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Representation and use of chemistry in the global electronic age†‡

Peter Murray-Rust,[a] Henry S. Rzepa,[b] Simon. M. Tyrrell[a] and Yong Zhang[a]
[a] *Unilever Centre for Molecular Informatics, Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge, CB2 1EW*
[b] *Department of Chemistry, Imperial College, London, SW7 2AY, England*

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We present an overview of the current state of public semantic chemistry and propose new approaches at a strategic and a detailed level. We show by example how a model for a Chemical Semantic Web can be constructed using machine-processed data and information from journal articles.

Introduction

The last ten years of the Internet as a medium for information exchange have created huge expectations in the general public. People look to the Web as their first (and often only) source of information and increasingly expect it to be delivered automatically. Novel forms abound, such as wireless technology, smart clothes and personal (music) devices. Many communities (media, finance, music, government) are making rapid advances in conveying instant services or information. One coherent vision of this new environment is epitomised by Berners-Lee's "Semantic Web" (SW)[1] where knowledge is instantly available and computers as well as humans can reason from it to make decisions.

The ethos of the Semantic Web is well summed up by two quotations from J. D. Bernal, made almost 40 years ago:[2]

"However large an array of facts, however rapidly they accumulate, it is possible to keep them in order and to extract from time to time digests containing the most generally significant information, while indicating how to find those items of specialized interest. To do so, however, requires the will and the means"

"[we need to] get the best information in the minimum quantity in the shortest time, from the people who are producing the information to the people who want it, **whether they know they want it or not**" (our emphasis).

Meanwhile the power of computation (speed, memory, bandwidth and software) continues to increase at Moore's-law speed. An impressive chemical use of the Internet and high-throughput computing was demonstrated by Richards and co-workers.[3] To quote from their site:

"Anyone, anywhere with access to a personal computer, could help find a cure for cancer by giving "screensaver time" from their computers to the world's largest ever computational project, which will screen 3.5 billion molecules for cancer-fighting potential […] over 2.6 million computers have joined the project with over 320,000 years of CPU power used…Through a process called "virtual screening", special analysis software will identify molecules that interact with these proteins…The process is similar to finding the right key to open a special lock—by looking at millions upon millions of molecular keys".

At a recent meeting,[4] Richards in his presentation of this project made a request to the chemical community to collaborate in utilising this immense computer power, which "for the first time in my scientific career is more than we alone can make use of." This particular project illustrates the concept of the Grid, a linking of vast computational power for immediate use. In science this is anticipated by the construction of the Global Grid (and nationally in the UK, the eScience project) where instant access to trusted information and services is possible. The combination of the Grid and the Semantic Web is seen as culminating in a Semantic Grid, in which vast power and knowledge are combined.

Much classical chemical knowledge has in turn been built on what is described as "data mining". For example, all chemists are familiar with the concepts introduced by the likes of Mendeleev, Trouton, Barton (conformational analysis), Woodward (pericyclic reactions) *etc.* At the time of these discoveries, the scientific literature was sufficiently small and these concepts were sufficiently focused that any necessary supporting data could be feasibly extracted from the literature by human labour alone. In 1973 Burgi and Dunitz[5] showed that the measured geometries of a range of similar compounds could map a reaction pathway, such as N···C=O addition. With the technology and access to data available at the time, it could typically take several months to extract sufficient information for a single system. In 1976 this process was revolutionised by introduction of crystallographic data files, which made coordinates available to the scientific community. This led to the possibility of automatically computing and mining many hundreds of geometries in a few minutes and which speeded such studies by several orders of magnitude. Using this technology it proved possible to show[6] that the intermolecular interactions involving O···I–C substructures were directional; this relied on computation of many crystal lattices and searching the substructures. There are now around 1000 articles describing the use of the crystallographic data file for primary scientific research.

One further example serves to illustrate how the availability of appropriate data has influenced the development of new techniques. Thus parametric semi-empirical quantum mechanical methods rely on a well-distributed set of molecules and data. The development of early semi-empirical MO parametrisations in the 1970s was based on (manual and laborious)[7] acquisition of data for at most 10–20 molecules per element parametrised. Nowadays[8] such parametrisations are conducted using datasets for 1500 or more molecules, and the bottleneck is now more likely to be the checking for self consistency and validity of the data used.

However, these various projects are not general or easily copied. The Cancer project[4] for example had to provide most of its infrastructure and is based on uniformity of data (proteins/ligands) and (proprietary) software. The chemical community needs to be able to operate on a wide range of problems without having to engineer each of them separately; in effect there is a need to incorporate semantics and ontologies into a generic set of tools for this purpose. Here we suggest that the Semantic Web can provide such an infrastructure.

The Chemical Semantic Web: characteristics

The domain-independent infrastructure of the Semantic Web is becoming omnipresent through *de facto* standards (mainly

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from W3C[9]) such as XML (eXtensible Markup language), RDF (Resource Description Framework) for relationships, RSS (Rich-Site Summary) and Dublin Core for metadata-based newsfeeds, OWL for ontologies and BPEL4WS for workflow and web services. It will shortly be possible to request a machine to discover existing knowledge or services and make appropriate transactions to obtain these, including security, trust, and metadata in a robust and efficient fashion. Its adoption will depend on "what there is to discover" and how valuable it is. We have variously argued[10] that chemistry is an almost ideal discipline for transition to such a next generation of informatics infrastructure; a Chemical Semantic Web. This in turn would be supported by domain-specific *de facto* standards such as the CML (Chemical Markup Language) family.[11,12]

In this article we argue that primary publications in this and similar journals should form a major substrate for such a Chemical Semantic Web. When rendered machine-understandable, in the form of what we have termed datuments,[13] journals will form the future knowledge base for the discipline. For simplicity we shall restrict ourselves in this article to small organic molecules, their properties and reactions. However the philosophy extends directly to computational, structural, thermo-, analytical and much inorganic and physical chemistry. The technology exists; it is up to the community to support the vision.

The Semantic Web and the emergence of Grid computing involve a qualitative change not only in the way that we manage information but in the way that science is carried out. We see computers becoming an integral part of the scientific process in many ways, in helping to:

Establish data quality. Scientific information can be corrupted during the publication process. Thus Stewart[8] has shown that in a comparison of calculated and observed thermodynamic data at NIST, many of the discrepancies were due to publication or transcription errors. Using the OSCAR publication checker[14] (which analyses data for self-consistency and acceptable ranges) it has been shown that a very high proportion of articles in synthetic organic chemistry contain at least one dubious data value. We note however that much of the (explicit or implicit) data in the current publication processes are created and maintained on or by machines. If the protocols are well agreed, then the data are implicitly machine-understandable. When machine-referees are used for data they have made valuable contributions. This is particularly true in areas such as crystallography, where crystallographic structures are routinely reviewed by programs which encapsulate more expertise than most humans, and *e.g.* thermophysical property databases[15] where management of data quality can be enforced. The biosciences are also used to running automatic processes over data of imperfect quality. For example many of the ligands in the Protein DataBank have fuzzy structures (imperfect coordinates, unknown charge, unlocated hydrogen atoms, *etc.*) Yet it is felt highly valuable to create resources derived from these such as PDBSum, HIC-UP, LigPlot and many others. These authors certainly wish access to as much data as possible and will use their judgments and robots to decide on how to process it.

Allow validation. Much chemical information is imprecisely defined. Scientific units are often omitted (*e.g.* in computational chemistry log files) and information can be interpreted differently by different readers. XML provides a basis for *validating* information. An XMLSchema[12] can require conformance to a given vocabulary, document structure, datatypes and data values and associated limits (uncertainties). Thus a valid CML[11,12] document must:

- Use elementTypes from a given enumeration (*e.g.* the IUPAC periodic table).
- Require hydrogen counts to be explicit and to be non-negative integers.
- Require that any molecule with bonds also includes atoms.

Any schema-aware XML tool can carry out this validation; a chemical application is not required. Even greater power (*e.g.* valence constraint) can be provided by ontologically-aware tools such as RDF and OWL. We are developing tools[12] whereby standard XML technology should be able to verify that any piece of chemical information was precise and made "basic chemical sense".

Enable re-usability. A very high proportion of chemistry is potentially re-usable for scientific discovery, in several ways:

- Data can be combined with similar measurements on related systems (*e.g.* molecular geometries for different compounds can be compared).
- Multiple quantities (structure, properties, reactivity) relating to the same system can be aggregated.
- Missing or dubious properties can be calculated.
- Quantities can be recalculated as improved methods become available.
- Comparisons (*e.g.* QSAR) can be repeated as new classificatory methods become available.

Ensure comprehensiveness. Most chemical data is never satisfactorily published due to the impedance of conventional processes. We estimate that less than a fifth of primary data ever has the possibility of being re-used.

Add metadata. Data can now carry metadata (information about data). In chemistry the most important types of metadata include:

- Identification of provenance, where the data came from, including an audit trail of past processes. Thus a molecular structure might have been built by a heuristics-based program, subjected to conformational analysis using specified methods, and re-optimised using declared procedures. All this metadata can and now should accompany published information.
- Discovery. Traditional methods have concentrated on keywords and classification for information retrieval. The success of full-content based searched (*e.g.* Google) highlight the possibility that computer-based methods of creating and storing discovery metadata will become common.
- Validation. These metadata allow the data to be evaluated as "fit for purpose". A common requirement is that error limits or uncertainty estimates are given. A good example is the formalisation of such quantities (using XML-dictionaries) for thermophysical and thermochemical property data.[16]
- Semantic and ontological. Most data require additional instructions and annotation to describe them precisely. A "bond order" depends on the convention used and the author should supply links to the ontology used to describe the data.

In many cases, the most viable way of enforcing complete and unambiguous metadata reporting would be the development by the major journals of a software infrastructure guiding users through the process of data submission and providing consistency tools between various related data types. In some fields such as chemical thermodynamics, this is already being done.[17]

Enable scale. Computers can hold every piece of significant scientific data. The scales of data acquisition and processing in particle physics, biosciences, medical and geoimaging are far greater than in most chemical operations. With a generous assumption of 2 million public chemical entities/year, and 100 Mbyte of data/metadata for each (measurements, calculations, analytical, safety) requires 0.2 petabyte/year. The Large Hadron Collider (in high energy physics) is already planning for 50 times this amount of data per year. The chemical community already has enough storage to hold the sum of chemical knowledge on its personal computers. Paradoxically, that is where most of it will remain until it decays, since in many ways it is not retrievable from this final resting place.

Provide power. A quantum mechanical calculation for a typical organic molecule (say at the B3LYP/631-G(d) self-consistent-field molecular orbital level) can be done in a day on a single processor. Complete geometry optimisation for all published compounds could be done on chemists' workstations while they sleep. It would be technically possible for any report of a new compound to be accompanied by a re-usable calculation of its molecular properties.

Allow distribution, immediacy and permanency. Retrieval of distributed information is rapid and reliable and the next generation of Grid systems will provide "instant availability" of scientific information. We have described a protocol based on RSS (Rich-Site Summary) and XML and known as CMLRSS[18] whereby the results of *e.g.* chemical computations, crystal structure determinations, database additions or merely tables of contents from journals can be made available within minutes either to a human (for rapid scanning) or to another machine for *e.g.* aggregation. High throughput information from *e.g.* 1000 compounds a day, each with 1 Mbyte of output can be "published" to digital libraries and other data portals, where the problems of archiving and curation can be addressed better than ourselves.

Automation. Humans can only respond to the exponential demand for and growth of data by automating their information processes. Nevertheless, high-throughput calculations on *e.g.* 200,000 molecules with an "error rate" of 0.1% still means 200 problems that a human must investigate. The protocols must therefore be completely automatic, allowing for and reacting to possible failures.

Convenience and expertise. The programs used to compute molecular properties almost invariably have manuals of several hundred pages, with an almost infinite combination of possible program options. When developing our automatic protocol (below) one of us (PM-R) made "elementary" mistakes (*e.g.* not requesting the program to use RAM instead of disk, and using an unnecessarily expensive and outdated method). We therefore asked the priesthood of computational chemistry (*e.g.* HSR) to devise a protocol which was automatic and more believable by the community. This process of developing and formalising the protocols allows for re-use by subsequent novices, hence providing for more (self)consistent data where outliers and trends can be more easily (and automatically) identified.

The Chemical Semantic Web: requirements

In this article we encourage chemists to develop a shared vision whereby information is communal and accessible. It is important to realise that *all information* is potentially valuable and that the producers may not realise at the time what their descendants will require. We argue that the technologies and protocols presented here can be implemented at marginal cost within the publication process, if the community desires. This approach is not novel in other domains.

It is a truism that the Web develops in unpredictable ways, but we believe that the success of Google and related search engines suggest that client-based discovery is likely to be a key component. In principle a "chemical Google" could be extremely effective and completely change the basis of chemical information management; in practice there are substantial cultural and technical barriers. We explore these in this article and urge all chemists (authors, editors, readers, examiners, funders, businesses and agencies) to consider how a change in practice could lead to much greater use and re-use of chemical information.

Chemical information as based on molecules and compounds is the cornerstone of the Chemical Semantic Web. Friedlich Beilstein[19] created a revolution in scientific informatics by introducing the data model of Compound-Properties-Source as far back as the 1860s! Effectively this concept still remains relevant today and is the basis of a multimillion informatics market, with near comprehensive abstraction of all new compounds and their properties from the primary literature. Whilst various modern aspects of chemistry extend this simple concept to the limit, especially those where the bonding is debatable or the chemistry is novel, "most" organic chemical structures are very well defined. For example it is possible to specify these in patents and have rigorous procedures for determining equivalences. The crystalline state is also well characterised for many applications and the International Unions (IUPAC, IUPAB and IUCr) have important ongoing projects to systematise chemical representation. XML[9] has become recognised as an essential specification for markup languages. Chemical Markup Language (CML)[11,12] itself was specifically developed as an XML-conforming language to support the communality of agreement within the community and to allow divergence of representation when it is essential. In broad terms, the CML design allows support for molecules and their properties and is becoming adopted by a wide range of organisations (patents, publishers, government agencies and software manufacturers). The fundamental architecture of CML contains no molecular concepts that are not in current use, and we showed some time ago that it is possible to publish complete journal articles using various XML components such as CML.[20] Other examples of XML-languages being used in this manner include MathML and ThermoML,[21] the latter developed by NIST (National Institutes of Standards and Technology) as part of their role in measuring and aggregating data for compounds. Most information however is still micropublished and has to be tediously (and expensively) extracted by humans. In contrast, the biosciences have developed an open model where much publication is directly to the public electronic domain, there being no distinction between the data in a published article and its representation in an international database such as SwissProt or the Protein Databank. Indeed the latter may be of more value, as the data can be annotated at intervals, whilst the original publication is "inviolate" but often dated.

Open Access initiatives

The current generation of Semantic Web tools require access to information and services with effectively no barrier. If a machine wishes to retrieve a unit of information, it cannot at present log in to a protected web site (even without cost), make (micro) payments, or verify that it is not violating copyright or other intellectual property rights. Semantic Web applications can therefore only currently be built upon publicly accessible Web resources. It seems appropriate therefore to raise at this stage the issue of what is termed Open Access (OA), purely here in the context of the Chemical Semantic Web. The OA model is epitomised by the *Budapest Open Access Initiative*,[22] which includes the following definitions:

"By "open access" to this literature, we mean its free availability on the public internet, permitting any users to read, download, copy, distribute, print, search, or link to the full texts of these articles, crawl them for indexing, pass them as data to software, or use them for any other lawful purpose, without financial, legal, or technical barriers other than those inseparable from gaining access to the internet itself. The only constraint on reproduction and distribution, and the only role for copyright in this domain, should be to give authors control over the integrity of their work and the right to be properly acknowledged and cited".

The OA model is supported by funders such as the Wellcome Trust,[23] which:

"[…] therefore supports open and unrestricted access to the published output of research, including the open access model as a fundamental part of its charitable mission and a public benefit to be encouraged wherever possible."

and organisations such as NIST, who are promoting OA models of efficient data re-use (using XML technology) between themselves, major journals and industry.[24]

At present the primary chemical literature is not openly accessible on the Internet. There are currently 33 chemistry journals cited by the Directory of Open Access Journals[25] as Open Access, and none of them are currently major publishers (*e.g.* from G8 nations). In a dissenting opinion, the American Chemical Society has argued[26] that:

"The open-access movement's demand that an entirely new and unproven model for STM publishing be adopted is not in the best interests of science."

Many chemistry publishers also currently prohibit the public self-archiving[27] of "fulltext", preprints or postprints. Very recently however, the Royal Society of Chemistry (publisher of this journal) announced[28] an official "Green" policy on author self-archiving of articles published in RSC journals. In this spirit, this article has itself been self-archived on the authors' own institutional archives.[29]

We restrict ourselves here to a plea that all primary chemical *data* be made openly available at time of publication. We emphasize "data" since "facts" are not copyrightable under the Berne convention, and primary publishers have little incentive or success in publishing the complete data associated with an article. In fact the current publication process is a dis-incentive to publishing experimental data. It is also notable that most supplemental data is not in re-usable form (often being found as Word or PDF files or as scanned images). In the case of crystallographic data it is often only available from the (non-open) Cambridge Crystallographic Data Centre. This results in further restrictions on access and re-use.

We therefore argue for publication *by the author* of data under Open Access protocols to a public or institutional repository. We appreciate that this change will take time, and involves investment in technology. It is, however, not novel, being a requirement in the biosciences for protein and nucleic acid sequences and structures and is common in many other areas. Whatever policy is adopted by publishers, it is essential that it is made clear to both human and robot readers and re-users what may be done with published articles. We therefore list below a series of issues for resolution and clarification.

• Extraction of factual data. We quote a legal opinion cited by the Open Crystallography Database,[30] where many similar issues are addressed:

"I [*] assume US law governs throughout; an inaccurate but necessary assumption here. If you extract only the actual coordinate data you have no copyright liability. One cannot copyright facts, only the expression incident to factual reporting. This principle was recognized by the US Supreme Court in 1915 with respect to news reports sent by telegraph. The idea/expression distinction has been held by the Supreme Court to prevent assertion of copyright over telephone white pages, where there is no originality in the concept of alphabetic organization of data. More complex forms of association or organization of data might give rise to claims."

By analogy, properties such as melting points, spectra, refractive indexes, and similar measurements are also facts. We therefore assume that by default humans can abstract and repurpose factual information (generally referred to as "data" in this article) without seeking copyright permission. We believe that this is current practice among many secondary data producers. We see no logical reason why robots cannot perform the same task. By default, therefore, if the owner/controller of a robot has access to one or more publications, their robots can extract the facts from these publications and re-use the collected information freely. We ask that publishers confirm that no copyright is violated in the extraction and reuse of factual information by robotic methods where the user has legitimate access to the information.

• Re-use of supplemental data. We show below that, at least for crystallography, the re-use of supplemental data is highly valuable, but the access to and copyright status of it varies from journal to journal. We would assert that it consisted of facts, but for many journals, the same copyright notice that applies to the primary article also by default covers the supplemental information. Whilst the experience of the present authors (HSR) suggests that requests to publishers for a more open non-exclusive copyright status for supplemental data are often granted, we suspect this is not common. We believe that the motivation behind the deposition of supplemental data is to make it available to the community for re-use, but that many authors do not realise the concerns of copyright. We ask that publishers confirm that their supplemental data, whether held by them or by a third party is freely reusable by humans and robots.

• In some cases it is not clear whether the supplemental data provided (*e.g.* by a publisher or data aggregator) is the original author's or has been creatively enhanced (*e.g.* by editing). We ask that publishers make it clear whether the changes have taken place, what their nature is, and if so to provide a copy of the author's original data for re-use.

• We also suggest that authors add a declaration in their manuscript and/or supplemental data that the data is freely readable and re-usable by humans or robots. We expect that The Creative Commons Science Project[31] is likely to provide useful protocols.

• We have noted that robotic indexing of publishers' sites may be discouraged (there may be valid reasons such as denial of service). We ask that publishers have a policy to allow known robots from the scientific community to access, index and extract publicly available facts from their sites.

We hope to collect the views of major publishers of chemistry on these questions. We appreciate the effort required to addressing these concerns but feel that solutions are essential if there is to be a thriving open chemical information process, on which applications such as the Semantic Web can be built.

Examples of the Chemical Semantic Web

In the second part of this article, we will proceed to show that our vision is realisable with today's technology and take as an example the high-throughput computation of the properties of molecules published in the present journal (*Organic and Biomolecular Chemistry*). Our general approach takes the form shown in Fig. 1.

1. We assume a molecule is precisely identifiable from the text (systematic IUPAC-like name) or supplemental data (connection table) of the publication. The adoption of the IUPAC/NIST unique molecular identifier (INChI)[32] will make this automatic.

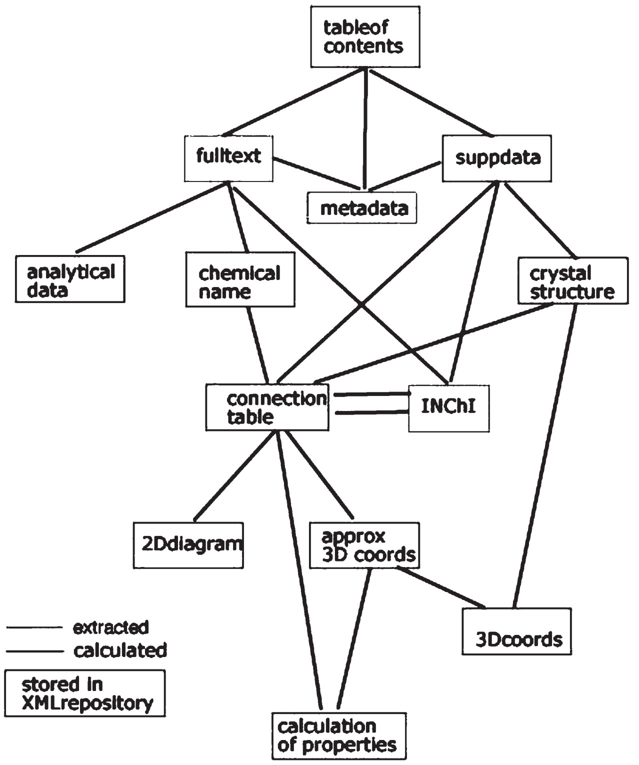


Fig. 1 Schematic for capturing and processing data from journal articles.

2. We use a parser (JUMBOName) to generate the connection table (in CML)[12] including stereochemistry. These steps would become unnecessary if authors used INChI to describe molecules.

3. D coordinates (in CML) are generated from the connection table, or converted from published 3D structures (*e.g.* CIF) to CML.

4. We use a semi-empirical SCF-MO method or molecular mechanics procedure for rapid optimisation.

5. This processed molecule is then submitted into a high-throughput computation system for more accurate calculation of properties.

In most cases the "legacy" input can be converted automatically to CML and input to the computational process. The results can be repurposed in several ways, including storage in an XML repository. If the authoring process is converted to using XML, then the whole chain can be seamless. A typical XML-based process in shown in Fig. 2. This will then allow the complete material in a primary publication to be used as a global knowledge base.

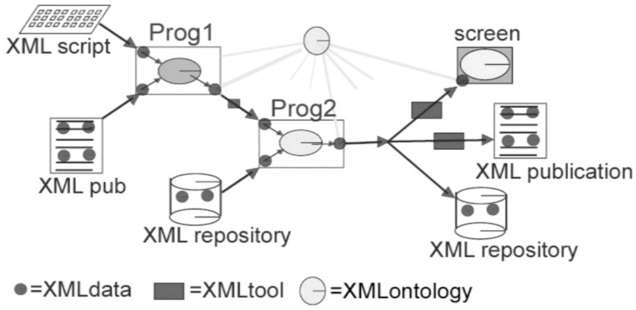


Fig. 2 Workflow schematic for XML-based data-processing for the journal article.

Structural chemiotics

Before describing how content can be transferred from the "pages" of current journals into a semantically rich environment, it is worth considering how such semantics are currently represented in journal form. We focus on organic chemistry, which still rests securely on many of the concepts developed in the nineteenth century. In our XML-based formalism of chemistry,[12] many of the core concepts (*e.g.* atoms, bonds, electrons *etc.*) would have been understood by an early 20th century chemist. The representation of more complete chemical entities, substances, and reactions has however also remained substantially unchanged. In particular chemists have learnt to communicate many concepts graphically, and until around 20 years ago these were necessarily restricted to the printed page.

In 1984 the introduction of *e.g.* the ChemDraw program provided arguably the first widely available mechanism for transfer of chemical ideas between computer and the printed page in a graphical form; concurrently, physical and theoretical chemists were starting to use programs such as LaTeX for handling equations. The key point is that these "electronic chemical stencils" did not change, and in fact reinforced, conventional (and often ambiguous) symbolism. In some cases the programs were designed to display excellently on paper, only adequately on the screen and much less so within formal data-structures. The creators of such programs often constrain the chemical author to a finite set of chemical glyphs with the consequence that semiotic innovation is thereby not encouraged.

Tools for the display of three-dimensional chemical objects have created enhanced chemiotics such as the Connolly surface, and the rendering of quantum mechanical concepts ("orbital photography"), which thereby became more accessible to chemists. But molecular structure and reactivity has largely remained rooted at the "arrow-pushing" level. Determination of the electron counts and configurations in a molecule often requires significant work, accompanied by the perception of many implicit semantics.

Overall therefore, we conclude that almost all current chemiotics is "fuzzy", it requires considerable experience to interpret it and an induction into the priesthood. There are frequent misunderstandings, often only resolvable by a deep knowledge of the chemistry of substances and reactions. It is "known" that in many structures hydrogen atoms are to be added, and in others not. For steroids the stereochemistry at centres is deducible "by analogy". Reactants are frequently inferred from textual annotations such as "aqueous workup". Carbon atoms are/not assumed where "bonds cross". These implicit semantics are difficult, dangerous and impossible for machines to understand. The discussion that follows illustrates how some of these difficult issues arise and where they can be addressed.

Case studies of current publications

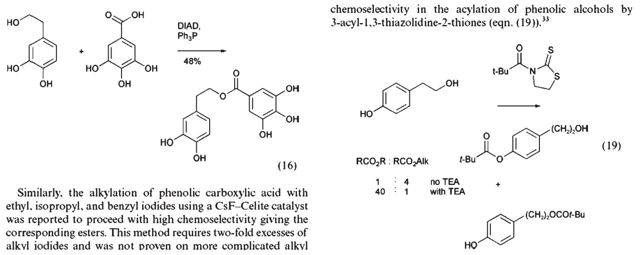
Methodology and analysis

We have chosen to illustrate the potential for the Chemical Semantic Web by analysing the current articles in this journal (June 2004). We show the potential for machine analysis, although here have deliberately carried it out manually as the RSC journals site restricts web trawling to Google (see editorial comment associated with this article). In principle, everything reported here would be scalable with robots. We have also tried to emulate the Web access of a non-subscriber (*i.e.* emulating what is available Openly). This also attempts to ensure that we do not abuse our subscription access.

For the *OBC* journal, (graphical) abstracts of all articles, 3–4 free articles per issue and supplemental data for a proportion of the articles is publicly available. We confine ourselves to articles reporting compounds (new or re-used) and their properties or reactions, addressing the perspectives of Human understandability and implicit semantics, the machine-understandability of *data in articles* and the machine-understandability of supplemental data. Our corpus therefore comprises two openly readable articles[33,34] and 24 (closed) advance articles, with graphical abstracts and optionally supplemental data. We have taken, as they appear, the first two articles together with one graphical abstract and supplemental data from several others. Authors and editors should not take this as specific criticism but simply as a sample of the current state of the art of graphical representation.

Transformation using journal articles as source

The first article[33] is a review of chemical reactivity in a synthetic context. It does not report details of individual molecules and the chemistry is almost entirely graphically based, so the article has no chemical machine-understandability. Some issues arising from this are shown by a typical snapshot (Fig. 3).

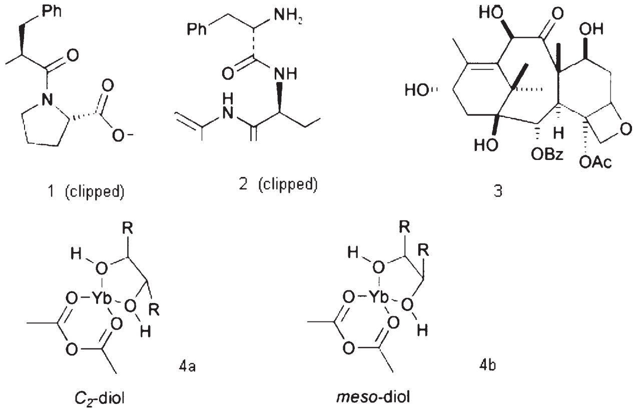

chemoselectivity in the acylation of phenolic alcohols by 3-acyl-1,3-thiazolidine-2-thiones (eqn. (19)).[33]

Similarly, the alkylation of phenolic carboxylic acid with ethyl, isopropyl, and benzyl iodides using a CsF–Celite catalyst was reported to proceed with high chemoselectivity giving the corresponding esters. This method requires two-fold excesses of alkyl iodides and was not proven on more complicated alkyl

Fig. 3 Two illustrative reaction sequences taken from ref. 33.

These reactions have almost certainly been authored using a computer, but are aimed for human-, not machine-understandability. Their layout is dictated not by chemical practice but the requirement to use two columns in a width-limited display constrained by journal paper sizes. Assuming the 2D coordinates of the graphics primitives were available in machine-readable form, a machine could, with sufficient heuristics, understand the content of the left hand frame, but the right-hand one is effectively impossible. The machine must recognise that the species over the arrow is a stoichiometric reagent, that the "+" means "mixture of" and that the text actually represents a two column/two row table. "TEA" and "Alk" are not explicitly defined. It is therefore unrealistic to expect machines to understand published reactions without new approaches (see below).

Machine-readable molecules (*i.e.* with connection tables) should, however be almost completely tractable. However a consistent approach is critical; significant variability of stereochemical representation within a single article and even within a single molecule can often be observed. Here four different conventions are used[33] for the same concept (a hatched "wedge" bond, Fig. 4).


1 (clipped)

2 (clipped)

3

4a

4b

C_2-diol

meso-diol

Fig. 4 Stereochemical notations taken from ref 26.

In **1** (our numbering), the stereochemistry can only be interpreted if it is assumed that the wide end of the hatched wedge is the chiral atom. In **2** no chiral atom is indicated, the reader needing to know that a carbonyl cannot be stereogenic. In **3** the solid wedged bonds have a different convention from **2** and *three* different conventions are used for the hatched wedge bonds. One stereo centre is not annotated (presumably the ring junction is assumed to be *cis* but the reader must know the conformational energetics of small rings.) Another centre is decorated with wedge and hatch bonds even though it is not stereogenic. In **4a** and **4b**, two stereoisomers are presumably indicated by the *positions* of bonds rather than a stereochemical convention.

A machine would be incapable of making these judgements. The diagrams have, however, almost certainly been created in a drawing program and can easily be analysed for validity and consistency using the IUPAC/NIST INChI program.[32] We show this process being used for molecule **3**. INChi reads a connection table, normalizes it (*i.e.* for different approaches to aromaticity), detects possible tautomerism and other possible variations and uniquely labels all atoms (Fig. 5). It also generates a unique string or XML (shown later) which can be used for indexing or editing and as a machine-understandable connection table. The message from this article, therefore, is that if authors use tools to create, *validate*, and publish their structures, a high degree of machine-understandability can be achieved.

The second article[34] reports around 20 novel compounds. They are reported in a concise, human-readable but not very human-friendly form (Figs. 6 and 7).

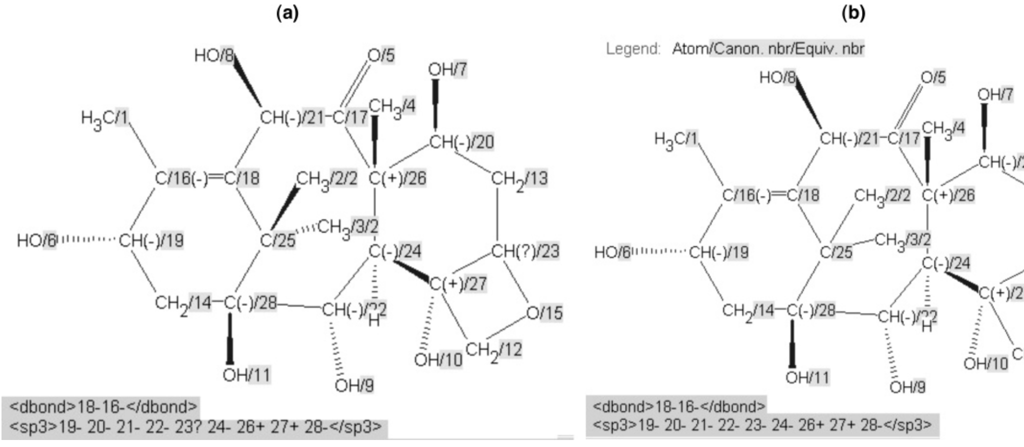
Fig. 6 contains much information, but it is a considerable effort to read. The reader first has to work out the semantics, which are that a series of related compounds are transformed by a series of reagents to a series of products. None of the identities of the compounds are explicit and have to be deduced by decoding the generic Markush-like substitutions. Note that not all compounds in a series follow the same paths. Only the starting compounds have the complete structural framework; the rest have cutaway diagrams. The reason for this is primarily to save space in the conventional representation. Although not explicit, we assume that the metal in the intermediates is coordinated to all four N atoms. Note also that the reagents are not explicitly given, but have to be decoded from the caption, again mandated by the need to save space.

The scheme is not machine-understandable but it is augmented by the running text and analytical data (Fig. 7) which are. These were not given in the main text for all numbered compounds, but additional material was provided in the supplemental data. Using the OSCAR program[14] the data for the 10 compounds in the text was robotically translated into CML and is shown as a summary (Table 1).

It is clear that a large amount of high-quality information, including molecular formula and spectral peaks can be understood. Unfortunately no connection tables are given, and the names cannot be interpreted, as the authors have just coined many of them. The publication would again be enormously enhanced by the generation of INChI identifiers[32] for all the unique molecules. This process is illustrated below for four of these compounds involved in one of the transformations (reagent v, Fig. 6) and believed to be **7bH2, 8BNi, 11** (a generic label?), and **10bNi**) These were redrawn by us using a CML-aware editor (Marvin[35]), saved as MOL files and CML files and the INChI identifiers generated from these (Table 2).

Transformation using supplemental data as source

We examined 24 advance articles but restricted ourselves to the publicly (and therefore robotically) visible material, which included the graphical abstract, and any supplemental data. All the articles had a graphical abstract, but only 14 had supplemental data. The latter was examined for machine-understandability (*i.e.* could a machine, given the likely nature of the data, extract a useful amount of material). Disappointingly,



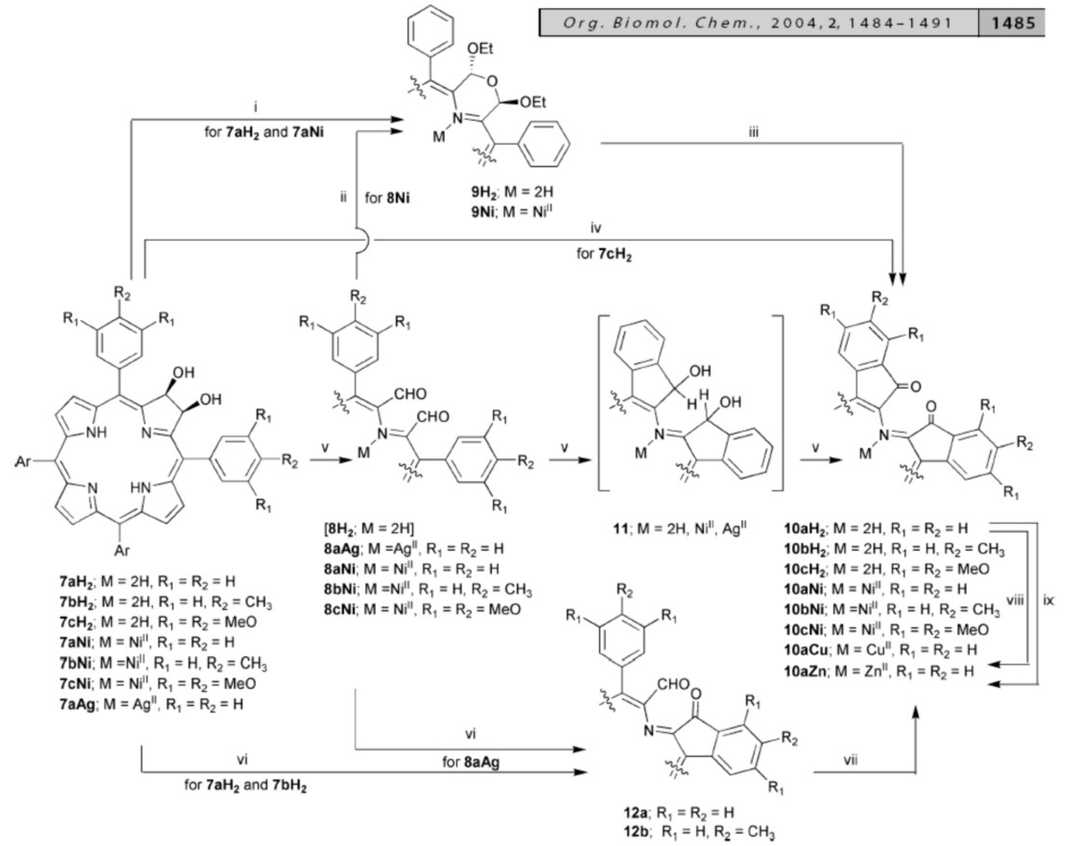
(a)

```
<dbond>18-16-</dbond>
<sp3>19- 20- 21- 22- 23? 24- 26+ 27+ 28-</sp3>
```

(b)

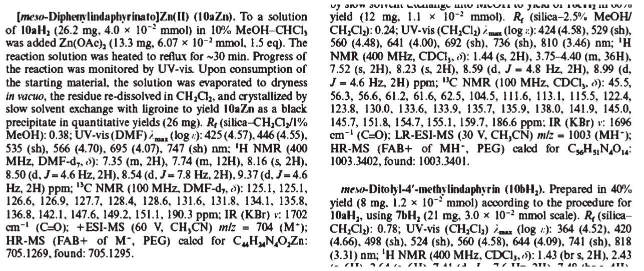
```
<dbond>18-16-</dbond>
<sp3>19- 20- 21- 22- 23- 24- 26+ 27+ 28-</sp3>
```

Fig. 5 INChI identifier generated for molecule **3**, derived from Fig. 4, showing (a) the published structure of **3** with unmarked stereochemistry for C-23 and no stereogenicity for C-25 and (b) with presumed "correct" stereochemistry.


Org. Biomol. Chem., 2004, 2, 1484–1491
1485
OEt
O
OEt
N
M
9H₂; M = 2H
9Ni; M = Ni^II
i
for 7aH₂ and 7aNi
ii for 8Ni
iii
iv
for 7cH₂
R₂
R₁
R₁
OH
OH
NH
N
N
HN
Ar
Ar
7aH₂; M = 2H, R₁ = R₂ = H
7bH₂; M = 2H, R₁ = H, R₂ = CH₃
7cH₂; M = 2H, R₁ = R₂ = MeO
7aNi; M = Ni^II, R₁ = R₂ = H
7bNi; M = Ni^II, R₁ = H, R₂ = CH₃
7cNi; M = Ni^II, R₁ = R₂ = MeO
7aAg; M = Ag^II, R₁ = R₂ = H
v
CHO
CHO
[8H₂; M = 2H]
8aAg; M = Ag^II, R₁ = R₂ = H
8aNi; M = Ni^II, R₁ = R₂ = H
8bNi; M = Ni^II, R₁ = H, R₂ = CH₃
8cNi; M = Ni^II, R₁ = R₂ = MeO
OH
H H OH
11; M = 2H, Ni^II, Ag^II
O
O
10aH₂; M = 2H, R₁ = R₂ = H
10bH₂; M = 2H, R₁ = H, R₂ = CH₃
10cH₂; M = 2H, R₁ = R₂ = MeO
10aNi; M = Ni^II, R₁ = R₂ = H
10bNi; M = Ni^II, R₁ = H, R₂ = CH₃
10cNi; M = Ni^II, R₁ = R₂ = MeO
10aCu; M = Cu^II, R₁ = R₂ = H
10aZn; M = Zn^II, R₁ = R₂ = H
viii
ix
CHO
12a; R₁ = R₂ = H
12b; R₁ = H, R₂ = CH₃
vi
for 7aH₂ and 7bH₂
vi
for 8aAg
vii

Scheme 2 *Reaction conditions:* i. $NaIO_4$/silica gel, EtOH; ii. EtOH, TFA; iii. 10% TFA/CH_2Cl_2; iv. [O]; v. $NaIO_4$/silica gel or $Pb^{IV}(OAc)_4$; vi. TFA vapors; vii. 2% TFA/CH_2Cl_2; viii. $Zn^{II}(OAc)_2$, 10% MeOH/$CHCl_3$, Δ; ix. $Cu^{II}(OAc)_2$, DMF, Δ.

Fig. 6 A complex reaction schematic, illustrating the degree of (human) perception required.



[*meso*-Diphenylindaphyrinato]Zn(II) (10aZn). To a solution of **10aH₂** (26.2 mg, 4.0 × 10^{-2} mmol) in 10% MeOH–$CHCl_3$ was added $Zn(OAc)_2$ (13.3 mg, 6.07 × 10^{-2} mmol, 1.5 eq). The reaction solution was heated to reflux for ~30 min. Progress of the reaction was monitored by UV-vis. Upon consumption of the starting material, the solution was evaporated to dryness *in vacuo*, the residue re-dissolved in CH_2Cl_2, and crystallized by slow solvent exchange with ligroine to yield **10aZn** as a black precipitate in quantitative yields (26 mg). R_f (silica–CH_2Cl_2/1% MeOH): 0.38; UV-vis (DMF) λ_{max} (log ε): 425 (4.57), 446 (4.55), 535 (sh), 566 (4.70), 695 (4.07), 747 (sh) nm; ^1H NMR (400 MHz, DMF-d₇, δ): 7.35 (m, 2H), 7.74 (m, 12H), 8.16 (s, 2H), 8.50 (d, *J* = 4.6 Hz, 2H), 8.54 (d, *J* = 7.8 Hz, 2H), 9.37 (d, *J* = 4.6 Hz, 2H) ppm; ^{13}C NMR (100 MHz, DMF-d₇, δ): 125.1, 125.1, 126.6, 126.9, 127.7, 128.4, 128.6, 131.6, 131.8, 134.1, 135.8, 136.8, 142.1, 147.6, 149.2, 151.1, 190.3 ppm; IR (KBr) ν: 1702 cm^{-1} (C=O); +ESI-MS (60 V, CH_3CN) *m/z* = 704 (M^+); HR-MS (FAB+ of M^+, PEG) calcd for $C_{44}H_{24}N_4O_2Zn$: 705.1269, found: 705.1295.

by slow solvent exchange into MeOH to yield of 10cH₂ in 60% yield (12 mg, 1.1 × 10^{-2} mmol). R_f (silica–2.5% MeOH/CH_2Cl_2): 0.24; UV-vis (CH_2Cl_2) λ_{max} (log ε): 424 (4.58), 529 (sh), 560 (4.48), 641 (4.00), 692 (sh), 736 (sh), 810 (3.46) nm; ^1H NMR (400 MHz, $CDCl_3$, δ): 1.44 (s, 2H), 3.75–4.40 (m, 36H), 7.52 (s, 2H), 8.23 (s, 2H), 8.59 (d, *J* = 4.8 Hz, 2H), 8.99 (d, *J* = 4.6 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, δ): 45.5, 56.3, 56.6, 61.2, 61.6, 62.5, 104.5, 111.6, 113.1, 115.5, 122.4, 123.8, 130.0, 133.6, 133.9, 135.7, 135.9, 138.0, 141.9, 145.0, 145.7, 151.8, 154.7, 155.1, 159.7, 186.6 ppm; IR (KBr) ν: 1696 cm^{-1} (C=O); LR-ESI-MS (30 V, CH_3CN) *m/z* = 1003 (MH^+); HR-MS (FAB+ of MH^+, PEG) calcd for $C_{56}H_{51}N_4O_{14}$: 1003.3402, found: 1003.3401.

***meso*-Ditolyl-4′-methylindaphyrin (10bH₂).** Prepared in 40% yield (8 mg, 1.2 × 10^{-2} mmol) according to the procedure for **10aH₂**, using **7bH₂** (21 mg, 3.0 × 10^{-2} mmol scale). R_f (silica–CH_2Cl_2): 0.78; UV-vis (CH_2Cl_2) λ_{max} (log ε): 364 (4.52), 420 (4.66), 498 (sh), 524 (sh), 560 (4.58), 644 (4.09), 741 (sh), 818 (3.31) nm; ^1H NMR (400 MHz, $CDCl_3$, δ): 1.43 (br s, 2H), 2.43

Fig. 7 A typical experimental section, illustrating the relatively structured nature of the data descriptions.

most supplemental data is not machine-understandable and a lot is not human-readable either, with images reduced below the resolution of the pixel grid. Two examples of this former phenomenon (Figs. 8 and 9) clearly show that the data was originally completely machine-understandable, but that the publication process has destroyed this by rendering on (physical) paper (note the presence of human annotations in both). It is worth emphasizing that not all supplemental data is so emasculated; that associated with *e.g.* ref 17 could in some ways be considered a superset of the main article, since an (XML-based) transformation of the supplemental information would in fact regenerate the formal article.

The only usable machine-understandable supplemental data provided within these 24 advance articles is a crystal structure attached as a CIF file to an advance publication.[36] The molecule of interest is indicated as a raster image in the electronic abstract (Fig. 10). This is shown full (Websize) at left and magnified right. Again this was (once) machine-understandable; the loss of information is due to conversion to a gif for web viewing, and adoption of a customary size for graphical abstracts.

Using the CIF provided by the original authors however, we believe that we have robotically extracted both the connection table and the 3D coordinates of a single molecule, using the following processing sequence.

1. Read the CIF into an XMLDOM[37] (our cif2cml library).
2. Discard minor disordered components.
3. Convert fractional coordinates to cartesian.
4. Join bonds using "reasonable" covalent radii.
5. Apply symmetry operations to generate the minimum number of molecular fragments (here two, as the molecule is a dimer in the crystal).
6. Generate a connection table (CT) for the molecule(s).
7. Check against chemical formula (often not given).
8. Analyse the CT(s) with INChI to assess chemical validity.
9. Identify potential stereogenic atoms and bonds.
10. Generate CML atomParity and bondStereo if appropriate.
11. Use the CDK library[38] to generate conventional "2D" coordinates.
12. Serialize the result as CML.

This process is not foolproof as CIFs do not in general report molecular charges, and any disorder may be difficult to interpret. In the current case there are no problems. The CML file was then robotically input to the MOPAC2002 program to invoke a PM5 calculation[8] (43 sec, done during the time it takes a human to read the abstract and the first paragraph of the article) to generate optimised gas-phase coordinates which were then subsequently input for GAMESS-US[39] *ab initio* re-optimisation. The result was used to generate an INChI identifier and then stored, without loss, in an XML repository (already containing around 250,000 other molecules processed using these automated procedures). This process has also provided two useful ring fragments for addition to *e.g.* a fragment database. All output from these programs was parsed into CML; the resulting molecules are shown in Fig. 11.

Finally, all new molecular entries can be added automatically to a CMLRSS newsfeed[18] which allows subscribers to this feed

Table 1 Automated parsing of experimental data using the OSCAR program[14]

name	id	formula	CNMR	HNMR	IR	MS	Nature	UV
meso-Diphenylindaphyrin	10aH2	C44H27O2N4	20 peaks 116.7…	9 peaks 1.49…	1 peaks 1699…	1 peaks 643…	powder	5 peaks …
[meso-Diphenylindaphyrinato]Ni(II)	10aNi	C44H24N4NiO2	18 peaks 110.7…	9 peaks 7.375…	1 peaks 1599…			
[meso-Diphenylindaphyrinato]Cu(II)	10aCu	C44H24N4O2Cu			1 peaks 1709…	1 peaks 703…	powder	8 peaks …
[meso-Diphenylindaphyrinato]ZnII	10Zn	C44H24N4O2Zn	17 peaks 125.1…	6 peaks 7.35…	1 peaks 1702…	1 peaks 704…	black	6 peaks …
meso-Triphenyl-1-formylindaphyrin	12aH2	C44H29N4O2	25 peaks 112.2…	15 peaks 1.90…	2 peaks 1655…	1 peaks 645…		6 peaks …
[meso-Di(3,4,5-trimethoxyphenyl) -3,4,5-methoxyindaphyrinato]NiII	10cNi			7 peaks 4.035…				2 peaks …
meso-Di(3,4,5-trimethoxyphenyl) -3,4,5-methoxyindaphyrin	10cH2	C56H51N4O14	26 peaks 45.5…	6 peaks 1.44…	1 peaks 1696…	1 peaks 1003…		7 peaks …
meso-Ditolyl-4-methylindaphyrin	10bH2	C48H35N4O2 C48H32N4NiO2	21 peaks 21.2…	17 peaks 1.43…	1 peaks 1703…	1 peaks 699…		10 peaks …
meso-Tritolyl-1-formyl-(4′-methyl)indaphyrin	12bH2	C48H37N4O2	29 peaks 21.6…	15 peaks 1.96…	2 peaks 1711…	1 peaks 701…		6 peaks …

to receive up-to-date information about the entry, including any generated 2D/3D coordinates and associated information.

Chemical reactions

The representation of molecules and compounds is relatively standard and primarily needs standardisation and discipline. Chemical reactions, however, are more challenging. There are relatively few tools for authoring chemical reactions, and those are not as widely used as those for molecules, being usually closely bound to non-interoperable proprietary software products. We believe that new approaches for representing chemical reactions are required and that these should move away from "paper-based" approaches. We present here an approach to chemical reactions that we believe should benefit both human and machine reuse.

Even confining ourselves to ground state species, a single reaction can involve, at many levels of detail:

- the precise description of the trajectory of atomic ensembles on the potential energy surface;
- the identification of two local minima and an intervening transition state;
- the identities of reactant species and product species;
- multiple successive or alternative reaction steps within a "reaction";
- the overall stoichiometry of a process, perhaps with associated physical data (heats, rates);
- the procedures required to carry it out, and the results and observations obtained.

In addition the term reaction is often used to mean a reaction type (*e.g.* esterification) where generic groups replace present atomic configurations. or a reaction scheme, whereby a set of reactions is laid out to show an overall synthetic strategy or enzymatic cascade.

We have extended CML to support these concepts ("CMLReact") and tested it on several systems, most notably the MACiE database of enzyme reactions.[40] The CMLReact scheme includes XML constructions for:

- reactant, product, spectator (*e.g.* protein side chains) or substance (which can include solvent, catalysts, *etc.*);
- mechanism and transition state;
- annotations (*e.g.* titles, names and labels);
- properties, both controlling conditions and observations/measurements;
- atoms, bonds and electrons. These can be explicitly included with a range of attributes (position, annotation, displayHints, *etc.*).

The conventional representation of a reaction with reactants and products may require a complex mapping of identities between them (*e.g.* atom–atom mapping and electron "movement" (curly arrows)) and CMLReact can support these. However CMLReact can also provide a much simpler approach, now described.

If we discard the need for static paper, and allow the dynamism of the electronic medium, the information presentation becomes dramatically simpler. Atoms (and electrons) remain unaltered during a reaction so there is no need to replicate them. Even if there are several steps and many disjointed fragments (as in an enzyme mechanism) they are always present (even if conceptually at an "infinite distance"). We illustrate this with an example where only one "molecule" is involved—the biosynthesis of the steroid nucleus. The product, reactant and intermediate configurations were sketched with a conventional editor and saved as CML. These were then converted into individual SVG[9] documents (Fig. 12) and combined using the SVG "animate" feature for morphing into an animated SVG by processing with the CMLSnap XSLT[9] stylesheet.

The first three steps are stylised conformational rearrangements but the final one involves bond breaking and formation (Fig. 12). Instead of using curly arrows, the bonds simply appear, disappear or change order. There are many ways in

Table 2 INChI identifiers generated for selected species described in Fig. 6

7bH2	INChI = 1.11Beta/C48H40N4O2/c1-27-5-13-31(14-6-27)41-35-21-22-36(49-35)42(32-15-7-28(2)8-16-32)38-24-26-40(51-38)44(34-19-11-30(4)12-20-34)46-48(54)47(53)45(52-46)43(39-25-23-37(41)50-39)33-17-9-29(3)10-18-33/h1-4H3,5-26H,47-48H,50-51H,53-54H/b41-35-,41-37-,42-36-,42-38-,43-39-,44-40-,45-43-,46-44-/t47-,48+
8bNi	INChI = 1.11Beta/C48H37N4O2.Ni/c1-29-5-13-33(14-6-29)45-37-21-22-38(49-37)46(34-15-7-30(2)8-16-34)40-24-26-42(51-40)48(36-19-11-32(4)12-20-36)44(28-54)52-43(27-53)47(41-25-23-39(45)50-41)35-17-9-31(3)10-18-35;/h1-4H3,5-28H,(H-,49,50,51,52,53,54);/q − 1;+4/p-1
11(?11bNi)	INChI = 1.11Beta/C48H36N4O2.Ni/c1-25-5-11-29(12-6-25)41-35-17-18-36(49-35)42(30-13-7-26(2)8-14-30)38-20-22-40(51-38)44-32-16-10-28(4)24-34(32)48(54)46(44)52-45-43(39-21-19-37(41)50-39)31-15-9-27(3)23-33(31)47(45)53;/h1-4H3,5-24H,47-48H,53-54H;/q-2;+4/b41-35-,41-37-,42-36-,42-38-,43-39-,44-40-,52-45-,52-46-;
10bNi	INChI = 1.11Beta/C48H34N4O2.Ni/c1-25-5-11-29(12-6-25)41-35-17-18-36(49-35)42(30-13-7-26(2)8-14-30)38-20-22-40(51-38)44-32-16-10-28(4)24-34(32)48(54)46(44)52-45-43(39-21-19-37(41)50-39)31-15-9-27(3)23-33(31)47(45)53;/h1-4H3,5-24H,(H2,49,50,51,52,53,54);/q;+4/p-2

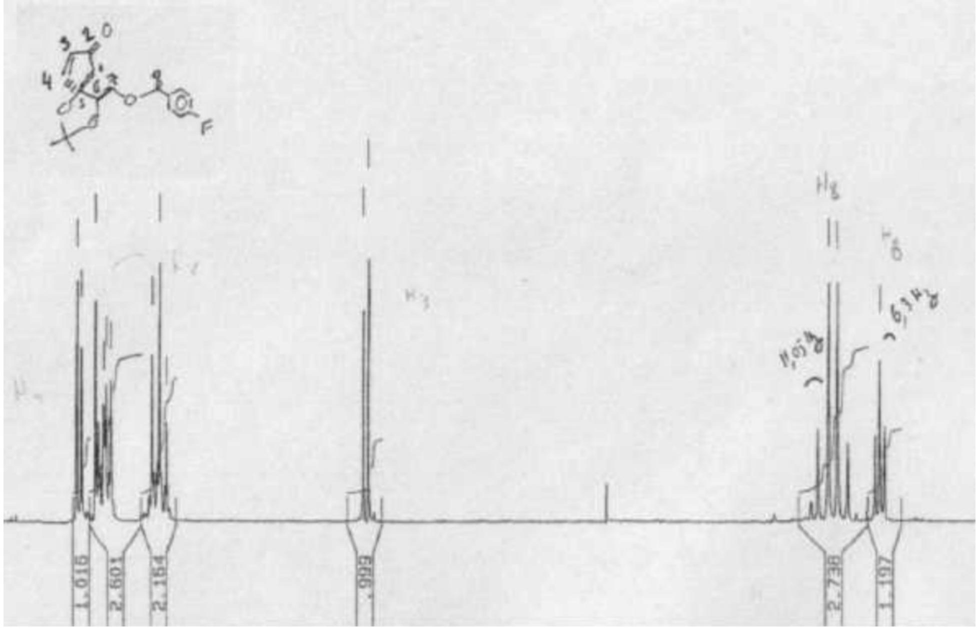


Fig. 8 NMR spectral data provided as supplemental information, illustrating the human annotations and lack of machine readability.

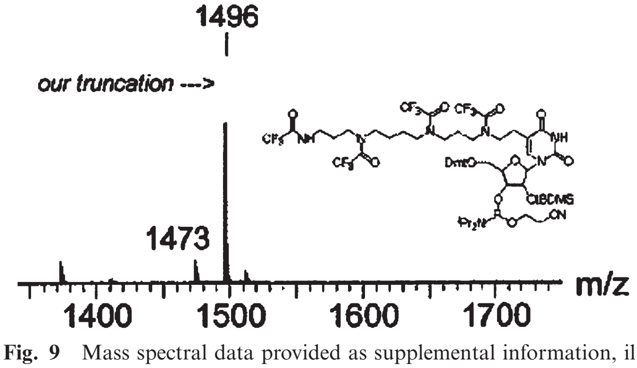


Fig. 9 Mass spectral data provided as supplemental information, illustrating human annotations and lack of machine readability.

which this display can be personalised or enhanced. No special tools are required and the authoring time is at least as short as for conventional diagrams and requires no artificially imposed restrictions on layout.

The same approach can be used to simplify the reaction scheme originally discussed and shown in Fig. 6.[34] As an example we take the "main horizontal path" which involves the four species: **7bH2** → **8bNi** → **11bNi** → **10bNi**. We make "snapshots" of these in the same coordinate frame (Fig. 13), again created with a standard editor (Marvin).[35] These frames can then be automatically combined into an animation with simple XSLT stylesheets and merged into a single SVG document. SVG provides automatic morphing so the graphic display shows a smooth transition between the species.

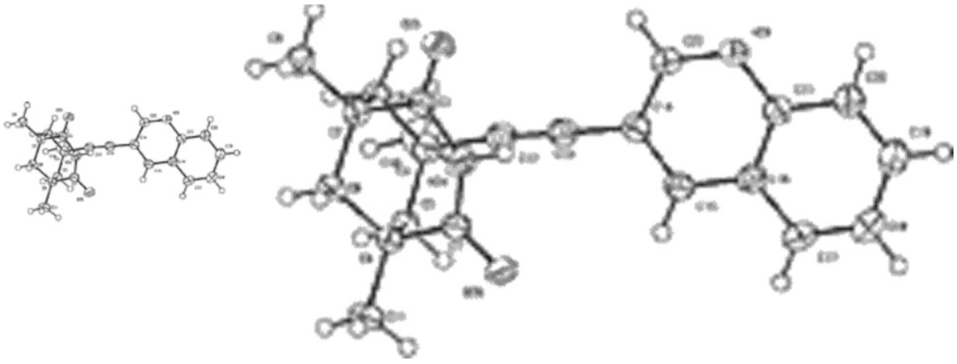


Fig. 10 Graphical abstract for ref. 36, shown original size (left) and magnified (right).

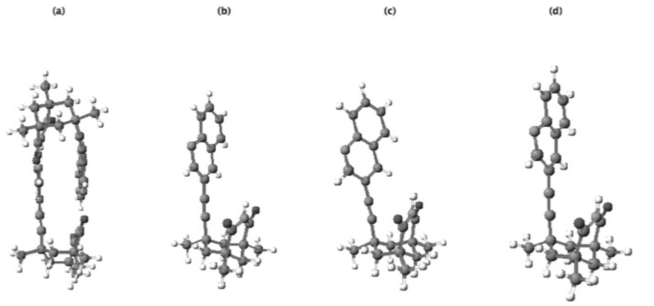


Fig. 11 (a) original (experimental) CIF data, (b) a single molecule selected from the experimental data, (c) after optimisation using the MOPAC PM5 method and (d) after optimisation using the GAMESS B3LYP/6–31G(d) method.

Rather than use curly arrows, we can explicitly include significant electron pairs, as illustrated for a five-step enzymic reaction[40] (Fig. 14).

Reaction procedures will also benefit from being cast into XML. The following proof-of-concept cartoon[41] (Fig. 15) shows the semantics of a chemical reaction procedure captured in XML and displayed by SVG animation. There is therefore great scope for changing the publication process for chemical reactions, but there is a need for standardisation and development of authoring tools.

Conclusions: a manifesto for open chemistry

We believe the preceding examples have shown that what advances there have been in the publication process over the last ten years are solely for human benefit; "electronic paper" is of little value to a machine. While much bioscience is published with the knowledge that machines will be expected to understand at least part of it, almost all chemistry is published purely for humans to read. This is compounded by the current business model in chemical information where authors do not deliberately publish information to be machine-understandable. With Chemical Abstracts and Beilstein, the traditional sequence of author→primary publisher→secondary publisher and the resale of data leads to an expectation that chemists will pay others to curate and collate their information.

This was inevitable until recently, but we argue that now the author is often the best person to evaluate the data produced. Almost all of an author's output (compounds, spectra, reactions, properties, *etc.*) is nowadays computerised and in principle redistributable to the community for re-use. Few journals actively validate the primary data (*e.g.* spectra) involved in a publication (chemical crystallography being a clear expectation where data are intensively reviewed by machine). We reassert that chemists must now move towards publishing their collective knowledge in a systematic and easily accessible form for re-use and innovation.

The easiest part of this to implement is publication of (new) molecular entities and their associated properties. A molecule reported in this journal requires the statement of its precise chemical identity, the analytical data used to confirm its identity (including spectral information) and the procedure in which it was created or used (as a starting point or intermediate). We urge that authors, funders, editors, publishers and readers move further towards the following protocol:

- All information should be ultimately machine-understandable in XML. Openly documented and reviewed XML data-centric languages include XHTML[9] (for running text), CML[11,12] (for molecular identity, including INChI, 2D structure and properties and 3D structures included when available), AniML[42] spectral and analytical data, STMML[43] for scientific datatypes and units and CatML[44] for managing catalyst information. In addition ThermoML[21] can be used for physicochemical data.
- Machine-understandable information for a compound should include a connection table, the IUPAC unique identifier (INChI) which guarantees that the connection table can be checked and regenerated, and a name (although in principle this can be generated from the connection table, it helps to check consistency and trivial names may also be used). Where available, information about physical nature of the compound, scalar analytical quantities (melting point, refractive index, optical rotation), full real-domain spectra (*i.e.* "continuous" data) for appropriate nuclei, and vibrational spectroscopy, high resolution mass spectrometric data and elemental composition and aggregate formula should also be included.
- Rights metadata. An explicit statement in the data that its re-use is consistent with the Budapest Open Access initiative and a requirement that this statement be preserved when the data is re-used.

The actual process of this publication is primarily organisational. An increasing number of Open tools emit CML and will emit other XML schemas. XHTML tools are universal and Open tools for SVG are available. Other Open tools (OpenBabel,[45] JUMBO, CDK,[38] Joelib[46]) can convert legacy to and from CML, and support substructure searches. MathML[9] is supported by many vendors. Open Office[47] supports the general authoring of XML documents. Xindice[48] stores native XML documents in a searchable repository. The main challenge is for chemists to recognise the value of making their data machine-understandable, rather than destroying it with traditional paper or slide-focused publication and dissemination processes.

Acknowledgements

We thank Ms G. L. Holliday for permission to reproduce Fig. 14 and Mr J. A. Townsend for Fig. 15, and for the inclusion of the animations in the XHTML version.

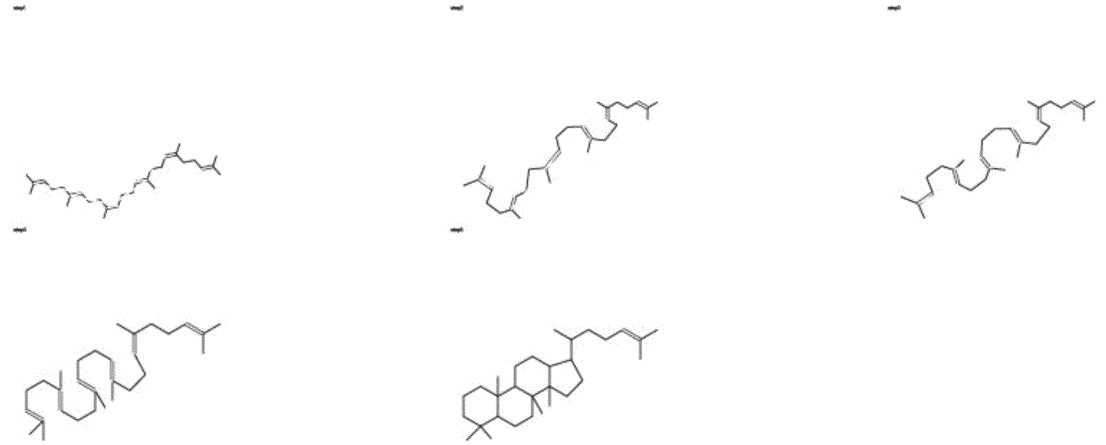


Fig. 12 SVG-format diagrams generated using XML stylesheet transformation from CML. An animated version of this diagram is available *via* the XHTML version of this article.

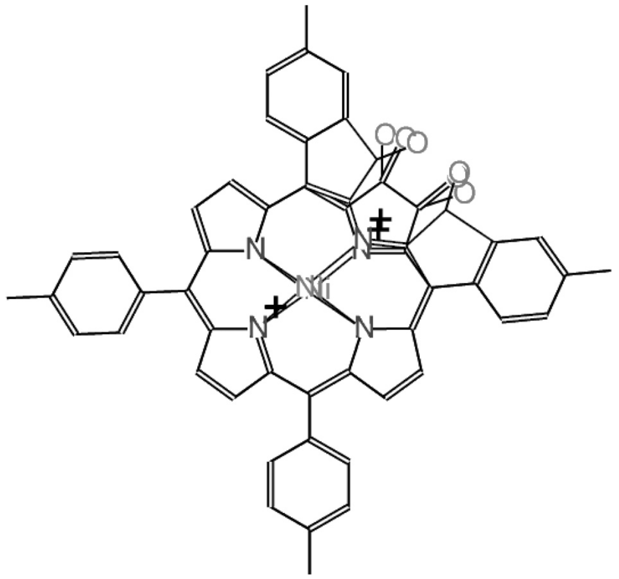


Fig. 13 Snapshots of a reaction path which can be transformed to an animated (SVG) presentation available *via* the HTML version of this article.

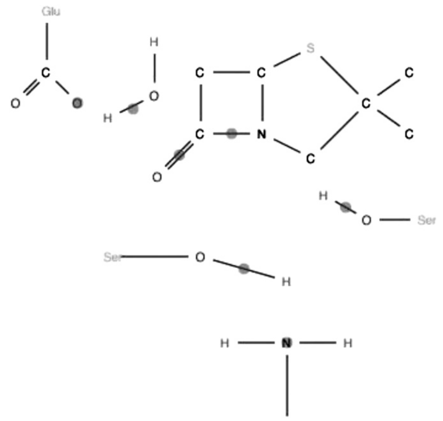
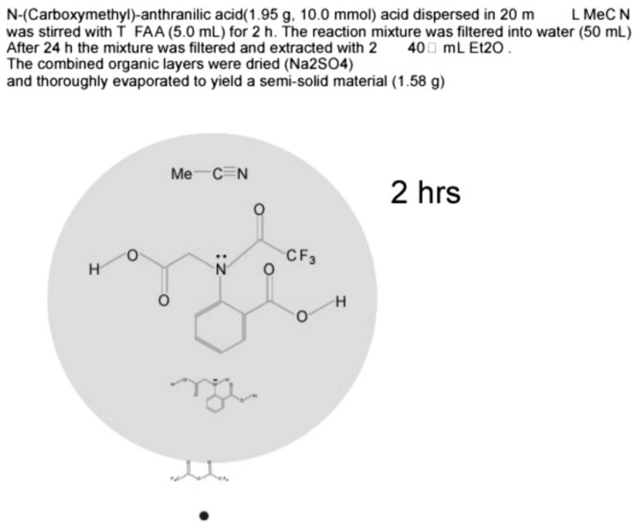


Fig. 14 Reaction mechanisms illustrated using SVG, generated from the corresponding CML.



N-(Carboxymethyl)-anthranilic acid(1.95 g, 10.0 mmol) acid dispersed in 20 m L MeC N was stirred with T FAA (5.0 mL) for 2 h. The reaction mixture was filtered into water (50 mL) After 24 h the mixture was filtered and extracted with 2 40□ mL Et2O . The combined organic layers were dried (Na2SO4) and thoroughly evaporated to yield a semi-solid material (1.58 g)

Fig. 15 Proof-of-concept cartoon showing the semantics of a chemical reaction captured in SVG.

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