Forty years ago—the first paper

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In the 1950s and 1960s, chemistry was seen as a romantic and thrilling scientific discipline that promised to improve people's lives beyond measure. It was during this exciting time that The Chemical Society decided to launch a new journal aimed at disclosing the latest research results in a quick, direct, and brief way. Organic chemist, Professor Hans Wynberg of the University of Groningen in the Netherlands wrote the very first paper in *Chemical Communications*. What was it like to do research then? Wynberg, now 82 years of age, gave Bert Meijer some insights when he recently visited him in his lake-side home in Groningen.

The first paper

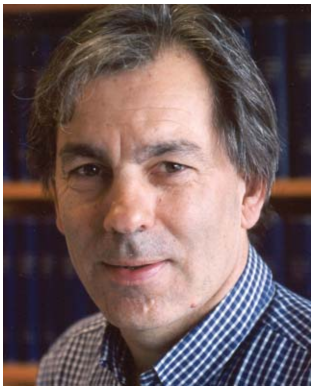
Forty years ago, what was then known as The Chemical Society, London, published the first issue of the first volume of a new addition to its successful group of journals. (It was not until 1980 that the various chemical institutions in the UK merged to form The Royal Society of Chemistry). Instead of publishing the usual lengthy, carefully written, full papers devoted to a specific area of chemistry, the idea was to elicit short contributions without experimental sections, in all areas of chemistry.

At that time, Hans Wynberg had recently been appointed professor of organic chemistry at Groningen. Being an advocate of simple, direct communication, he appreciated this new style of publishing, so submitted a manuscript on the synthesis of 3,4,5-tri-*tert*-butylthiophene (Fig. 1).[1] As a thiophene chemist with an interest in Dewar-thiophene, he had been intrigued by results from E. E. van Tamelen—a chemist with Dutch ancestry at Stanford University in the US—who had shown that 1,2,3-tri-*tert*-butylbenzene was unstable and rearranged to a Dewar-benzene structure. When Wynberg made the *tert*-butylthiophene analogue, it remained stable and did not rearrange. He proposed that it was due to the lower steric hindrance of the five-membered structure. Remember, steric hindrance was a new concept at the time!

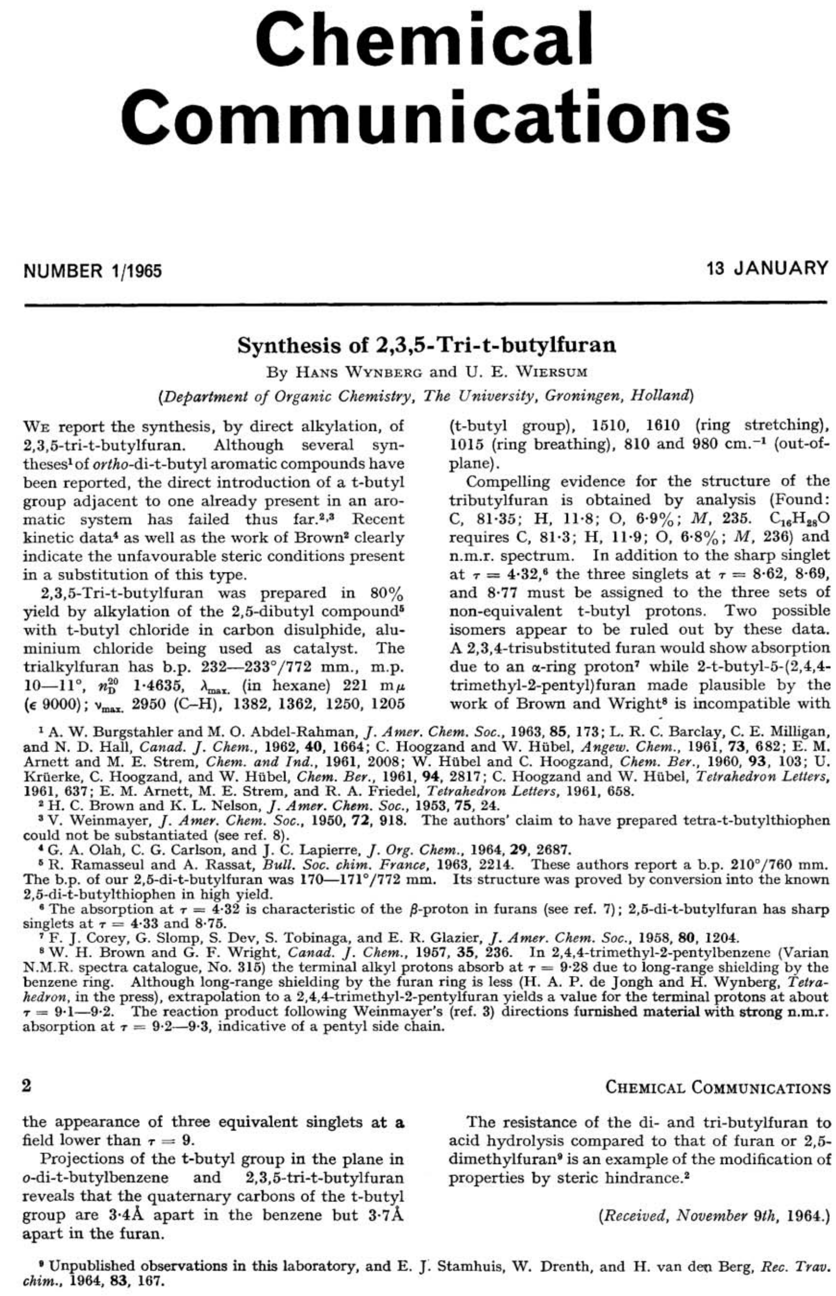
Fig. 1 shows the whole paper. It will certainly surprise younger chemists: it is extremely short, to the point and says something new. It is worth noting that one of Wynberg's first students in Groningen, Ulfert Wiersum, was awarded his PhD in 1968 on the basis of just a handful of similar papers and a thesis. In many ways, it was easier then to make important discoveries about the structure and reactivity of small molecules than it is now. Organic chemistry was more clearly defined. Ulfert carried out the work on *tert*-butyl derivatives of thiophene, furan and pyrrole over 4 years, and more details of his work can be found in his thesis—although written in Dutch. (Today, all Dutch PhD theses are written in English, not only to reach a broader readership, but also as the result of the changing style of publishing in the past 40 years).

Embracing Europe

Publishing in a British journal was considered a good move for the young Groningen professor. Although Dutch by birth, Wynberg had been educated in the United States (see Box 1), and when he returned to the Netherlands, he still regarded American journals—those published by the American Chemical Society, especially the *Journal of the American Chemical Society* and the *Journal of Organic Chemistry*—as the obvious publications to which to submit papers. While admiring the European journals (mainly published by the national chemical societies) for their elegant style, he knew that they were not widely seen by his American friends at that time. Wynberg liked the US system of research and wanted to introduce it into the Netherlands. But he had to deal with local politics, and his colleagues, particularly Jan Strating, persuaded him to concentrate first on putting Groningen firmly on the European chemistry map. This meant increasing the visibility of the department by publishing in leading European journals rather than American ones. In that way Groningen could compete with the University of Leiden, then considered the leading centre for Dutch organic chemistry. The fortuitous launch of the new Chem. Soc. journal provided the ideal vehicle. "Every month, Jan Strating counted all the



Bert Meijer was born in 1955 in Groningen and he received his PhD degree with professor Hans Wynberg in 1982 with a thesis entitled: Chemiluminescence in action; synthesis, properties and applications of 1,2-dioxetanes. After 10 years in industry, he is now professor of Organic Chemistry in Eindhoven, The Netherlands and adjunct professor of Macromolecular Chemistry in Nijmegen, The Netherlands. He is also a member of the *Chemical Communications* Editorial Advisory Board.



Chemical Communications

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Synthesis of 2,3,5-Tri-t-butylfuran

By HANS WYNBERG and U. E. WIERSUM

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WE report the synthesis, by direct alkylation, of 2,3,5-tri-t-butylfuran. Although several syntheses[1] of *ortho*-di-t-butyl aromatic compounds have been reported, the direct introduction of a t-butyl group adjacent to one already present in an aromatic system has failed thus far.[2,3] Recent kinetic data[4] as well as the work of Brown[2] clearly indicate the unfavourable steric conditions present in a substitution of this type.

2,3,5-Tri-t-butylfuran was prepared in 80% yield by alkylation of the 2,5-dibutyl compound[5] with t-butyl chloride in carbon disulphide, aluminium chloride being used as catalyst. The trialkylfuran has b.p. 232—233°/772 mm., m.p. 10—11°, n_D^{20} 1·4635, $\lambda_{max.}$ (in hexane) 221 mμ (ϵ 9000); $\nu_{max.}$ 2950 (C–H), 1382, 1362, 1250, 1205 (t-butyl group), 1510, 1610 (ring stretching), 1015 (ring breathing), 810 and 980 cm.$^{-1}$ (out-of-plane).

Compelling evidence for the structure of the tributylfuran is obtained by analysis (Found: C, 81·35; H, 11·8; O, 6·9%; *M*, 235. $C_{16}H_{28}O$ requires C, 81·3; H, 11·9; O, 6·8%; *M*, 236) and n.m.r. spectrum. In addition to the sharp singlet at $\tau = 4{\cdot}32$,[6] the three singlets at $\tau = 8{\cdot}62$, 8·69, and 8·77 must be assigned to the three sets of non-equivalent t-butyl protons. Two possible isomers appear to be ruled out by these data. A 2,3,4-trisubstituted furan would show absorption due to an α-ring proton[7] while 2-t-butyl-5-(2,4,4-trimethyl-2-pentyl)furan made plausible by the work of Brown and Wright[8] is incompatible with the appearance of three equivalent singlets at a field lower than $\tau = 9$.

Projections of the t-butyl group in the plane in *o*-di-t-butylbenzene and 2,3,5-tri-t-butylfuran reveals that the quaternary carbons of the t-butyl group are 3·4Å apart in the benzene but 3·7Å apart in the furan.

The resistance of the di- and tri-butylfuran to acid hydrolysis compared to that of furan or 2,5-dimethylfuran[9] is an example of the modification of properties by steric hindrance.[2]

(*Received, November 9th, 1964.*)

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[3] V. Weinmayer, *J. Amer. Chem. Soc.*, 1950, **72**, 918. The authors' claim to have prepared tetra-t-butylthiophen could not be substantiated (see ref. 8).

[4] G. A. Olah, C. G. Carlson, and J. C. Lapierre, *J. Org. Chem.*, 1964, **29**, 2687.

[5] R. Ramasseul and A. Rassat, *Bull. Soc. chim. France*, 1963, 2214. These authors report a b.p. 210°/760 mm. The b.p. of our 2,5-di-t-butylfuran was 170—171°/772 mm. Its structure was proved by conversion into the known 2,5-di-t-butylthiophen in high yield.

[6] The absorption at $\tau = 4{\cdot}32$ is characteristic of the β-proton in furans (see ref. 7); 2,5-di-t-butylfuran has sharp singlets at $\tau = 4{\cdot}33$ and 8·75.

[7] F. J. Corey, G. Slomp, S. Dev, S. Tobinaga, and E. R. Glazier, *J. Amer. Chem. Soc.*, 1958, **80**, 1204.

[8] W. H. Brown and G. F. Wright, *Canad. J. Chem.*, 1957, **35**, 236. In 2,4,4-trimethyl-2-pentylbenzene (Varian N.M.R. spectra catalogue, No. 315) the terminal alkyl protons absorb at $\tau = 9{\cdot}28$ due to long-range shielding by the benzene ring. Although long-range shielding by the furan ring is less (H. A. P. de Jongh and H. Wynberg, *Tetrahedron*, in the press), extrapolation to a 2,4,4-trimethyl-2-pentylfuran yields a value for the terminal protons at about $\tau = 9{\cdot}1$—9·2. The reaction product following Weinmayer's (ref. 3) directions furnished material with strong n.m.r. absorption at $\tau = 9{\cdot}2$—9·3, indicative of a pentyl side chain.

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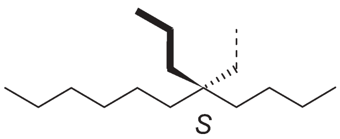
[9] Unpublished observations in this laboratory, and E. J. Stamhuis, W. Drenth, and H. van den Berg, *Rec. Trav. chim.*, 1964, **83**, 167.

Fig. 1 The first article of *Chemical Communications* in 1965 by Hans Wynberg and Ulfert Wiersum.

papers coming out of Groningen and Leiden; with *Chemical Communications* I could publish very rapidly, and I really liked that," says Wynberg.

The philosophy of the journal was indeed highly suited to Wynberg's style of publishing short communications without many follow-up papers on the same topic. "I liked the brevity of style—not too much hokum or repetition," he remarks. While many organic chemists of the time concentrated on natural product synthesis, Wynberg focused on novel ideas in small molecule chemistry, combining careful observations with sparkling imagination. He was one of the first scientists to use chiral phase-transfer reagents based on quinine to perform catalytic asymmetric synthesis. This work also brought him to the topic of asymmetric autocatalysis. Although not always recognised, his seminal work gave him great satisfaction. Within the framework of stereochemistry, he also studied optical activity in bio- and chemiluminescence, in collaboration with scientists from the Leiden school.

One of Wynberg's benchmark experiments, now included in many organic chemistry textbooks, concerned the optical inactivity of an enantiomerically pure branched alkane **S**.[2] The lack of optical transitions in the UV-visible region and the high degree of flexibility of **S** was argued to be the reason for this unconventional behaviour.



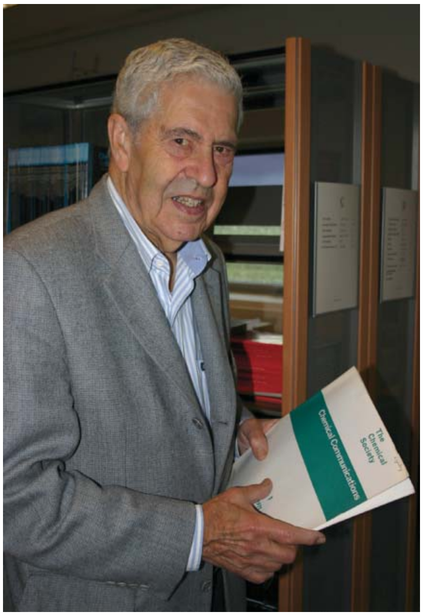
S

Wynberg also worked for many years on derivatives of two molecules, adamantane and thiophene. The chemistry on thiophenes was used later in his collaborations with Philips Research on semiconducting oligo- and polythiophenes. The isolation of the first stable bromonium ion is another example of his sparkling chemistry. The work was carried out by PhD student Joop Wieringa and published in the direct style so characteristic of both Wynberg and *Chemical Communications* in its early form. This very short article is presented in its original form in Fig. 2 and is a landmark paper in organic chemistry.[3]

In recent years, and long after his formal retirement, Wynberg and colleagues working at his contract research company Syncom, co-founded by him more than 15 years ago, introduced the Dutch resolution technique. Discovered by his last PhD student, Ton Vries (currently CEO of Syncom), a combinatorial approach is used to speed up the discovery of successful combinations in the selective crystallisation of diastereoisomers. This methodology provides a rapid route to enantiomerically pure compounds.[4]

Of course, this kind of chemistry, which Wynberg devoted his academic life to, has had significant commercial applications, which was readily recognised both within and outside the university system. The decades between 1950 and 1970 were golden years for the pharmaceutical industry. Society was waiting for new medicines and chemists were able to provide them. University

From penicillin to poetry



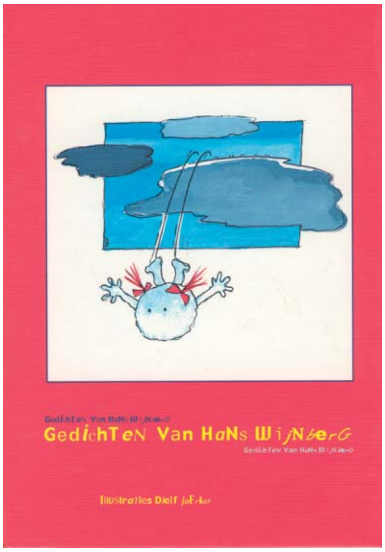
Hans Wynberg was born into a Jewish family in Amsterdam in 1922. His parents owned a small chemical company, which produced glue for repairing bike tubes. In 1939, his father—being politically acute—wisely sent the 16-year-old Hans and his twin brother to the United States.

After finishing high school in New York, Wynberg's interest in chemistry developed when he took a job for a year with Pfizer, and was actually present at the first batch of real penicillin—produced by fermentation in the summer of 1943. However, he was drafted into the US army that summer and served in the OSS—the secret service that preceded the CIA—jumping behind the lines in Europe and spying for the allies.[6]

In New York, he met Elly Dekker, also Dutch and daughter of Maurice Dekker, the founder of Interscience. She was studying at Cornell University and Wynberg joined her. After the war they married and Wynberg started studying chemistry, using a grant provided by the US Government to support soldiers that had served in the War. He carried out his PhD work with professor William Johnson in Wisconsin, studying the abnormal Riemer–Tiemann reaction for preparing the substituted A and B rings of steroids.

After a postdoc in Minnesota with professor William E. Parham and an assistant professorship in Grinnell College in Iowa, Wynberg, his wife and four children moved to the Netherlands. A Fullbright award in 1959 first brought them to Leiden University. The family found they liked the Netherlands and when the scholarship ended, Wynberg eventually accepted an offer to become full professor of organic chemistry in Groningen. To start with, Wynberg found it a traumatic experience starting again, with a young family, in the country where his parents had been murdered. The salary was low and housing was not easy to find, but the laboratory, the students and the colleagues were great—and the chemistry was excellent. He has remained in Groningen ever since, retiring in 1987.

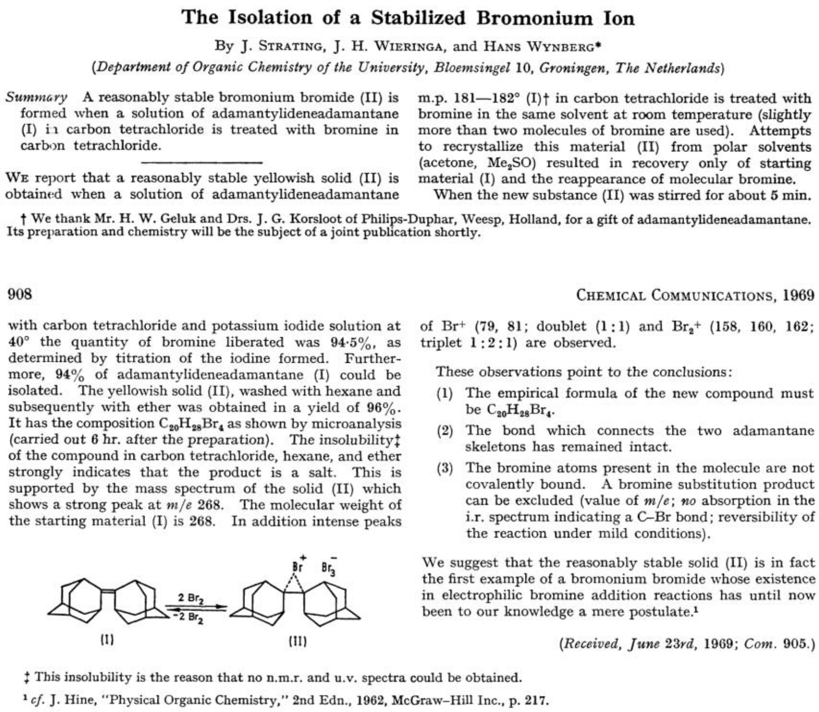
Today, Professor Wynberg is still active in science. He keeps up to date with new developments through his daily presence at his company, Syncom, and still comes up with new ideas on modern developments in organic chemistry. He says that if he were to start again today, he would still concentrate on the core of organic chemistry. Being a small molecule chemist, he sees an enormous potential in the area for the many decades to come. Small molecules, made in the most effective way, shaped the world in the 20th century and will continue to do that in the decades to come. Next to science, he also spends time with his children and grandchildren. Only recently he published a book of children's poetry (written during lectures and meetings!).[7]



chemical research increased rapidly and almost exploded. For instance, under Wynberg's management, the number of professors in organic chemistry at Groningen increased from one in 1960 to eight in 1975; in 2005 they are back to two. "The funding system in the Netherlands was then almost ideal," recalls Wynberg. "There was no grant proposal system whatsoever. The University employed all people, including the graduate students and they were well paid. When we needed an NMR machine—a Varian A60—I just phoned the University secretary and explained the reasons why. He agreed and paid the bill. I believe that scientists should be in the laboratory and discussing science. The current focus on paperwork, lengthy proposals and reports is wrong. I'm glad I'm not part of the system anymore; I couldn't stand the bureaucracy!"

Wynberg also feels that the current academic system and competition for funding has had a detrimental effect on the quality of scientific publications. He thinks that most authors publish too much (the number of chemistry papers published doubles every 10 years, according to Derek de Solla Price[5]), and that they do not spend enough time perfecting the style. Most articles now are badly written, he says: "The use of buzzwords has increased dramatically, and everyone tries to rationalise the possible impact of the work presented, without actually demonstrating it. It is seldom a pleasure to read the current articles. We should return to the old style of using brief communications."

Wynberg loves organic chemistry and the pictorial language associated with it. It was in 1855, he teaches, that chemists sketched the first structures of molecules and it became the language of the molecular world. For an organic chemist it is much easier to see at a glance the importance of a chemical substance by looking to its chemical structure than by reading pages of text. Therefore, an article should have the figures as the



The Isolation of a Stabilized Bromonium Ion

By J. STRATING, J. H. WIERINGA, and HANS WYNBERG*

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Summary A reasonably stable bromonium bromide (II) is formed when a solution of adamantylideneadamantane (I) in carbon tetrachloride is treated with bromine in carbon tetrachloride.

WE report that a reasonably stable yellowish solid (II) is obtained when a solution of adamantylideneadamantane m.p. 181—182° (I)† in carbon tetrachloride is treated with bromine in the same solvent at room temperature (slightly more than two molecules of bromine are used). Attempts to recrystallize this material (II) from polar solvents (acetone, Me_2SO) resulted in recovery only of starting material (I) and the reappearance of molecular bromine.

When the new substance (II) was stirred for about 5 min. with carbon tetrachloride and potassium iodide solution at 40° the quantity of bromine liberated was 94·5%, as determined by titration of the iodine formed. Furthermore, 94% of adamantylideneadamantane (I) could be isolated. The yellowish solid (II), washed with hexane and subsequently with ether was obtained in a yield of 96%. It has the composition $C_{20}H_{28}Br_4$ as shown by microanalysis (carried out 6 hr. after the preparation). The insolubility‡ of the compound in carbon tetrachloride, hexane, and ether strongly indicates that the product is a salt. This is supported by the mass spectrum of the solid (II) which shows a strong peak at *m/e* 268. The molecular weight of the starting material (I) is 268. In addition intense peaks of Br^+ (79, 81; doublet (1:1) and Br_2^+ (158, 160, 162; triplet 1:2:1) are observed.

These observations point to the conclusions:

(1) The empirical formula of the new compound must be $C_{20}H_{28}Br_4$.

(2) The bond which connects the two adamantane skeletons has remained intact.

(3) The bromine atoms present in the molecule are not covalently bound. A bromine substitution product can be excluded (value of *m/e*; *no* absorption in the i.r. spectrum indicating a C–Br bond; reversibility of the reaction under mild conditions).

We suggest that the reasonably stable solid (II) is in fact the first example of a bromonium bromide whose existence in electrophilic bromine addition reactions has until now been to our knowledge a mere postulate.[1]

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† We thank Mr. H. W. Geluk and Drs. J. G. Korsloot of Philips-Duphar, Weesp, Holland, for a gift of adamantylideneadamantane. Its preparation and chemistry will be the subject of a joint publication shortly.

‡ This insolubility is the reason that no n.m.r. and u.v. spectra could be obtained.

[1] *cf*. J. Hine, "Physical Organic Chemistry," 2nd Edn., 1962, McGraw–Hill Inc., p. 217.

Fig. 2 The article from 1969 describing the discovery of the first stable bromonium ion by Jan Strating, Joop Wieringa and Hans Wynberg.

central theme and some text to explain these figures. Obviously, that is much easier for organic chemistry than for biochemistry as an example: "I am highly impressed by the enormous progress in biochemistry and molecular biology. If you compare a textbook of organic chemistry now and 40 years ago, roughly 90 per cent is the same. For a biochemistry textbook almost 90 per cent is new! Isn't that remarkable?"

Would it be possible to publish papers of the type shown in Figs. 1 and 2, nowadays? It's hard to say. One thing is clear though: papers would be studied more closely if brevity was reintroduced, and the objective and the results of the study would be easier to see. It will be interesting to analyse the publishing trends and style when *Chemical Communications* celebrates its fiftieth anniversary in ten years' time.

At the end of the visit to Groningen, Wynberg added: "Don't make the article too long and don't describe all of my chemistry and career, please read my lips—keep it brief." I have done my best.

Acknowledgements

The author would like to sincerely thank Nina Hall for her valuable assistance in the preparation of this article.

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