

between artificial membranes, indicating that it can release ceramide at an acceptor membrane. Third, the G67E mutation (which renders CERT defective in the LY-A mutant cells) is found in the PH domain, and this mutation prevents CERT from binding to the Golgi — suggesting that targeting to the Golgi is important for CERT function. Finally, wild-type CERT can be added back to LY-A extracts to restore ceramide transport *in vitro*, and this activity is lost if any one of the START, PH or FFAT domains is deleted.

So, a clear model emerges in which CERT carries ceramide across the cytosol by binding to VAP on the ER, extracting a ceramide molecule, and then binding to the Golgi (Fig. 1b). As always, however, several questions remain. For instance, the cell must ensure that ceramide is moved from the ER to the Golgi but not back again, and it is not clear whether this directionality is provided simply by the ceramide's being made in the ER and then, on arrival in the Golgi, being converted to sphingomyelin (which is not a substrate for CERT). Another issue is why the *in vitro* transport assay requires ATP⁵. This molecule, as well as being the main cellular energy store, also supplies phosphate groups for protein and lipid modification. The Golgi-specific PH domains bind to the membrane lipid phosphatidylinositol-4-phosphate⁷, so perhaps ATP is required for producing this lipid. But it may also be that the cycle of ceramide binding and release is regulated by phosphorylation.

These detailed issues aside, the discovery of CERT also has broader implications for the cell biology of lipids. As noted above, there are several well-conserved eukaryotic proteins that have FFAT or Golgi-specific PH domains, and in some cases putative lipid-binding domains^{8,9}. These proteins' functions are unclear, but they are clearly excellent candidates for transporting other lipids between organelles. Moreover, ceramide has been suggested to have an additional role in transmitting signals into the cell from the plasma membrane¹⁰. So ceramide transport to intracellular organelles might be important in attenuating these signal-transduction processes. Finally, the presence in CERT and in other proteins of targeting domains for more than one organelle raises the possibility that these proteins might not simply be shuttles. Instead, they could actually form physical bridges between organelles, with rapid transport mediated by oscillation of the lipid-binding domains (Fig. 1c)⁸.

There is still much to be learnt about the non-vesicular movement of lipids between membranes, but Hanada and colleagues' elegant combination of cell biology and lipid biochemistry has provided much food for thought. ■

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Organic chemistry

Aromatics do the twist

David M. Lemal

For nearly 40 years, organic chemists have been fascinated by the idea of aromatic molecules that have the topology of a Möbius strip. No such molecule has been isolated — until now.

The first example of a Möbius aromatic molecule to be synthesized and isolated is described by Ajami *et al.*¹ on page 819 of this issue. Although topologies resembling a Möbius strip (Fig. 1) are not unknown in chemistry, a stable aromatic molecule with this configuration had escaped fabrication because the obligatory twist could always be circumvented by a change in shape of the molecule. The authors have overcome this difficulty by assembling their molecule from two fragments, one of which was rigidly constructed in such a way as to enforce a twist when it was linked to the other.

To an organic chemist, an aromatic molecule is one that resembles the famous benzene molecule. This odd meaning for the description 'aromatic' came about early in the history of organic chemistry when it was discovered that certain derivatives of benzene have pleasant odours — wintergreen, anise, almond and cinnamon are examples. The benzene molecule consists of a planar, cyclic array of six CH fragments, each carbon atom contributing a *p*-type atomic orbital bearing one electron to a so-called π -system (Fig. 2a). This loop of overlapping *p* orbitals, in which the six electrons move freely, contributes much to the bonding in the ring, making the benzene ring a robust structural element that is present in myriad drugs, dyes, foods and plastics, as well as in all living systems.

In the 1930s Erich Hückel realized^{2,3}, with the help of quantum mechanics, that cyclic systems containing $4n+2$ π -electrons, where n is an integer, should be relatively stable — so not just 6-electron systems, but those with 2, 6, 10 or 14 electrons, and so on. His insight stimulated intensive research, beginning in the 1950s, that resulted in the creation of many such ring systems and the confirmation of their resemblance to benzene. In contrast, cyclic π -systems with $4n$ electrons (4, 8,



Figure 1 *Möbius Strip II* by M. C. Escher. The red ants marching along the surface of the twisted loop show that the Möbius strip has a single continuous surface — a topology that has now been realized in an aromatic compound by Ajami *et al.*¹. (M. C. Escher's "Moebius Strip II" © 2003 Cordon Art B. V. – Barn – Holland. All rights reserved.)

12, 16 and so on) were found to be either highly unstable or, at best, lacking the special stability of $4n+2$ compounds. Stability is an important criterion for aromaticity, but a variety of other measures, such as equivalence of bond length and magnetic properties, are also used to detect and quantify it⁴.

In 1964, not long after the first large annulenes (hydrocarbons with cyclic π -systems) had been synthesized, Edgar Heilbronner began to wonder about their π -orbital topology. He suggested that rings of about 20 members or more could incorporate a 180° twist without being strained: the π -system would assume the topology of a Möbius band⁵ (Fig. 2b). The cyclic π -systems known at that time could be represented schematically by a circular band with two sides and two edges, but the twisted Möbius band would have just a single surface and a single edge.

Heilbronner used simple quantum mechanical methods to predict the properties of Möbius π -systems. He concluded that, although the half-twist strongly destabilized $4n+2$ π -systems, $4n$ systems were actually stabilized, if the weakening effect of diminished π -orbital overlap caused by the twist were ignored. In his calculations, these two effects in $4n$ systems exactly cancelled, so the topological switch from simple loop to Möbius strip would leave the system unchanged in energy. Thus, there seemed to be no driving force that would encourage annulenes to twist, and many chemists may have regarded Heilbronner's imaginative insight as just an interesting academic curiosity.

Two years later, however, an important application of Heilbronner's idea was discovered. There is a large and important family of organic transformations called pericyclic reactions that proceed via a cyclic array of overlapping orbitals. For many of these reactions, two different orbital topologies for their (transient) transition states are geometrically feasible, leading to different products. The two topologies, it was realized^{6,7}, are Hückel (like benzene) and Möbius, and the observed product can be correctly predicted from the number of electrons in the cycle, $4n$ or $4n+2$. That number determines which topology enjoys aromatic character and thus which pathway requires less energy to traverse. Here the topologically different orbital arrays suffer a comparable amount of twisting, so the Möbius array is not energetically disadvantaged. Although nearly all textbooks of organic chemistry analyse pericyclic reactions in other terms⁸, the concept of Hückel and Möbius aromaticity offers a particularly simple, clear way of understanding them that is broadly applicable.

In recent years theoretical calculations more sophisticated than were possible when Heilbronner published his findings have

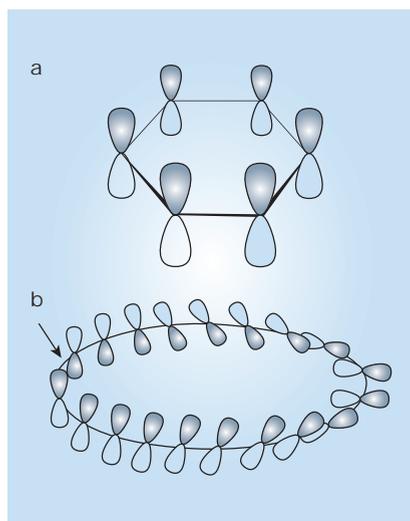


Figure 2 Twist in the tale. a, The π -system of benzene. The lobes represent the p orbitals contributed by each carbon atom. b, A hypothetical Möbius π -system. The arrow indicates the node that results from the 180° twist.

revealed that a variety of hydrocarbons with cyclic π -systems can assume Möbius conformations with aromatic character. As Ajami *et al.*¹ note, however, in every case but one the Möbius species are calculated to be less stable than others; the exception is a short-lived hydrocarbon ion that has not been directly observed. The challenge of creating a stable, isolable Möbius aromatic molecule has not

been easy. But Ajami *et al.* have accomplished that feat. A key feature of their design is a rigid structure incorporating a linear array of overlapping p orbitals, the end orbitals of which are forced to lie in a plane. To connect these termini to a second flexible p -orbital array requires the introduction of a twist. The twist takes three different forms, giving rise to three different Möbius structures, one of which has both Möbius topology and aromatic character.

Cleverly designed as it is, Ajami and colleagues' molecule does have some structural features that limit its aromaticity (orbital pyramidalization, benzo substitution and larger-than-optimal twist angles). But the fact that the authors have quite convincingly detected aromaticity in this molecule suggests that, in the future, Möbius molecules will be synthesized whose aromatic character far exceeds Heilbronner's modest expectations. ■

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Biomechanics

Early birds surmount steep slopes

John R. Hutchinson

Even before they can fly, some young birds can run up vertical surfaces by using their wingbeats to add traction to their legs. Such behaviour may be relevant to understanding the origin of avian flight.

Birds, of course, typically use their wings to lift, then propel themselves through the air, and their legs to move on the ground. So the recent news that birds can use both sets of appendages together to scale inclined surfaces came as a surprise. The story began in 2001, with Terry Dial, 15-year-old son of Ken Dial of the University of Montana–Missoula Flight Laboratory. Dial junior noticed an unusual behaviour among the Flight Lab birds: he saw that some partridges could run up near-vertical surfaces, and that they seemed to use their flapping forelimbs (wings) and loping legs to do so.

The upshot was a study by Ken Dial¹, published in *Science* earlier this year, presenting evidence that chukar partridges (and three other close relatives of chickens) use their

wings much like the spoiler on an Indy 500 racer. The effect is to increase the load on their hindlimbs. In this way they can improve traction to get themselves up steep ascents. Dial dubbed this behaviour wing-assisted incline running (WAIR). He showed that the maximum slope the birds could traverse increased with age, wing feathering and surface friction. He also found that birds with full wings were able to use WAIR beyond the vertical, up to a slope of 105° , after which only free flight was viable. So without obvious specializations for climbing, ground birds could run straight up or even upside down. Not only was this a startling finding for those studying avian behaviour, natural history and flight biomechanics, but — as Dial argued¹ — it could tell us something about the evolution of flight.