



# A high-speed train trip through 'Alice's Wonderland' of Small Molecule Crystallography

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With Lewis Carroll's *'Alice in Wonderland'* as backdrop,<sup>1</sup> this presentation will give a quick and brief (and unavoidably biased and thus selective, based on presenter preferences!) account of small molecule crystallography from the personal view of the author.

It is however noted that at best, attempting to describe just some highlights and not in even in detail, requires a typical 'high-speed' train trip through this fascinating 'world'.

Currently, small molecule chemical crystallography is often considered as trivial due to the phenomenal developments in hardware, computing power, and applications in, for example, molecular biology. However, since many dynamic processes (still) occur at the molecular level and at **metal** cores, fundamental understanding of structural behavior, and the associated influence on (kinetic) properties are of continued and prime importance. This is emphasized in conjunction with an *integrated* mechanistic approach to evaluate bonding and structures utilizing spectroscopic techniques and reaction kinetics, to counteract trivialized conclusions based on thermodynamic observations alone.<sup>2</sup> These range from, but are not limited to, aspects such as stability, redox properties, acid base behaviour, ease of synthesis and many more, to enable better understanding and more accurate predicting their behaviour, and must be considered.<sup>2,8</sup>

Small molecule crystallography, or rather, crystallography in general, came a long way since Bragg's pioneering work which followed from Von Laue's initial experiments<sup>3</sup>, yielding the (correct) structure of sodium chloride.<sup>4</sup>

Clearly, nobody could foresee a century ago what impact crystallography would make in a global context. Apart from all achievements, including a multitude of Nobel Prize winners, just consider what has happened in the world during IYCr2014!<sup>5</sup>

There is some similarity in the development of crystallography and *Alice's* journey through *Wonderland*, as summarized by her following classic conversation *en route*:<sup>1</sup>

"One day Alice came to a fork in the road and saw a Cheshire cat in a tree.

Alice: 'Would you tell me, please, which way I ought to go from here?'

The Cheshire Cat: 'That depends a good deal on where you want to get to.'

Alice: 'I don't much care where.'

The Cheshire Cat: 'Then it doesn't much matter which way you go.'

Alice: '...So long as I get somewhere.'

The Cheshire Cat: 'Oh, you're sure to do that, if only you walk long enough.' "

As mentioned above, the exponential progress in computing power and technique development had a significant impact on crystallography; not the least manifested in the

number of structures in the respective databases<sup>6</sup>, allowing data mining to be utilized as part of typical statistical analyses of structures.

A question which however begs an answer is: *What is 'small molecule' crystallography?*

That which has been considered a 'small molecule' some 30-40 years ago, and which took weeks if not months to complete, even under favourable data collection conditions, is now trivial. In fact, high throughput even ensured that biological crystallography and subsequent large structures are currently solved in extremely short times.

Photocrystallography and the hardware associated with large facilities such as the ESRF enables multiple large datasets (approaching teraBytes) to be collected within days, defining the dynamics in solid state materials on the few nanosecond levels!

Thus, depending on the mode of interest, and the particular field, 'small molecules' can mean different things to different people.

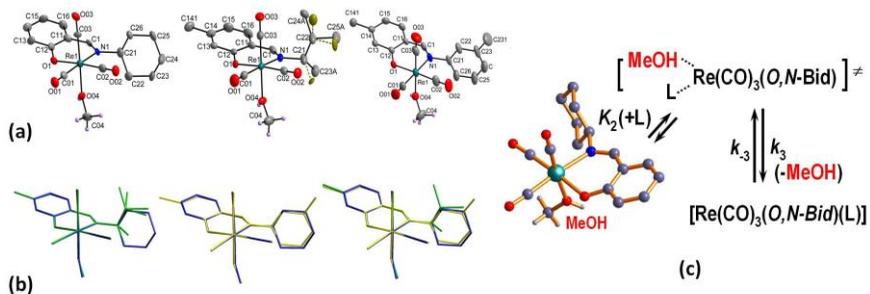
Regardless; this presentation does not aim to rigidly define 'small molecule' crystallography. It rather prefers to highlight selective studies, projects, research foci and the like, which is invaluablely supplemented and strengthened by appropriate structure elucidation.

It also aims to give the listener/ reader just a small (biased) perspective on the fascinating world of crystallography as experienced by the author.

As examples, structures and dynamics in small coordination compounds utilised in a number of research projects will be highlighted. Broad examples are briefly expanded on below but will be presented in detail in the lecture. These selective examples from the presenter's laboratory will be described wherein (small molecule) crystallography has been impossible to do without.

A first example covers model radiopharmaceuticals of the 4<sup>th</sup> and 5<sup>th</sup> row elements of the manganese triad, and in particular the <sup>99m</sup>Tc, <sup>188</sup>Re, <sup>186</sup>Re isotopes, which find widespread application in nuclear medicine.<sup>7,8</sup> In particular, the *fac*-[M<sup>I</sup>(CO)<sub>3</sub>]<sup>+</sup> core (M = <sup>99m</sup>Tc, <sup>99</sup>Tc, <sup>188</sup>Re, <sup>186</sup>Re), which is of continued interest due to its potential in biomedical, photocatalytic and chiral catalytic applications, is presented. A basic characteristic of this versatile synthon is its low-valent, low-spin, kinetically 'inert' organometallic core and therefore the high potential *in vivo* stability. It coordinates many types of ligands and it is possible to design bifunctional chelator ligand systems which determine the hydro-, lipophilic and kinetic properties of the organometallic molecular material.

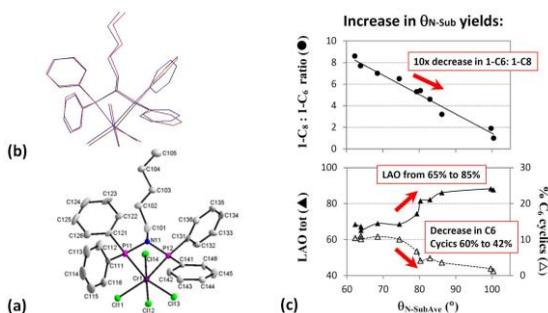
Utilising small molecule crystallography for characterization of reactants and products, and also geometric parameters indicative of bond strengths, a complete picture of the total reaction scheme could be built over a period of time; as illustrated in Fig. 1.<sup>9</sup>



**Figure 1:** (a) Similarity in three Schiff base Re(I) complexes; (b) underlying the good agreement in overlaid illustrations; (c) leading to the final simple reaction scheme.

The above arguments are valid for many other processes and complexes utilised for example in homogeneous catalysis, separation chemistry, bio-mimetics, environmental, bio-inorganic and a large number of other (chemistry, physics, geology etc.) sub-disciplines.<sup>10</sup>

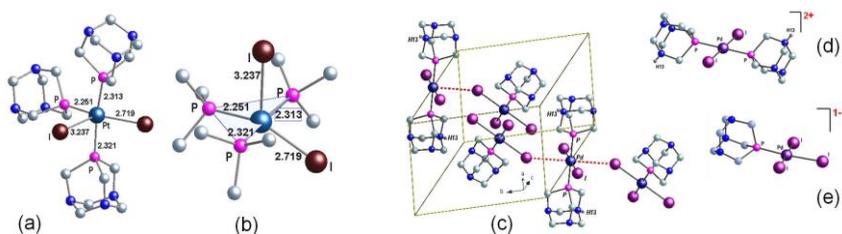
In an additional example the indispensable, in fact probably irreplaceable, contribution of small molecule crystallography, together with structural optimization via theoretical calculations, is illustrated. It enabled quantification of the interplay between the structural properties and product yields in the (selective) catalytic oligomerization of ethene.<sup>11</sup>



**Figure 2:** (a) Model chromium catalyst complexes containing the PNP type ligands with N-substituents (varying steric demand of R) for ethene oligomerization; (b) agreement with DFT optimizations illustrated; (c) providing significant tunability of products.

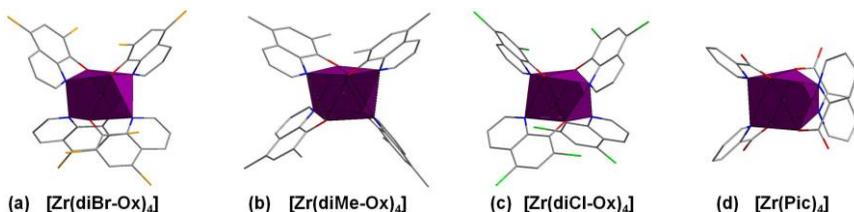
In a third example, the catalyst precursor composition in a platinum group metals (PGMs) pair is illustrated when a small, water soluble tertiary phosphine ligand (PTA) based on the adamantane structure is utilised. It clearly formed a highly unusual 5-coordinate Pt(II) complex.<sup>12</sup> Moreover, when replacing Pt with Pd, different species, both cationic and anionic are formed and crystallises together in the unit cell, augmented by the selective

protonation of the PTA. The reactivity in solution and the dynamics make it impossible to characterise these species without small molecule crystallography.



**Figure 3:** Small molecule crystallography on PTA complexes, elucidating structures of products: (a) and (b): 5-coordinate Pt(II). However, with Pd(II), mixed species in (c) the same unit cell both (d) cationic also showing double protonation; and (e) anionic.

As a fourth example is illustrated a range of tetrakis oximate complexes of Zr(IV), potentially important in extraction and separation of the zirconium from the zircon ore, critically important in the nuclear industry. However, the photochemical activation via these ligand systems may also be studied for other metals. In Fig. 4 the subtle differences in the coordination polyhedron are illustrated, clearly not displaying cubic geometry; rather square anti-prismatic, even edging to dodecahedral. Yet again, it is obtained via small molecule crystallography.



**Figure 4:** Subtle variation in the coordination polyhedron at the 8-coordinate Zr(IV) centre by periphery group variation in oxime-type ligands and analogs.

Additional examples from the author's laboratory will be very briefly introduced, time allowing. Details are described in literature.<sup>13-21</sup>

An important message from this presentation is the fact that although small molecule crystallography, and crystallography in general, allow 'eyes' to see the structures of compounds, it should *never* be seen in isolation.

Care should also be taken *not* to overinterpret, nor make conclusions, and in particular predictions, *unless* processes are (properly) understood. Thus, different additional overarching aspects in many systems, coordination compounds and other chemical, physical, and the like, are imperative for successful application, *i.e.*, via a typical *Applied Systems Analysis* approach, such as promoted by IIASA.<sup>22</sup>

The above underlines some aspects of small molecule coordination compounds, and illustrates the central importance of both *structure* and *kinetics* in different processes/factors which significantly influence the course of the particular reaction.

Either way, it is hoped that the reader/ listener, will equally experience a similar adventurous trip, which 'small molecule' crystallography has enabled the author to have.

A truly fascinating ride through the *Wonder Land*. Fortunately, there is no need wake up, as in *Alice's* case, since the wonders of this beautiful Science are quite *real*.<sup>23</sup>

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