI) content [5]; held in an exchangeable anionic form [6]. The most abundant crystalline phase in the COPR from Glasgow, however, is hydrogarnet (20-30 wt. %)

and it was speculated [5] that most of the remaining Cr(VI) in COPR was structurally incorporated in hydrogarnet. The garnet structure consists of alternating corner sharing tetrahedra and octahedra. In classic rock-forming garnets the tetrahedra are silica $SiO_4{}^{4-}$ tetrahedra, whereas in hydrogarnet the tetrahedra are composed of four hydroxyls, $H_4O_4{}^{-4}$,

Figure 5. Hydrogarnet structure, illustrating proposed substitution of chromate (yellow) for hydroxyl tetrahedra.
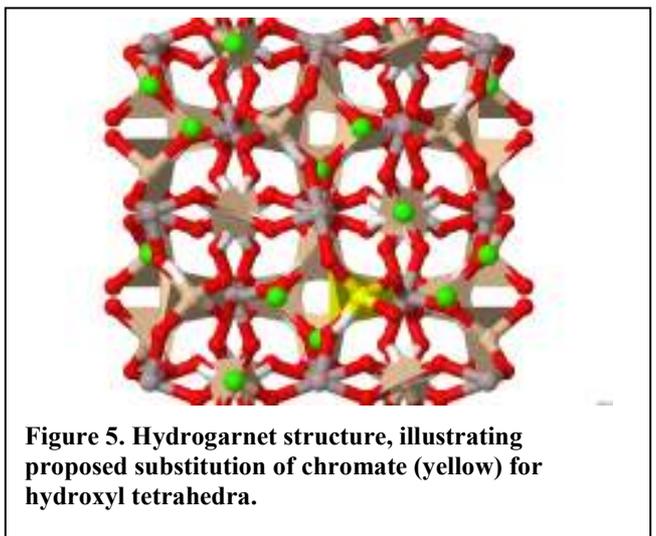
although solid solutions with some silica tetrahedra are common (Figure 5). Octahedral sites in garnets are occupied by trivalent cations such as aluminum in 6-fold coordination. The cavities formed between the corner-sharing tetrahedra and octahedra have the shape of distorted cubes and contain divalent cations, such as calcium in 8-fold coordination. As an example, the end member hydrogarnet, known by its mineralogical name of katoite, has an ideal formula unit of $Ca_3Al_2(H_4O_4)_3$ and there are eight such formula units per unit cell [7]. The capacity of hydrogarnet to host Cr(VI) by substitution of $CrO_4{}^{-2}$ tetrahedra was subsequently confirmed by a combination of diffraction and spectroscopic methods [8]; an investigation supported throughout by access to the CDS. Although hydrogarnet is the most stable calcium aluminate phase at the high pH of COPR, it is likely to dissolve and release chromium if pH is lowered. The understanding gained from these environmental mineralogy investigations underpins attempts to find strategies and technologies for the remediation of these contaminated sites [9,10]. Many of these sites lie along the proposed course of the M74 motorway extension through Glasgow, which it is planned to build by 2010, at an estimated cost of £500 million [11], and effective methods to deal with chromium contamination will be needed.

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