One of the most efficient of many approaches to the enantioselective preparation of a small molecule is to use a catalyst that is itself chiral, usually comprising a chiral group, or ligand, bound to a central metal atom. But chemists' ability to predict the structure of a ligand that will help to synthesize a product with high enantioselectivity is limited. This is because the difference in the size of the energy barriers that must be overcome to form each enantiomer — even in substantially different amounts — is typically small relative to the size of the barriers. In practice, ligands are often tested by trial and error. Unfortunately, the selective synthesis of one enantiomer of a ligand is itself challenging, and the synthesis of a series of such ligands is usually the slowest step in the development of enantioselective catalysts. Progress therefore depends on the improved ability to control small differences in energy, on developing better methods to produce single enantiomers of chiral ligands, or on developing approaches that bypass, at least partially, the need to produce sophisticated chiral ligands.

Consequently, the focus of some efforts to design enantioselective catalysts has in recent years shifted away from chiral ligands and towards achiral ligands. These ligands are either bound to the central metal atom of the catalyst, like a chiral ligand, or can adopt a chiral arrangement at the appropriate stage in the catalytic cycle (for a review of these developments, see refs 5, 6). Such approaches in effect subdivide the catalyst's structure, and allow pieces of the catalyst to be varied in a modular fashion, instead of varying portions of whole molecules that must be made one at a time.

Several years ago, Walsh and co-workers demonstrated that zinc complexes containing both an achiral and a chiral ligand react with higher enantioselectivity, and at higher rates, than do complexes containing only the chiral ligand[7–9]. Varying the size and shape of the achiral catalyst components — much as one might vary the shape and size of the (achiral) fingers on a (chiral) hand to accomplish an intricate physical task — leads to large swings in the excess of one enantiomer product over the other. It can even cause the enantiomer formed using the same combination of zinc and chiral ligand to switch from left-handed to right-handed, or vice versa. Even higher enantioselectivity has been demonstrated by reactions conducted with zinc binolate complexes in combination with a ligand that is achiral when free from the zinc, but chiral when bound[8]. Such combinations of chiral and achiral ligands should allow the rapid, parallel synthesis of families of potentially enantioselective catalysts.

These techniques have now been used[10–12] to develop catalysts for hydrogenation, the most common class of reaction for preparing single-enantiomer drugs. Rhodium complexes bound by two separate chiral ligands catalyse hydrogenation reactions with enantioselectivities rivalling those achieved by catalysts comprising two ligands tethered together. Significantly for practical applications, derivatives of these new catalysts can be prepared simply by mixing two different chiral ligands, or a chiral and an achiral ligand, with the rhodium catalyst precursor.

In a similar vein to the work[7–9] on zinc complexes, Reetz and Li[3], writing in *Angewandte Chemie International Edition*, investigate the formation of catalysts that combine a variety of phosphorus-based chiral and achiral ligands. In the same journal, Feringa and colleagues (Hoen *et al.*)[4] focus on a combination of chiral phosphoramidite and achiral tertiary phosphine ligands. Both groups find that, as with zinc complexes, enantioselectivity is in some cases higher in the presence of achiral ligands than in their absence.

Reetz and Li[3] take this design further by combining a single enantiomer of a chiral phosphite ligand with a second phosphite that is an equal, 'racemic' mixture of two enantiomeric conformations when free in solution. They find that the single enantiomer of one chiral phosphite can dictate the chiral configuration of the second phosphite; the combination of these two ligands can then preferentially form one enantiomer of the reaction product. The authors use this process to generate chiral amines, which are substructures of a host of pharmaceutical candidates, from hydrogenation of an enamide, with high enantioselectivity.

Although the focus on varying both chiral and achiral ligands is new, it borrows from the first successes in enantioselective catalysis. There, the enantioselectivity of a catalyst was generally controlled by varying achiral component groups, such as flat benzene-like aromatic rings, in a chiral ligand. The array of aromatic rings created a chiral object, much as flat propellers — themselves symmetrical and superimposable (and so achiral) — combine to form a symmetrical, but non-superimposable (chiral) object such as a ceiling fan. The size and the shape of these aromatic propeller blades affect the chiral structure of the metal active site and so the enantioselectivity of the catalyst.

The developments outlined here[3,4,7–9], and others[11], which combine a chiral ligand with a second achiral ligand, developed out of attempts to avoid the laborious and time-consuming nature of the sequential modification of these achiral groups. This simplified approach to preparing catalysts for enantioselective chemistry significantly increases the number of catalysts that can be tested. The chances of discovering highly enantioselective catalysts for useful chemical reactions — including those for developing new drugs — are thus vastly increased. ■

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TECHNIQUES

Imaging at a distance

Siegfried Stapf

Magnetic resonance imaging is often limited by the need to encode information and acquire the resonance signals in less-than-ideal locations. Performing these two steps at different places provides a solution.

Nuclear magnetic resonance (NMR) is an outstandingly versatile technique, used across the sciences. The basic principles — manipulating the nuclear spins of atoms in a sample by means of radio waves and magnetic fields, and recording the resonance signal obtained — can be applied to provide information in such disparate fields as chemistry and medical diagnostics. Yet the method has its limitations, leaving scope for further innovation. One such advance, reported in *Physical Review Letters*[1], stems from the work of Pines and colleagues.

The problem they have tackled is that of obtaining sharp images of fluid flow inside a rock. Studies of this kind of sample are limited by the many interfaces and, in some cases, the metal content of natural rocks, which bend the applied magnetic field and blur the magnetic resonance image. NMR is used in oilfield prospecting and provides valuable

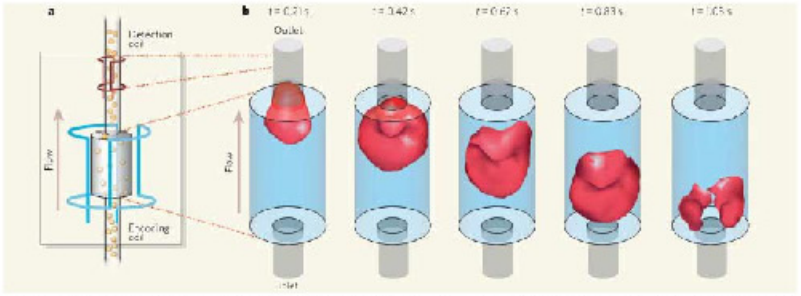

Figure 1 | Remote-detection NMR. a, In this approach, the first step (excitation of spins in the sample by the encoding coil) is separated in space from the second step (detection of the resonance signal in the detector coil). **b**, Results from an experiment on a rock sample[1]. Following spin manipulation of the gas mixture inside the entire 38-mm-long sample, spin-density images (red) were acquired at different time delays at the remote detector downstream from the sample's end. Short delays indicate molecules close to the sample outlet; increasing delays bring those from near the inlet into view. In this way, the pattern of fluid residence times, and heterogeneities owing to fractures or isolated pores, can be deduced. (Figure modified from ref. 1.)

information about the oil and water content of rocks. But taking a closer look at the fluid distribution remains a difficult task, even under laboratory conditions.

Similar obstacles dog the application of NMR to samples that are very large, very small or highly diluted, and researchers have long tried to adapt their hardware to cope with the field distortions induced by such samples. Pines and colleagues[2] have previously questioned the view that the whole NMR procedure needs to take place in one location. They aimed at obtaining a sharper view of the object under study by the counterintuitive approach of moving away from it. The two steps of manipulating the spins and acquiring the resonance signal are usually combined in the NMR apparatus, but in the authors' 'remote-detection' approach they are separated not only in time, but also in space. Excitation of the spins occurs at one place and the signal is collected at a different location, with magnetic fields and detectors independently optimized in the two steps to maximize signal quality (Fig. 1a).

For their latest work[1], Pines and colleagues joined forces with researchers at Schlumberger–Doll, a company that provides technical advice and NMR hardware for the oil industry. The sample they used was a small cylinder of sandstone rock, 20 mm in diameter and 38 mm long, and the test fluid was a gas mixture that included the isotope xenon-129. In the first stage of the procedure, the nuclear spins in the gas were manipulated inside the encoding coil by a combination of radio-frequency pulses and varying magnetic-field gradients. As a result, the gas had a 'memory' of its position at the time of spin encoding. In the second step, fluid flow carried the gas through the sample and then past a small, highly sensitive detector coil, where the stored NMR information was collected.

Notably, the authors modified their original concept by exploiting the information contained in the travelling time to the detector. Each image acquired with a particular delay provides a snapshot of the fluid distribution at the corresponding instant (Fig. 1b). The molecules closest to the sample outlet are the first to pass the detector coil; by contrast, those trapped in dead-end rock pores remain undetected, and so heterogeneities in the pore space can be identified.

The ultimate goal of this particular line of research is to be able to perform such experiments in the field. By lowering an entire NMR spectrometer inside a small borehole, the residence-time distribution of a fluid inside the rock might identify pockets of oil that would be too costly to recover. So the technique could potentially provide more complete information than can be obtained by even a full three-dimensional rendering of the pore space. Problems to be overcome before this goal can be achieved include the small space available for the probe and the limited timeframe for executing the measurement while drilling. The currently used inside-out configuration for NMR — where the sample is outside the instrument — can be modified by Pines and colleagues' two-coil design so that the otherwise weak signal is 'concentrated' into a small and efficient receiver coil.

Although the experiment used gas as the test fluid, liquids could be used. However, xenon gas has the advantage of ensuring that the spin magnetization has a long enough lifetime to survive the transport process. Moreover, xenon-129 is extremely sensitive to its molecular environment[3] and its spin polarization can be boosted dramatically by optical methods[4], making it a popular tracer in NMR studies. The distributions and transport properties of gases, however, are notoriously difficult to detect by conventional approaches because of their low density, and here the two-coil design pays dividends because the gas can be collected outside the sample.

The concept of remote detection is being explored further, opening up other possibilities. For instance, combining NMR with advanced spin-detection technologies, such as using superconducting quantum interference devices, or SQUIDs[5,6], becomes feasible. Such a prospect had previously seemed unpromising because of the restrictions of conventional NMR conditions. More achievable applications might exploit the advantages of small magnetic fields for the encoding step[7]; even Earth's weak magnetic field can suffice[7], because magnetic couplings between nuclei are independent of field strength and become the dominant source of information about molecular structure in small external fields.

Finally, NMR remote detection has promising applications in chemical engineering. Here, the same issue of the imaging of flow through tiny channels occurs in the microreactors used in fine chemical synthesis. Recently, Pines and colleagues have monitored fluid residence times inside a microreactor, and find that the remote-detection approach might well be used to optimize transport and reaction efficiency in such microstructured devices[8]. ■

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