A tribute to Philip Hodge: the integration of polymer chemistry and organic synthesis

Published on line 01-07-2021
Phil Hodge was born in Greater Manchester and spent his schooldays there, being awarded a Major Scholarship for University entrance in 1957. Manchester was one of the great cities of the Industrial Revolution, and from the mid-19th century onwards the city was full of self-belief. The establishment of a civic University started with the foundation of Owen’s College in 1851, originally in the centre of the city but moving, in 1873, about a mile further south to a site that is still the focal point of the modern University. In 1903 Owens College was reconstituted as the Victoria University of Manchester and over the next century became a major centre for the Sciences. It developed an international reputation in Chemistry, being associated with no fewer than nine Chemistry Nobel Prizewinners in the 20th century, including prizes awarded to former staff, postdoctoral fellows and postgraduate students. Hence, Phil did not need to look much further afield when applying to University. Like many local contemporaries, he probably considered that the reputation of his preferred course fully justified his choice of Manchester University. He was destined for a career in Organic Chemistry from the very outset. During undergraduate summer vacations he worked for Dr. Herchel Smith in the University’s research laboratories and later, as part of an organised Summer School, in UK pharmaceutical research. Phil graduated with First-class Honours, and chose to remain in Manchester for his PhD.

In 1957 Manchester appointed the distinguished Australian chemist Arthur J. Birch to the Chair of Organic Chemistry and he in turn appointed his young Sydney colleague, Rod Rickards, to a Lectureship. Phil joined their research group, working on a project based on novel pyrrole chemistry. He co-authored two full papers arising from his work with Rod Rickards\textsuperscript{1,2} and he also played a key part in solving the structure of the natural pyrrole-containing product pyoleuteorin, so completing a project that had been initiated by Arthur Birch in Sydney\textsuperscript{3}. Phil successfully submitted his PhD thesis in late 1963 and chose to conduct postdoctoral work with Sir Ewart Jones and Gordon Lowe in the Dyson Perrins laboratory, Oxford. Here he was supported by an SRC fellowship, and gained experience in a different area of natural product chemistry. Jones’s interests included polyacetylene chemistry, and a further joint publication arose from Phil’s input to this field\textsuperscript{4}. In addition, Phil later published an independent paper elucidating the biological oxidation pathway of the natural polyacetylene, dehydromatricaricaneol,\textsuperscript{5} Following his work in Oxford he spent a year in Palo Alto, CA, working with John Fried at the steroid-hormone specialist company Syntex, developing the diverse chemistry of difluorocarbene\textsuperscript{6,7}.

Early independent career
Given his strong record at this early stage he was appointed directly in late 1966 to a Lectureship at the newly established University of Lancaster, with the opportunity to forge an independent research career. Initially he continued in research related to natural products, with early publications including a full synthesis of pyoleuteorin, exploratory chemistry of quinones, and selective cleavage of non-enolisable aromatic ketones.\textsuperscript{8-10} These interests continued and developed over the ensuing years, but the first hints of his main future direction of research arose from work on aromatic ketones. He realised that their selective cleavage with strong base offered a useful synthetic route to aromatic carboxylic acids.\textsuperscript{11} This promised a valuable method for attaching functional groups to cross-linked polystyrene (PS) beads, including carboxylic acids and peracids. There was one related approach reported in the literature\textsuperscript{12}, but this led to explosive polymers! Using Phil’s chemistry, comparably functional polystyrenes could be prepared and used smoothly and uneventfully.\textsuperscript{13} Later on he made a further important contribution to the development of safe polymer reagents: functional polystyrenes, from Merrifield resin onwards, had been made by chloromethylation of terminal phenyl groups, using the carcinogen precursor, methyl chloromethyl ether. Phil discovered a safer route using a two-stage
procedure employing methoxyacetyl chloride that decarbonylates to the corresponding ether in situ, producing the key reagent without need for a hazardous isolation step.\textsuperscript{14}

Having realised the scope for a good organic chemist to work in the field of solid-supported chemistry, he subsequently made a series of distinctive contributions to the development of functional polystyrene beads as reagents or catalysts (Scheme 1), whilst continuing his natural products research. His objectives were clear – for a polymer-based reagent or catalyst to have an impact on organic synthesis, high levels of substitution with the reactive entity were needed. At that time the closest precedent was a route to formylated PS, but at <20% loading of the pendant aromatic rings.\textsuperscript{15} Phil systematically optimised methods that led to 75-87% loading, achieved via a high-yield chloromethylation of commercial PS beads in the initial step.\textsuperscript{16}

\begin{center}
\textbf{Scheme 1.} Routes to polystyrene-based peracids with high functionality (PSt signifies an accessible styrene residue)\textsuperscript{15,16}.
\end{center}

Phil’s first synthetic application of his high-loading functional polymers was the epoxidation of alkenes with PS-bound percarboxylic acids (Scheme 2a).\textsuperscript{17} His reagent was shown to be effective for 1,2-disubstituted alkenes for which the reaction was three times faster, and also higher-yielding, when compared with a soluble model peracid as reagent.\textsuperscript{18} The same PS reagent converted sulfides to sulfones, and with penicillins and cephalosporins a single sulfoxide of defined configuration was formed (Scheme 2a).\textsuperscript{19} As a notable innovation, this oxidation was performed under flow conditions, using slow passage of the dissolved reactant through a chromatography column packed with PS-percarboxylic acid beads. PS-Triphenylphosphine-was used as co-reactant with \textit{CCl}_4 to transform primary alcohols into alkyl chlorides, and carboxylic acids into the corresponding acid chlorides.\textsuperscript{20} Under similar conditions, carboxamides formed nitriles (Scheme 2b) and oximes formed imidoyl halides.\textsuperscript{21}

A further procedure that he developed involved PS-supported protecting groups for aldehydes and ketones.\textsuperscript{22,23} For example, a PS-supported diol was successfully used to protect the aldehyde group of undec-10-enal whilst the terminal vinyl group was transformed into –\textit{C}_2\text{H}_4\text{CH}_2\text{OCOPh}. 

\begin{center}
\textbf{Scheme 1.} Routes to polystyrene-based peracids with high functionality (PSt signifies an accessible styrene residue)\textsuperscript{15,16}.
\end{center}
Scheme 2. (a) Polystyrene-supported peracid as reagent; (b) Polystyrene-supported triarylphosphine as reagent.

Mid-career
Over the ensuing years his work on polymer-supported organic synthesis was extended, and rational mechanistic explanations for the results were sought. He showed that the periodate counteranion, when bound in a macroporous ion-exchange resin, was an efficient reagent for a range of oxidations of hydroquinols, 1,2-diols and sulphides. A related discovery demonstrated that solid sodium periodate fails to oxidise a variety of substrates in CH₂Cl₂ under standard conditions, but oxidation may be achieved using sodium periodate supported on silica gel. The promotional effect of the support was attributed to the reactivity of a surface-monolayer of periodate anions H-bonded to the silica gel. Phil's earlier work on organic halogenations was later augmented by general methods for bromination reactions, where two distinct methodologies gave good results. Para-bromination of the phenyl rings of crosslinked PS followed by reaction with Li/PPh₃ yielded a substituted ArPPh₂ polymer. Stoichoimetric reaction with Br₂ gave a hypervalent phosphine dibromide that was an effective reagent for conversion of alcohols into the corresponding alkyl bromides. Alternatively, in a further development of ref. 20, reaction of a carbonyl compound with CBr₄ or CCl₄ in the presence of PS-supported ArPPPh₂ gave rise to both vicinal and geminal dihaloalkenes – the latter the formal product of a Wittig ylid-type reaction. Polymers with different levels of cross-linking were examined, with the conclusion that those with low levels promoted the latter reaction whilst high levels led to failure. A novel mechanism involving intrapolymer halogen-transfer from the initial CX₃ adduct was indicated (Scheme 3). Phil examined variations of the arene structure in vinylarene polymerizations, and with poly(vinylthiophene) was able to add functionality directly to the polymer through lithiation and substitution. Using a polymer-based oxazaborolidine from norephedrine, as a recyclable catalyst for ketone reductions by Me₂S.BH₃, it was shown the enantiomeric excess in asymmetric reduction of prochiral ketones was comparable to that obtained with the parent oxazaborolidine, but with a more convenient workup step.
Scheme 3. Intra-polymer two-site halogen exchange; the pre- and post-reaction sites are in the same bead but not necessarily adjacent (refs 20,27).

Career progression
Phil's prominence in the emerging field of polymer-supported organic synthesis brought broad professional recognition. He developed a very fruitful collaboration with the late David Sherrington, resulting in two successful multi-author books, and he was co-author of David’s Biographical Memoir after his untimely death; prior to that he had overseen a 60th birthday tribute to David.30,31 The first of these, “Polymer-supported Reactions in Organic Synthesis” was published in 1980 by Wiley and described by a reviewer as “an excellent addition to the literature on the synthesis and the application of reactive polymers in Organic and Biochemistry”. The field advanced sufficiently rapidly that a second, similarly-structured book “Syntheses and Separations using Functional Polymers” was published in 1988, again by Wiley.32,33 From 1989 onwards, Phil was a Member of Council for the High Polymer Research Group, whose function lay in supporting annual conferences in the UK that attracted international leaders in the field of polymer science. Expertise that was important to both academia and industry made him a popular lecturer both in the UK and abroad, with > 250 presentations overall. He was in demand for consultancies and grant-awarding committees, and chaired the Innovative Polymer Initiative of EPSRC from 1991-1997.

Phil’s career development followed naturally. After earlier promotions, first to Senior Lecturer and then to Reader, he was awarded a Personal Chair by Lancaster University in 1986, and was then Head of Chemistry for three years. In 1989 he moved back to his Alma Mater as Professor of Polymer Chemistry at Manchester University, becoming Emeritus Professor in 2004. Whilst in Manchester he held Visiting Professorships in China, Japan, Australia and France. He was able to develop diverse collaborations with colleagues in other Manchester departments, and with polymer scientists worldwide. This broadened his range of publications to include, for example, polymeric Langmuir-Blodgett films where he was a co-author on over forty papers, and liquid crystals. In 1998 he received the RSC Medal and Prize for “Contributions to Polymer Chemistry”, and in 2004 he was the RSC/SCI Macro Group Gold Medallist for "Outstanding Achievement in Polymer Science". Through his membership of the IUPAC Polymer Group he was closely involved in defining the standard terminology and nomenclature of polymers and their precursors through a series of thirteen publications, before and after his formal retirement; see, for example, refs 34-36. He wrote several reviews in this period that summarised the state of the areas of Organic/Polymer Chemistry to which he had contributed, and in this way the extent and importance of his own contributions became part of the record. The two most significant reviews cover his early preparation of polymers, especially PS derivatives and their applications to organic synthesis 37, and his later interests where the synthetic interplay between macrocycles and linear polymers was the main focus.38 His interest in fundamental aspects of the relevant reaction mechanisms led to clear and general conclusions.
Late career
The coupling reactions that lead to polymer formation are potentially reversible, and under specific (generally catalytic) conditions this can lead to equilibration between linear polymers and cyclic oligomers. Phil realised that not only was there purely scientific interest in this but also that the recovery of such oligomers from a "used" polymer might have potential commercial benefits, particularly as a route to recycling the polymer. In terms of macrocycle synthesis he demonstrated that cyclic oligo-esters, predominantly dimers and trimers, were formed as the major products from self-condensation of linear bromocarboxylates when these were present as counterions in beads of a cationic ion-exchange resin. Elegantly, he showed that the intermediate linear oligomers remained bound to the ion-exchange resin via their carboxylate end groups, but upon cyclocondensation the resulting macrocycles were released into solution (Scheme 4). A three-phase test confirmed that cyclisation was indeed an intra-bead reaction.\(^{39}\)

Scheme 4. Synthesis of macrocyclic oligo-esters on an ion-exchange resin as solid support.

Phil also emphasised the importance of entropic factors in determining the product-balance between polymers and cyclo-oligomers. Polymerisation is favoured, thermodynamically, at high concentrations of monomer, whilst cyclo-oligomerisation is favoured at low concentrations, and this approach enabled the synthesis of a mixture of cyclo-oligomers of nylon 11, mainly the dimer and trimer.\(^{40}\) Moreover, under equilibrium conditions, a high molecular weight linear polymer in dilute solution rapidly depolymerises to a family of homologous macrocyclic oligomers; at high concentration the reverse reaction (ring-opening polymerisation) predominates. Phil was able to apply this principle to a wide range of polymer systems, including some with considerable industrial significance. High-performance aromatic poly(ether-sulfone)s such as Udel\(^{\text{TM}}\), for example, are manufactured by polycondensation of diphenoxides with bis[(4-chloroaryl)sulfone]s in which the chloro-substituents are activated towards S\(_{\text{N}}\)Ar-type substitution by an electron-withdrawing \(para\)-sulfone group. Phil discovered that, in dilute solution, such polymers readily undergo cyclo-depolymerisation in the presence of catalytic quantities of a soluble fluoride salt such as CsF.\(^{41}\) The fluoride ion cleaves the poly(ether-sulfone) chain reversibly at the ether linkages, and the resulting phenoxide end-groups can then "bite back" onto the polymer chain at many different sites, producing high yields of cyclic oligomers. A number of these macrocycles were isolated and characterised crystallographically (e.g. Scheme 5), and were shown to be recyclable to high molecular weight polymer by incorporation into the conventional (S\(_{\text{N}}\)Ar) manufacturing process.\(^{42}\)
Scheme 5. Cyclodepolymerisation of Udel™ poly(ether-sulfone) and the X-ray structure of the resulting cyclo-trimer (hydrogens omitted for clarity).

Phil went on to explore a wide range of ring-chain interconversions and showed that macrocycles were invariably formed during the step-growth synthesis and/or cyclodepolymerisation of important linear polymers, notably poly(ether-sulfone)s\(^{41-44}\), poly(ether-ketone)s\(^{45,46}\), aromatic polyesters\(^{47}\), polyurethanes\(^{48}\) and polyamides\(^{49}\). Cyclic ether-ketones were, for example, present to the extent of some 13 wt% in laboratory-synthesised poly(ether-ketone) ("PEK") and several such macrocycles were isolated by exhaustive extraction of the polymer. Separation and purification by column chromatography, enabled their structures to be confirmed by single crystal X-ray analysis (Scheme 6).\(^{45}\) He also demonstrated polymer-macrocyle interconversion via catalytic alkene metathesis, so enabling both ring-opening polymerisation of macrocyclic alkenes and formation of the latter by cyclodepolymerisation of high molecular weight poly(alkenamer)s.\(^{50}\)

Scheme 6. Macrocyclic components of poly(ether-ketone) (PEK) synthesised by self-polycondensation of 4-hydroxy-4'-fluorobenzophenone in diphenyl sulfone as solvent at 325°C in the presence of base. Macrocycles from trimer to nonamer were identified by mass spectrometry, and the pure trimer (X-ray), tetrimer (X-ray) and pentamer were isolated by chromatography (ref. 45).
Phil’s further work in this period included a novel method for reversible cross-linking of polystyrene, utilising Diels-Alder addition between pendant maleimide and furanyl substituents\textsuperscript{51}, and a review of his contributions to the entropy-driven conversion of polymers to macrocyclic oligomers as a potential storage point for recycling of the polymer.\textsuperscript{52} In collaboration with his Manchester colleague Gareth Morris, he showed that DOSY NMR had the capability to recognise and identify specific components of a molecular library through transient interactions with different polymers.\textsuperscript{53} By analysing crystal structures arising from work in this period, he found evidence for a specific interaction between a C=O group and a neighbouring π-system in a family of substituted anthraquinones, and supported this by UV-vis spectral data and electrochemistry.\textsuperscript{54,55}

**Conclusion**

With Emeritus status enabling him to continue in research at Manchester, the period after his formal retirement in 2004 was remarkably fruitful. Over 50 papers and reviews were published, with particular focus on achieving a better understanding of the interconversion between polymers and macrocycles, the role of entropic factors in this process and the potential that the research generated for novel synthetic advances.

Phil’s work has thus focused on the profound but often neglected relationship between synthetic/mechanistic organic chemistry and polymer science. His work at the interface between these disparate fields has uncovered both new principles, such as the broad generality of entropically-driven ring/chain interconversion chemistry, and potentially valuable new materials and processes – notably in his development of polymer-supported organic synthesis and his demonstrations of its wide-ranging utility. The present review gives only a snapshot of his scientific achievements across nearly six decades now, but these are more completely described in his >300 published papers, reviews, patents and books. He successfully supervised more than 70 Ph. D. students. He combined his science with a successful family life. He and Marian lived in a village close to Lancaster, with commuting access to Manchester (and the Lake District!) throughout his career. They raised a family of two daughters and a son, and later enjoyed the development of their seven grandchildren.

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**Selected Publications**

   [https://doi.org/10.1039/jr9650000459](https://doi.org/10.1039/jr9650000459)
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https://doi.org/10.1039/c39780000813

https://doi.org/10.1002/chin.197709159


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