Chemistry beyond the molecule

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Supramolecular chemistry has grown in importance because it goes beyond the molecule — the focus of classical chemistry. It also offers a fresh interface with biological and materials science.

For a long time chemists tried to understand nature at a level that was purely molecular — they considered only structures and functions involving strong covalent bonds. But some of the most important biological phenomena do not involve making and breaking covalent bonds — the linkages that connect atoms to form molecules. Instead, biological structures are usually made from loose aggregates that are held together by weak, non-covalent interactions. Because of their dynamic nature, these interactions are responsible for most of the processes occurring in living systems. Chemists have been slow to recognize the enormous variety — in terms of structure, properties and functions — offered by this more relaxed approach to making chemical compounds.

The slow shift towards this new approach began in 1894, when Emil Fischer proposed that an enzyme interacts with its substrate as a key does with its lock[1]. This elegant mechanism contains the two main tenets of what would become a new subject, supramolecular chemistry[2,3]. These two principles are molecular recognition and supramolecular function.

Molecular recognition is implicit in the lock-and-key model — provided both the geometry and the non-covalent interactions are compatible between the interacting partners, you get recognition. Such highly specific interactions also lead to useful supramolecular functions. For example, it is important that an enzyme works only on the appropriate substrate. A key without its own lock or a lock without its own key is quite useless.

The initial motivation behind supramolecular chemistry was to design chemical systems that mimic biological processes. The rise of the supramolecular approach was aided by observations of stable compounds that did not involve covalent bonds. Early examples of these 'addition products' include donor–acceptor complexes and clathrate compounds (Fig. 1). Some donor–acceptor complexes do not involve normal covalent bonding. Instead, they are held together by one molecule donating electrons, or perhaps sharing a hydrogen atom, with another.

A classic example of a donor–acceptor complex is formed by silver ions (Ag^+) and ethene ($CH_2{=}CH_2$), in which the ethene donates some electrons from its double bond to Ag^+ (Fig. 1a). The interaction is not so strong that it leads to a covalent bond, but it is strong enough to form a stable complex.

Back in 1948, H. M. Powell[4] described a series of what he called clathrates — derived from the Latin *clathratus*, meaning 'enclosed by the bars of a grating'. These inclusion compounds are formed when small molecules, such as methanol, hydrogen sulphide or sulphur dioxide, are completely enclosed in cavities formed by a host compound, such as the β-quinol network (Fig. 1b). Here we have addition products with little or no direct attachment — and no covalent bonds — between the 'host' and the 'guest'. Powell's work was the beginning of what would eventually become a major part of supramolecular chemistry — the design of host cages that allow the selective inclusion and expulsion of guest molecules. One of the oldest uses of clathrates is in crude oil refining, in which undesirable paraffins are removed from gasoline by trapping in clathrate lattices.

The early clathrates were discovered by chance, but rational design has led to enhanced properties. For example, a host matrix made from a copper-based polymer material absorbs and releases methane. This organic–inorganic hybrid competes with porous zeolites in its absorptive capacity, and could offer new applications for clathrates, such as the purification of drugs and trapping and storage of toxic materials[5].

Chemists could not understand these inclusion compounds in terms of normal covalent bonding, and they were often relegated to the fringes of chemistry. But with the discovery of useful properties, chemists had to take these compounds seriously — the citadel of the isolated molecule was vulnerable after all.

Intermolecular interactions

The term supramolecular chemistry was coined in 1969 by Jean-Marie Lehn in his study of inclusion compounds and cryptands (Fig. 1c)[2]. The award of the 1987 Nobel Prize in Chemistry to Charles Pedersen, Donald Cram and Lehn signified the formal arrival of the subject on the chemical scene. Lehn defined supramolecular

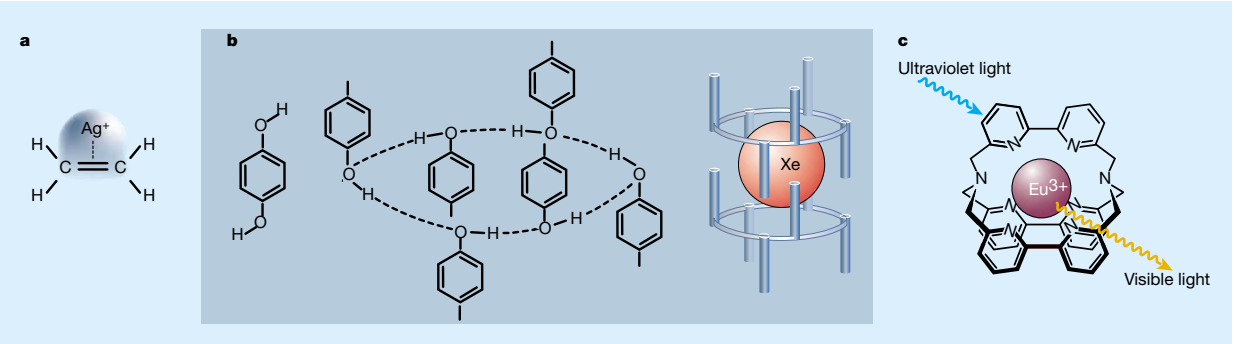

Figure 1 **Supramolecular structures formed by intermolecular interactions.** a, **A donor–acceptor complex involving silver and ethene.** b, **Hydroquinone molecules assemble into a clathrate using hydrogen bonds. This means they can form solid-state host–guest complexes in which the hydroquinone network is the host and the guest is a small molecule, such as the xenon atom shown.** c, **A cryptand contains a spherical internal cavity studded with donor sites, suitable for enclosing a metal ion. Ultraviolet light absorbed by the cryptand shown here excites the metal ion, Eu(III), which then emits radiation at longer (visible) wavelengths.**

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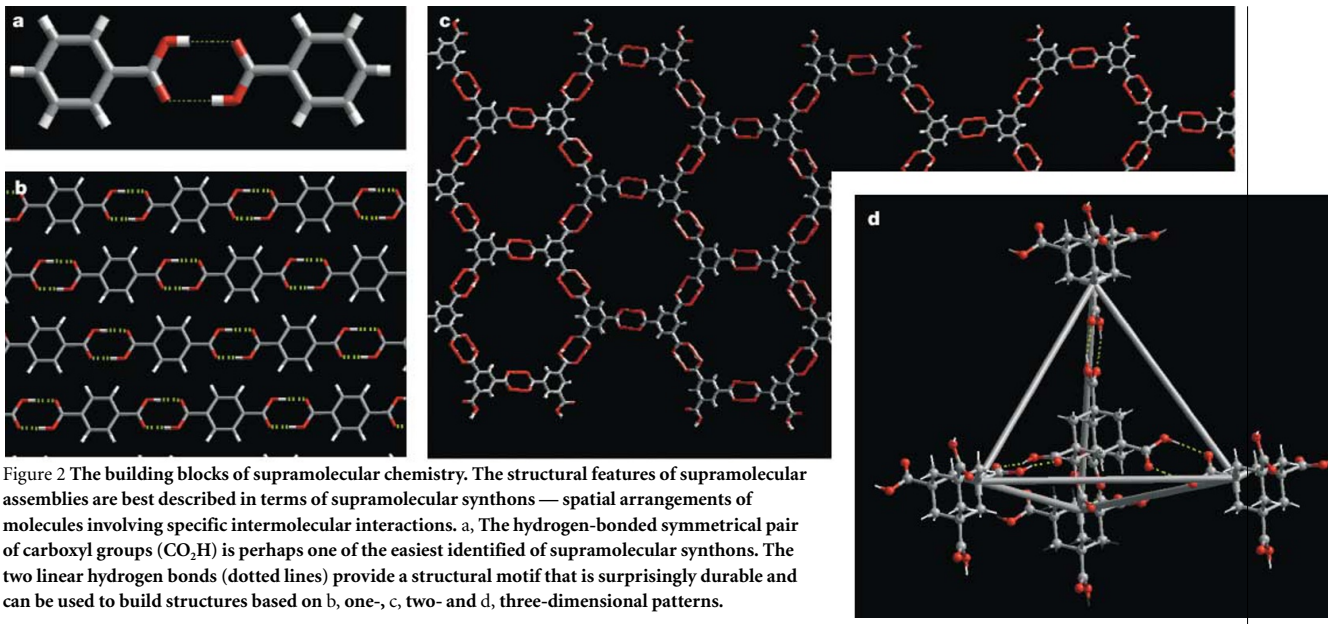

Figure 2 **The building blocks of supramolecular chemistry. The structural features of supramolecular assemblies are best described in terms of supramolecular synthons — spatial arrangements of molecules involving specific intermolecular interactions.** a, **The hydrogen-bonded symmetrical pair of carboxyl groups (CO_2H) is perhaps one of the easiest identified of supramolecular synthons. The two linear hydrogen bonds (dotted lines) provide a structural motif that is surprisingly durable and can be used to build structures based on** b, **one-,** c, **two- and** d, **three-dimensional patterns.**

chemistry as "the chemistry of the intermolecular bond". Just as molecules are built by connecting atoms with covalent bonds, supramolecular compounds are built by linking molecules with intermolecular interactions.

Supramolecular structures are the result of not only additive but also cooperative interactions, and their properties generally follow from their supramolecular character (Boxes 1, 2). So even with the clathrates, their whole is more than the sum of their parts. These properties are important in both materials science (magnetism, conductivity, sensors, nonlinear optics) and biology (receptor–protein binding, drug design, protein folding).

In any supramolecular assembly, a large number of intermolecular interactions is possible — but only a few are actually observed. The weakness of these interactions makes it difficult to predict supramolecular structures and means that, in solution, supramolecular structures are not always stable over time. But this flexibility also means that they are frequently favoured in important mechanisms, notably in biological reactions and in crystallization processes, where the ability to form short-lived transition states and to perform trial-and-error correction easily is essential.

Intermolecular interactions are divided into two classes: isotropic, medium-range forces and anisotropic, long-range forces. Isotropic forces define the shape of the individual molecules, as well as size and close packing of molecules, whereas anisotropic forces determine intermolecular orientations and functions. For example, the three-dimensional shapes of biomolecules, such as proteins and enzymes, are the result of medium-range intermolecular interactions. At a simple level, all molecular recognition can be said to arise from isotropic interactions, in other words by the fitting together of bumps and hollows among the components of the supramolecular structure. But most directional effects — and function is related to these effects — depend on the anisotropic interactions. Generally, the anisotropic interactions

Box 1 Hard applications

Supramolecular chemistry has always been associated with new materials and applications. Chemistry is driven by the desire for new functions, with the study of structure as a necessary first step towards the achievement of that goal. Ideally, useful materials would be designed by taking a single molecule and 'sticking it' to others of its kind to form three-dimensional assemblies. Implied in such a strategy is the ability to fine-tune function without necessarily disturbing structure. Accordingly, the total synthesis of a useful material can be dissected into molecular and supramolecular components. Traditional organic chemistry already provides all the necessary technology for the synthesis of the molecular building blocks. Supramolecular synthesis, which requires manipulation of intermolecular interactions, is still evolving.

Most solid-state devices, such as electronics, require a degree of order that is only possible with crystalline materials. Unlike porous materials, crystals have densely packed molecules and any chemical change is likely to destroy the crystal and its properties. But organoplatinum molecules have successfully been engineered to make a crystalline material that reversibly binds sulphur dioxide (SO_2) gas[18]. When the colourless organoplatinum crystals are bathed in SO_2 they turn bright orange and their total volume increases by about a quarter, but the crystals remain perfectly ordered. The SO_2 can be absorbed and expelled many times without loss of crystallinity. Part of the reason for this remarkable behaviour is that the crystalline framework is held together by supramolecular interactions — a string of hydrogen bonds — which can more easily tolerate such deformation. These organoplatinum crystals might find use as a gas-storage device, a sensor or even as an optical switch.

Nanocrystalline materials with ultrafine grains are potentially useful in molecular-scale electronics as magnetic[19], semiconducting, dielectric and ferroelectric materials. Part of the problem chemists have with molecule-based systems is connecting them to the macroscopic world. One approach is to modify a nanocrystalline surface with supramolecular components. For example, a ruthenium complex bound to nanocrystalline titanium dioxide gives a supramolecular structure that undergoes photochemically driven electron- and energy-transfer processes. This makes them attractive materials for use in solar cells[20]. Supramolecular aggregates of organic molecules have also been used to make molecular switches, whose conductivity is controlled by the chemical state of the molecule. Chemical sensors based on such switches could in theory be used to detect individual molecules of a pollutant. **G.R.D.**

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involve partially charged atoms, such as nitrogen, oxygen, chlorine, phosphorus and sulphur.

Isotropic interactions include van der Waals forces, which act between all atoms and molecules. These can be repulsive or attractive depending on the distance between the interacting non-bonded atoms, and are responsible for gross supramolecular arrangements. Although these forces are individually weak — they have bond energies of 8 kJ mol^{-1} compared with the 400 kJ mol^{-1} of covalent bonds — they become significant when considered in numbers. This is the essence of supramolecular thinking. The remarkable ability of the house lizard to stick to a ceiling is a result of millions of van der Waals interactions formed by the spatulae at the ends of fine hairs that cover the soles of its feet[6].

Although at a simple level molecular recognition can be said to hinge on isotropic interactions, at a higher level it is an anisotropic interaction that is the master key: the hydrogen bond[7]. In any hydrogen bond, X–H···A, a hydrogen atom acts as a bridge between two atoms X and A. These atoms always tend to be negatively charged (electronegative), which gives the hydrogen bond an electrostatic character, as the electropositive hydrogen atom holds the negative atoms in thrall.

If X and A are both quite electronegative, for example in N–H···O, the hydrogen bond is 'strong' or 'conventional' (20–40 kJ mol^{-1}). But if either or both X and A are of moderate to weak electronegativity, such as in C–H···O, the hydrogen bond is 'weak' or 'non-conventional' (2–20 kJ mol^{-1})[8]. In some systems, such as those involving the HF_2^- ion, the strength of the hydrogen bonds can reach quasi-covalent levels (170 kJ mol^{-1}). Hydrogen bonds can also form between more than two atoms. The importance of hydrogen bonds that are formed with double and triple bonds, such as C=C and C≡C, is increasingly being recognized. For example, hydrogen bonds formed by groups such as OH, NH and CH with the double bonds in aromatic rings are recognized as being key in the stabilization of biomolecular structures[9].

In general, the hydrogen bond is a composite interaction, which can have pronounced covalent, electrostatic or van der Waals components and consequently spans a wide energy range. The strength of interaction dictates the length and orientation of the hydrogen bond: short, linear bonds are almost always the strongest. But even weak bonds can be significant. Weak interactions tend to be hydrophobic, so they can persist in ionic solvents better than stronger hydrogen bonds.

Predicting supramolecular structures is hard, not only because of the sheer numbers of possible interactions involved, but also because in energetic terms there is not much to choose between these various interactions. If one interaction is not much more energetically favourable than the others, then there is no clear winner to predict. The challenge for the supramolecular chemist attempting to synthesize these structures is to ensure that the molecules involved are oriented in such a way that maximizes the strength of the desired interactions. Two examples of instances where intermolecular interactions are crucial are crystal engineering and crystallization.

Crystal engineering

Organic crystals are supramolecular entities in that they are built from molecules. In crystal engineering, the supramolecular chemist aims to design and control packing arrangements to design crystals with specific properties. But this is not routinely possible from knowledge of the molecular structure alone. The best chemists can do is to find recurring packing patterns adopted by certain functional groups and rely on the robustness of such motifs to create new solid-state structures. These small repetitive units are called supramolecular synthons[10]. They economically but fully define the essence of a structure, and embody specific intermolecular interactions (Fig. 2). Repetition is what qualifies a structural motif to be considered a synthon and it is repetition that is the key to successful crystal engineering.

Even after identifying an important intermolecular interaction, failure to predict a crystal structure can arise because the same interaction can be used to make many different synthons. For example, the carboxyl group (CO_2H) usually assembles in crystals via pairs of O–H···O hydrogen bonds[11]. But in cubane acids, the carboxyls form a synthon containing both O–H···O and C–H···O interactions (Fig. 3, overleaf).

Crystal engineering is shifting its focus from devising structures to designing properties. Property design can only follow from structure and our understanding of the principles by which molecules assemble into crystals is still rudimentary. Chemists are trying various computational and experimental approaches towards crystal design. And the synthon concept tries to simplify what is essentially a very difficult problem. But even with apparently straightforward synthons, things can go wrong.

In coordination polymers, for example, the relatively strong coordinate bonds (a type of covalent bond) between organic molecules and metal atoms are used to generate a solid network. This approach offers greater structural repetition because the coordinate bonds have both strength and explicit geometries. The first metal–organic networks were developed to mimic zeolites — microporous materials used for catalysis and separation processes. But even these seemingly reliable synthons failed when the packing density was low — more often than not the porous structure was unstable to collapse. The latest generation of open networks, which use a dicarboxylate linker to help stabilize the structure, can survive the loss or exchange of guest molecules[12].

Crystallization of molecules in solution is also a supramolecular process. Like other chemical reactions, it is governed by thermodynamic and kinetic factors. In molecular chemistry, pure energy considerations — enthalpy — are usually the decisive factor, so chemists only have to worry about identifying the strongest and weakest bonds, because they usually want to make the strongest

Box 2 Soft solutions

On the softer, non-crystalline side of supramolecular chemistry, desirable properties include solubility and chirality (molecular asymmetry). For example, a water-soluble polyfullerene has been synthesized using supramolecular methodology[21]. The reactants are prearranged in the cavity of a cyclodextrin, a container molecule, and then the polymerization is carried out. Potential biomedical applications of this supramolecular polymer follow from the fact that it scavenges the natural 'free radical', 1,1-diphenyl-2-picrylhydrazyl, more strongly than C_{60} itself, and that it cleaves DNA oligonucleotides in the presence of light.

Hydrogen-bonded systems often display chirality at the supramolecular level. Chemists want to control chirality so that supramolecular products are purely left- or right-handed isomers, and not a mixture of both. Supramolecular structures can now be designed to form sufficiently stable hydrogen bonds that pure-handed isomeric assemblies can be isolated[22]. The efficacy of drugs that are administered in crystalline form as fine powders can depend strongly on whether they have the correct isomeric structure and also the correct polymorphic structure.

Polymorphism is when a given molecule can exist in different crystalline forms, which are stable under different conditions. Polymorphs can therefore be thought of as supramolecular isomers, species in which the relative positioning of the same molecules is different. Polymorphs of a drug can have quite different properties. Their solubilities can be different, as well as their biological activity. In some cases, the less stable form will crystallize first, and then slowly transform, over time, into the more stable crystal. This can be a problem if the active form of a drug is the less stable polymorph, and turns into the more stable — but less active and perhaps even harmful — form during storage. In this context, can one design a molecule that is guaranteed to crystallize in a particular polymorphic form under physiological conditions? This is now a supramolecular challenge for the pharmaceutical industry. **G.R.D.**

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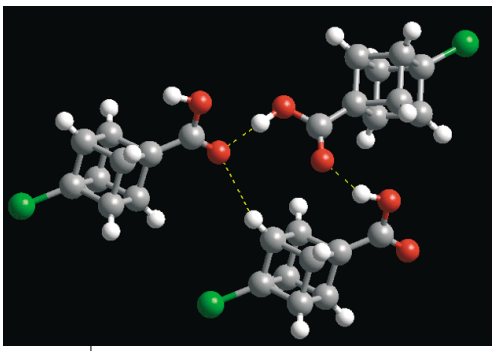

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Figure 3 **In many cubane acids, the carboxyl groups (CO_2H) form a synthon based on extended O–H···O and C–H···O bonds. In 4-bromocubanecarboxylic acid, for example, the C–H···O hydrogen bond provides the overall synthon with additional support[11]. It is thought that without this interaction, the exotic topology could not be realized.**

bonds and break the weakest. But in supramolecular chemistry, there are so many possible interactions that you have to consider both the enthalpy and entropy (disorder) inherent in every interaction. It is surprising, then, that although putative crystal structures can be similar in terms of energy, many organic molecules yield only one crystal structure under given conditions. Molecules seem to know how to crystallize into the correct structure, even if chemists cannot predict it.

Crystallization is a complex but highly efficient process in which a number of molecular groups compete with each other to be sites for intermolecular interactions that might lead to a stable crystal structure. Before the earliest stage of crystallization — known as nucleation — all molecular groups present in the solution try out different possible routes to alternative intermolecular interactions. But only a few of these interactions will be thermodynamically, kinetically or statistically sustained. The stable interactions lead to robust synthons and alternative possibilities are quickly and efficiently excluded. In this respect, there are similarities between the crystallization of a small organic molecule and the folding of a protein. Both proceed through intermediate, structure-determining clusters, resulting in a considerable increase in crystallization or folding efficiency.

A fascinating example of such a mechanism is provided by molybdenum chemistry. Molybdenum can form giant molecular clusters or rings with nanometre-sized cavities. Addition of two Mo_{36} 'hub-caps' to the wheel-like Mo_{176} cluster results in a Mo_{248} cluster[13]. The hub-caps are not stable in solution, showing that crystallization can proceed in steps, with complex structures forming from more simple ones that are not necessarily stable on their own.

Similarly, solvation — roughly the opposite to crystallization — is a phenomenon in which the enthalpic advantage of retaining solvent in a crystal outweighs the entropic advantage of expelling it into the bulk solvent[14]. An understanding of crystallization is important for the development of supramolecular chemistry and crystal engineering; both experimental and computational approaches (molecular dynamics) are currently being used to tackle this exciting problem.

A study of the protein apoferritin recently provided the first ever observations of protein nucleation[15]. By using atomic force microscopy, tiny clusters of apoferritin can be watched as they slowly grow or dissolve. Protein crystallization is more an art than a science, yet it is vital for determining protein structure.

A quiet revolution

Almost unobtrusively, chemistry is changing from a subject to a language that is needed to communicate core issues in biological and materials science. This change will surely lead to striking and unexpected practical applications, and supramolecular chemistry is at the vanguard (Boxes 1 and 2). Stephen Lippard recently made a 'wish list' for chemistry that represents this change[16]. Beyond what I have already discussed here, new goals for supramolecular chemistry include building porous structures — clathrates or coordination compounds — that have internal sites for catalysis, and designing solid-state reactions that are environmentally friendly because they are solvent free.

So far, the success stories include one published on page 452 of this issue[17]. The authors of this paper have created supramolecular nanotubes that have important biological activity *in vivo* (Fig. 4). By synthesizing cyclic peptides consisting of alternating D- and L-amino acids, a synthon that self-assembles into a nanotube is created. The resulting nanotubes have selective antibacterial activity in mice by increasing the permeability of bacterial membranes. They are highly effective against drug-resistant bacteria, highlighting the advantages of a non-biological treatments over conventional ones.

Friedrich Wöhler's synthesis of urea in 1828, the first laboratory synthesis of a naturally occurring compound, symbolized the end of the vitalistic approach to chemistry — the idea that living organisms differ from non-living substances because they possess a 'vital force'. But with the arrival of Emil Fischer and supramolecular chemistry, chemists are now more than ever concerned with the transition from chemistry to biology. How do life processes work? The fantastic levels of specificity achieved by biological machines may be reduced to weak interactions, to chemical recognition and function, and inexorably down to physics itself. Yet, a reductionist approach is simplistic beyond the extreme. A scientifically more acceptable view of vitalism is that living and non-living matter differ not in content but rather in organizational complexity — and our understanding of this theme may well turn out to be the biggest breakthrough in supramolecular science. ■

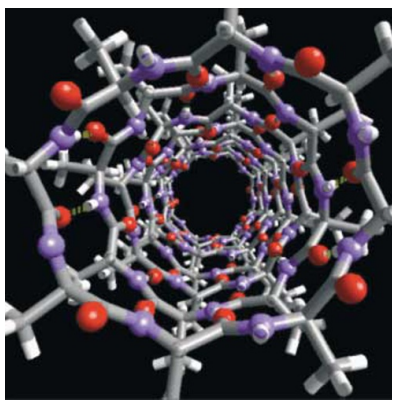

Figure 4 **Supramolecular approach to a biological problem. Cyclic peptides with alternating D- and L-amino acids create a flat, ring-shaped synthon. When several cyclic peptides are stacked together they can self-assemble into a stable nanotube. The walls of the tube are β-pleated sheets. In mice, these nanotubes have selective antibacterial activity by increasing the permeability of bacterial membranes[17]. (The structure shown here features different side groups from those used by Fernandez-Lopez *et al.* in ref. 17.)**

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