A New Fundamental Type of Conformational Isomerism

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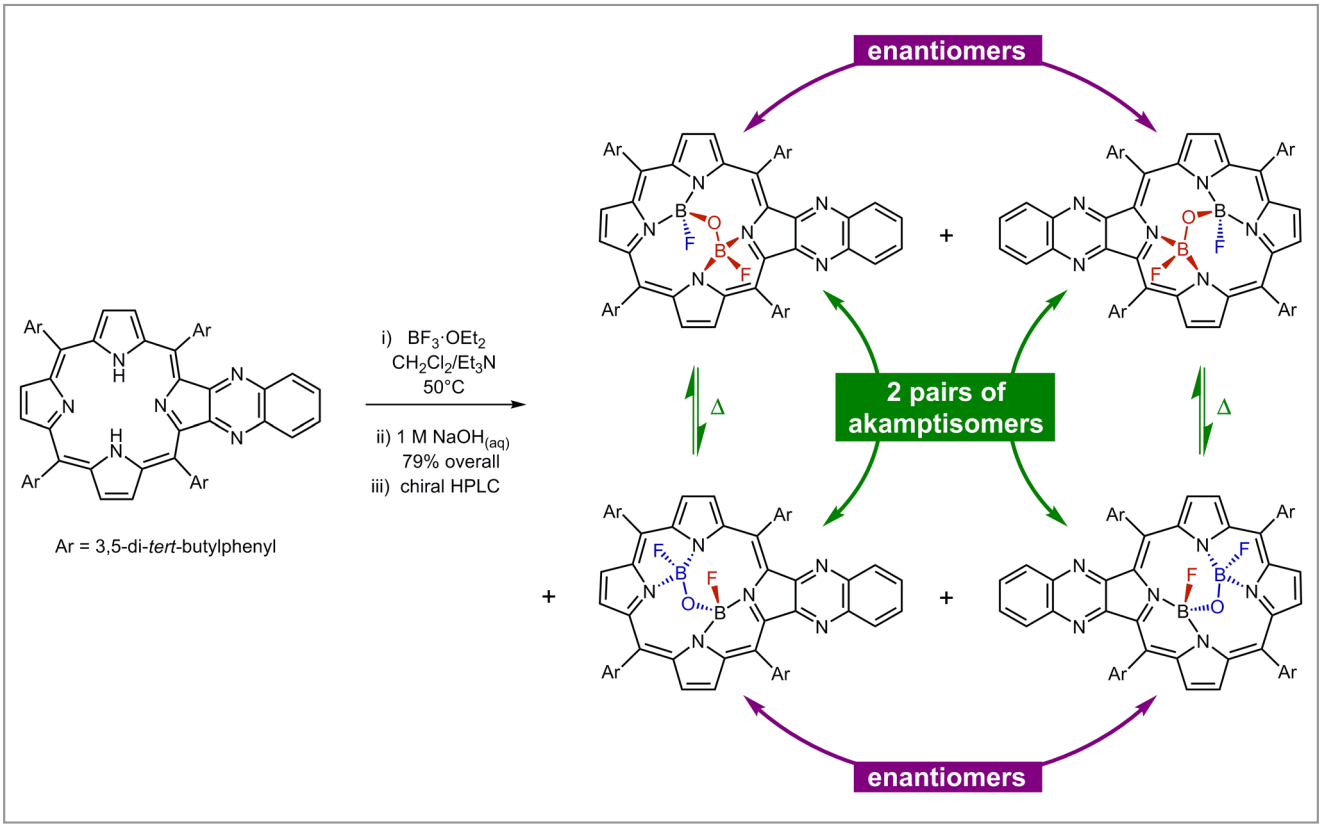
Isomerism plays a central role in modern chemistry and biochemistry. Its initial discovery in 1830 was followed by the revelation of chirality in 1848, the revelation of *cis–trans* isomerism about double bonds ca. 1890, the isolation of hindered rotamers about single bonds in 1914, and the isolation of hindered invertomers at pyramidal centres in 1961.

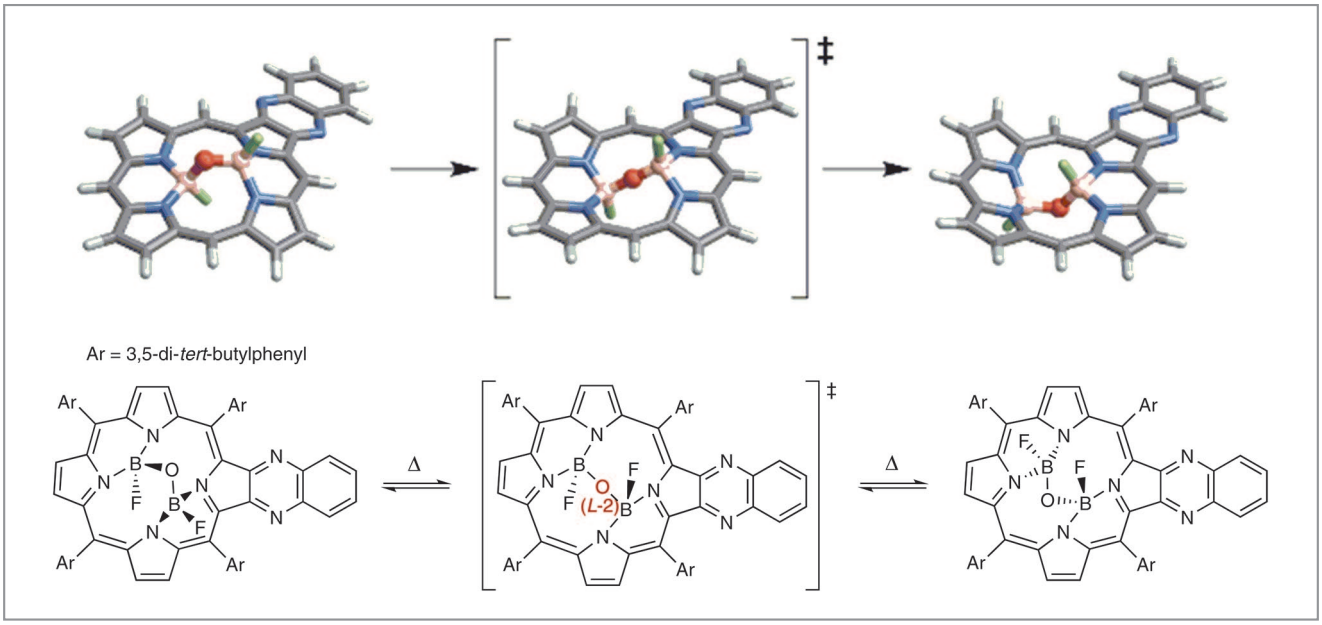
Now, in the latest issue of *Nature Chemistry*, Peter Canfield, University of Sydney (Australia) PhD candidate, his research supervisor Professor Maxwell Crossley (University of Sydney), co-supervisor Professor Jeffrey Reimers (University of Technology Sydney and Shanghai University, P. R. of China), and co-workers including Elmars Krausz and Rika Kobayashi (Australian National University) described a new, previously unclassified, fundamental form of conformational isomerism.

Professor Crossley said: "We performed a single 'BOFylation' reaction (a synthetic strategy developed by Penelope Brothers at The University of Auckland, New Zealand) on a free-base quinoxalinoporphyrin, yielding four chiral *transoid* B(F)OB(F)-quinoxalinoporphyrin products (see Scheme 1). When separated by chiral HPLC as enantiopure stereoisomers, we found them to slowly interconvert in a highly stereoselective way that could only be explained by a bond angle inversion (BAI) mechanism. Each reaction involved an intermediate featuring a linear B–O–B geometry as shown in Scheme 2."

Summarizing the results, Mr. Canfield noted: "I always expected four reaction products and knew of BAI as a *possible mechanism* for certain examples of *cis–trans* isomerism of a double bond. However, it came as a surprise that isolable compounds involving only single bonds (in the present case B–O



Scheme 1 Synthesis of the four chiral products showing their stereoisomeric relationships and pattern of unimolecular interconversion.



Scheme 2 Models depicting the bond angle inversion mechanism that converts between pairs of akamptisomers via the intermediate transition structure featuring a linear B–O–B geometry. For clarity, the models are of the *meso*-unsubstituted analogues.

bonds) distinguishable in this way had not previously been prepared. After all, the observed process just directly parallels rotamerism about single bonds and pyramidal invertomerism."

Rationalizing this, Professor Reimers explained: "The reason that compounds displaying this feature had not previously been isolated is that, in most molecules, rotation can happen about single bonds extremely quickly. Any BAI reaction can therefore normally be undone by Hula-twist rotations about the two involved bonds, making the reactants and products non-isolable conformational isomers. In the synthesised molecules, an external, low-symmetry porphyrin macrocycle encapsulates the reacting B–O–B system. This bounding macrocycle prevents rotation about the two B–O bonds, allowing unique configurational isomers to be isolated."

The original intent of the synthesis was to design molecules that would yield different spectra to those of normal porphyrins, with focuses on possible technological applications. Professor Krausz said: "We hoped the molecules would yield novel spectral properties so that we could learn more about how magnetic circular dichroism originates and its interpretation for porphyrins and chlorophylls. This is part of our ongoing collaboration on the electronic properties of porphyrins, which are ubiquitous in biochemistry." Dr. Kobayashi added: "My interest was in how well the density functional theory computational methods that I was developing would work given the anticipated high-quality data from Professor Krausz's lab."

"A comprehensive analysis of porphyrin substitution patterns in the context of conceivable isomerisation pathways revealed that the 2,3-disubstituted pattern gave us the simplest and therefore most elegant system with which to unequivocally demonstrate the anticipated phenomenon," said Mr. Canfield. Professor Crossley remarked: "Fortunately, my group has developed the quinoxalino[2,3-*b'*]porphyrin class (Schemes 1 and 2) for numerous applications, so we had the right in-house expertise." "And our long-standing collaboration meant we also had the theoretical tools in place that proved critical for assigning structures based on spectroscopic measurements," added Professor Reimers.

"However, it all worked out very different to expectations," continued Professor Reimers. "Some properties of the molecules were strikingly different to anything seen before. The compounds are soluble in almost everything but 100% water, making crystallization difficult and mounting crystals in X-ray spectrometers even more so. Then the spectra were not as distinctly characteristic as we expected, but we had to rely on them and the associated calculations, along with 2D NMR, to identify which isomer was which."

Focusing on the future, Professor Crossley noted: "In principle, many compounds showing the novel isomerism could be obtained. The essential features are an external environ-

ment such as a rigid macrocycle used to constrain BAI at some two-coordinate atom linked by only single bonds. Very many macrocycles, and very many reacting groups, could be combined in this way. It does not have to be a porphyrin, it does not have to be B–O–B."

Mr. Canfield emphasised "As Scheme 2 suggests, new isomers should have very different 3D structures. In the compounds synthesised, the fused quinoxalino group makes the porphyrin asymmetric. In this way the diastereomeric pairs of compounds related by BAI are different to each other. Through synthetic control of the asymmetry, the relative stability of the isomers can be adjusted. In a similar way, the barrier height to interconversion, measured at 104 kJ/mol for the BOFylated porphyrins, can be adjusted over a wide range through variation of the inner bridging species and through control of the macrocycle induced compression of this bridge."

Each author had their own reasons for making the molecules. The large differences in the shapes of the isomers would facilitate binding modulation for drug candidates, allow different electrical, magnetic, and optical properties for molecules used in functional materials and devices, and provide basic theoretical insight into chemistry and its spectroscopic techniques. The authors commented: "We believe that exploitation of the synthetic flexibility and accessibility of this new form of isomerism may lead to a wide range of new molecules and materials tailored for specific purposes."

Expounding on their possible pedagogical role, Professor Reimers noted: "The existing IUPAC naming rules are inadequate for the description of the new compounds and their reactions. Hence, we considered a wide range of conceptually feasible isomers using computational means, proposing definitions intended to be proven adequate for naming future compounds and processes."

The isomerism process was named "akamptisomerism", meaning "without bending", in direct analogy to the name "atropisomerism", which means "without turning", that is applied to name hindered rotamers. In addition, the new stereodescriptors "*parvo*" and "*amplo*" were introduced specifying the relationship between the host and its surrounding macrocycle, facilitating unique chemical names for akamptisomers.

"The conceptual basis for understanding akamptisomerism was already known," explained Mr. Canfield. He continued: "Historically, the discovery of new isomerism phenomena came about and was understood somewhat in isolation. Seeking an understanding of processes in complex systems like ML5 and those of higher coordination numbers, Muetterties introduced the geometric concept of polytopal rearrangements in the late 1960s. This unified previous discussions of isomerism and is now utilised by IUPAC as its central concept in classifying stereoisomerism. It was just that this rigorous mathematical approach to stereoisomerism had never been applied to the very simple case of BAI. Now all possible scenarios have been examined, indicating that there are no more fundamental forms of isomerism remaining to be discovered."

About the authors

P. J. Canfield

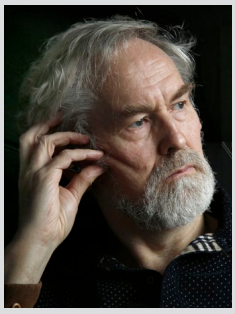
Peter J. Canfield was born in Sydney, Australia. Following an early interest in chemistry, he attended the first Australian Chemistry Olympiad in 1988. He received a BSc at the University of New South Wales (Australia), majoring in chemistry and physics and was awarded first class honours under the guidance of Prof. Michael Paddon-Row in 1994. Following several roles in the public and private sectors, in 2003 he commenced doctoral studies in quantum chemistry with Prof. Reimers at the University of Sydney (Australia). Deferring completion of his PhD, he took on a private sector role heading Research and Development for the aquaculture company, Jewelmer, based in the Philippines. Following time at Shanghai University (P.R. of China), he then returned to doctoral studies at the University of Sydney under the guidance of Prof. Crossley and Prof. Reimers. His research interests centre around the mechanistic underpinnings of chemical processes and how such understanding can be directly applied to beneficial, real-world applications. His latest venture involves the creation of a technology start-up company researching and exploiting the akamptisomerism phenomenon.

Prof. E. Krausz

Elmars Krausz graduated and received his PhD from the University of Sydney (Australia). He held positions at the Australian National University (Australia, 1971–1973, 1978), Oxford University (UK, 1974–1975), the University of Virginia (USA, 1976–1977), and the University of Sydney (Australia, 1979–1980) before being appointed as Research Fellow at the Research School of Chemistry at the Australian National University. He was awarded fellow of the Royal Australian Chemical Institute and was appointed Professor at the Research School of Chemistry in 2002. He is known for his roles in understanding electron-transfer spectroscopy (the "PKS model"), understanding energy capture and water splitting in natural photosynthesis, and the development of laser selective spectroscopies and many novel magnetic circular dichroism measurement and interpretation techniques.

Dr. R. Kobayashi

Rika Kobayashi was born in Sydney, Australia and graduated with a Bachelor of Science (Hons I) from the University of Sydney (Australia) in 1988. She obtained her PhD from the University of Cambridge (UK), under the supervision of Nicholas Handy, where she derived and implemented an analytic gradient for the Brueckner coupled cluster method. Subsequent work has primarily been in programming new methods in various software packages: coupled cluster and response properties in DALTON, the original CCSD(T) module in NWChem and the CAM-B3LYP density functional in Gaussian 09. Since 2001 she has been an Academic Consultant specialising in computational chemistry at the Australian National University Supercomputer Facility with main responsibilities being porting, maintaining and providing user support for a wide range of computational chemistry packages, particularly in the context of high-performance computing. Her research interests are focused around application of these methods to novel problems, recently together with Professor Jeffrey Reimers through the award of a foreign expert travel grant from Shanghai University.



Prof. J. R. Reimers

Jeffrey R. Reimers FAA, FRSN, FRACI studied organic spectroscopy under Ian Ross and Gad Fischer before completing a PhD with Robert Watts on the structure, thermodynamics, and spectroscopy of water and ice. He then studied semiclassical quantum mechanics in USA under Kent Wilson and Rick Heller before returning to Australia to be an ARC Research Fellow from 1985 to 2010 at the University of Sydney. There he collaborated extensively with Noel Hush and Max Crossley on problems involving electron transfer, molecular electronics, porphyrin chemistry, self-assembly, electronic-structure theory, and photosynthesis. In 2014 he moved to a joint appointment at University of Technology Sydney and Shanghai University (P. R. of China), focusing on basic chemistry and molecular electronics. His work spans a wide range of chemical applications, from biochemical function to electronic devices to the origins of consciousness. He has received the RACI Physical Chemistry Division Medal (2014) and the H.G. Smith Medal (2009), the

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About the authors

David Craig Medal of the Australian Academy of Science (2016), and the Shanghai Magnolia Medal (2017); he is a Fellow of the RACI (1999), the Royal Society of NSW (2017), and the Australian Academy of Science (2010).

Prof. M. J. Crossley

Maxwell J. Crossley FAA, FRSN, FRACI is currently Professor of Chemistry (Organic Chemistry) and University Professorial Fellow at The University of Sydney (Australia). He was educated at The University of Melbourne (Australia, Ph.D. advisor Professor Donald W. Cameron). Crossley then became a post-doctoral fellow at the Research Institute for Medicine and Chemistry in Cambridge, Massachusetts (USA) with Professor Sir Derek Barton FRS, then spent two years as a Research Associate at MIT in Cambridge, Massachusetts (USA) with Professor Jack E. Baldwin FRS. In 1978 he moved to Oxford University (UK) where he continued to work with Professor Baldwin and returned to Australia in 1980 as a Research Fellow at the University of Melbourne (Australia). Later that year he moved to Sydney where he has been based since. He has held visiting appointments at the University of Cambridge (UK), the University of Strasbourg (France), the University of Nijmegen (the Netherlands), Osaka University (Japan), and IPC, Chinese Academy of Sciences, Beijing (P.R. of China). Crossley is a Fellow of the Australian Academy of Science (elected 2001). He has received a number of accolades for his research excellence, including the Birch Medal (1998), the H.G. Smith Memorial Medal (2001), a Centenary Medal (2003), the David Craig Medal (2012), the Robert Burns Woodward Career Award (2012), and the Leighton Medal (2013). His main research interests are porphyrin chemistry, functional materials for applications including photochemical upconversion and optics, and molecular electronics.