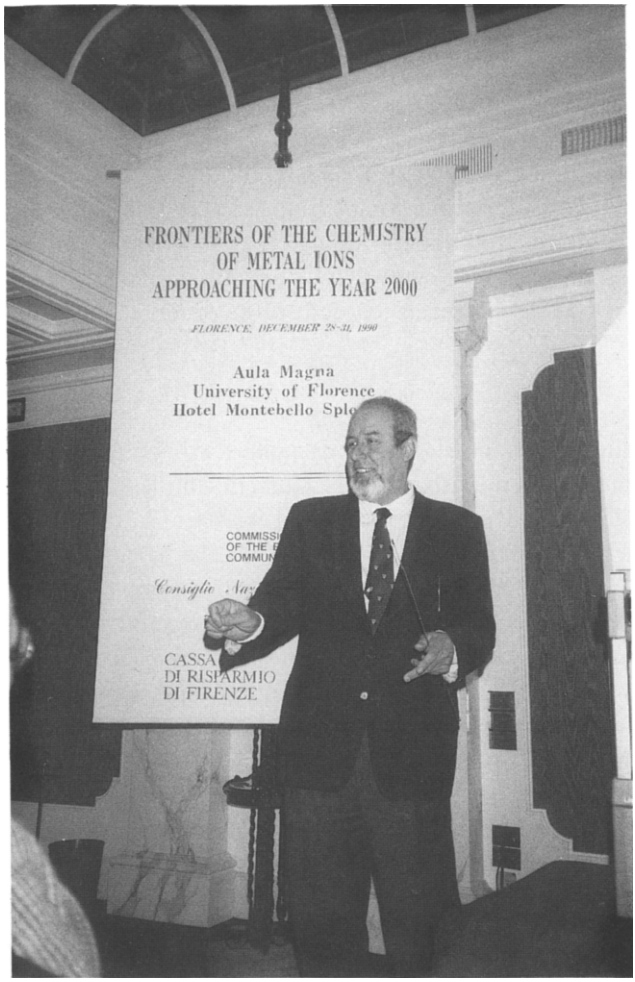
Coordination Chemistry Reviews, 110 (1991) 275–287
Elsevier Science Publishers B.V., Amsterdam

FRONTIERS OF THE CHEMISTRY OF METAL IONS APPROACHING THE YEAR 2000 REPORT OF A CONFERENCE ORGANISED BY LUCIA BANCI, DANTE GATTESCHI, CLAUDIO LUCHINAT AND ANDREA SCOZZAFAVA, FLORENCE, ITALY, DECEMBER 28–31 1990

A.B.P. LEVER
Department of Chemistry, York University, North York (Toronto), Ont. M3J 1P3 (Canada)

(Received 16 June 1991)



Professor Ivano Bertini at the conference poster.

0010-8545/91/$4.90

At the festive end of 1990, a group of scientists gathered in a hotel in Florence, Italy to talk science, exchange information, think about the development of their area of expertise during the coming decade, and celebrate the 50th birthday of their colleague and friend, Ivano Bertini. This document tries to convey the excitement felt at the conference by these participants planning their future research.

Although the conference title includes the words *metal ions*, the ensuing discussion was rather more general, as reflected in this document. Moreover, this document does not pretend to look at all future avenues in chemistry, but only those areas encompassed by the interests of the participants. The intent is to indicate where important progress might be made in the coming decade, to identify significant frontiers, and to identify specific needs for further study and development.

To set a frame of reference, it is useful to identify the factors which have most influenced the development of our subject during the past 20 years or so, if only because the next period may be very different.

These factors include: the phenomenal growth in, and availability of, modern instrumentation, the development and widespread availability of lasers, significant developments in synthetic strategies, a major growth in theory which enables us to calculate electronic and geometric structures in the ground and excited states, a much greater understanding of factors controlling the stabilities of molecules and their dynamics, and computer simulation of molecules and their reactions.

For convenience, this document will be split into sections covering specific areas with no special significance accorded to the order.

A. BIO-INORGANIC TOPICS

The growing power of molecular dynamics will be used more extensively to study substrate interactions with proteins. Current frontiers include the development of appropriate force field parameters to deal with transition metal ions [1–3]. Ab initio molecular orbital studies of ferredoxin [4] are in hand and one may expect that such methods will be increasingly used for more complex proteins in the future.

The success being achieved in mapping protein conformations using X-ray and multidimensional NMR (including using isotopically labelled proteins, e.g. ^{15}N and ^{13}C) suggests that the folding processes in proteins may soon be thoroughly understood [5]. The use of synchrotron radiation and increasingly sophisticated detectors will greatly improve the speed and quality of protein analyses, approaching atomic resolution. Thus it would become possible to predict the folding patterns of synthetic oligopeptides and determine crevices, surface charge distributions, regions of hydrophilic and hydrophobic behaviour, etc. From here it is a short step to design oligopeptides having pre-described active sites for specific purposes. Combining this with our knowledge of catalysis, with protein expression in microbes etc., and with site-directed mutagenesis should permit a future where "any" molecule could be manufactured by a synthetic protein constructed to catalyse the formation of such

a molecule. One may then see such specific proteins (enzymes) and their products being biologically produced.

Developments in bright white radiation from synchrotron sources, permitting the recording of a complete data set in milliseconds, offer the opportunity in the future to follow protein-catalysed processes in real time. Great strides are being taken in understanding electron transfer in proteins [6–9] through the incorporation of redox active residues in specific sites of the protein. It is important to understand the relative importance of covalent bonds, hydrogen bonds, ionic and through-space contacts, and the roles played by aliphatic, aromatic and conjugated residues. Similarly, the mechanism of donor–acceptor electronic coupling and the factors which determine its magnitude (H_{AB}) are poorly understood. Computational methods for understanding such processes are being developed [10,11] and a greater understanding of their specificity and their rates is evolving.

Additional areas in which one may expect progress in the short-term future include understanding the role of metal ions in the biological reduction of carbon dioxide [12] to CO [13] or CH_4, the biological carboxylation of organic substrates [12,14], the further development of model systems for nitrogen fixation, and, indeed, the general area of artificial photosynthesis [15] for the conversion, using sunlight, of very abundant raw materials. The goal is to make commodity or specialty chemicals directly from CO_2. Fuels might be obtained from CO_2 and water using sunlight. This might drive chemical, electrochemical or photoelectrochemical processes. Further, we need to develop systems which are more efficient than natural photosynthesis and develop new light harvesting systems and new catalysts for CO_2 reduction or fixation. A principal goal of artificial photosynthesis is to produce hydrogen gas from water, and perhaps also from hydrogen sulphide (freely available in many gas wells). All these processes involve electron transfer, which is an area that has developed enormously during the past ten years. We can reasonably expect that artificial photosynthetic procedures can approach economic reality during the next ten years.

Understanding how life developed on this planet has always been a vital area of concern with great potential for using such knowledge. One may speculate that life began on an RNA (ribonucleic acid) world [16], where RNA was formed spontaneously from simpler molecules. Such simpler molecules probably included ATP (adenosine-5′-triphosphate) [17] whose metal complexes can involve purine stacking and thereby play a structuring role; thus ATP acts as its own hydrolytic "enzyme" [17,18]. Evidence exists that metal ions also play a role in controlling such stacking [19], and that they, in addition, facilitate inter-ligand recognitions [20,21], aside from the fact that nucleic base–metal ion interactions are highly specific [22,23].

The reactions to which metal ions give rise in the eco- and biosphere nowadays represent a frontier of chemistry. Life has developed in equilibrium with the earth's crust by taking the essential elements and avoiding the toxic ones. Essential elements have important roles in determining potential and chemical gradients in catalyzing

reactions, and in providing electron transfer pathways. The mechanism of action of metalloproteins is a fundamental chapter in chemistry and biochemistry.

The reactivity of metal ions in metalloproteins is dramatically dependent on the residues, charged or hydrophobic, around the metal ion itself. Typical investigations have been reviewed [24]. A new frontier is represented by metal clusters in proteins. Typically, the electronic structure of Fe_4S_4 clusters in ferredoxins and similar proteins represents a puzzle for inorganic chemists. NMR data are useful in this respect [25].

Metalloproteins are generally involved in the degradation of organic pollutants, either aerobic or anaerobic. Typically, Cyt-P450 introduces one oxygen atom into the C–H bond, and, for aromatic pollutants, *ortho*-catechols are formed. Dioxygenases (iron-containing proteins) can degrade pollutants by breaking an aromatic ring. Research in environmental chemistry must focus more on the elucidation of these degradative enzymatic reactions.

Molecular dynamics (MD) can play a fundamental role in the characterization and rationalization of many macromolecular properties, in particular those of biological interest [26,27]. Internal motions, reaction pathways, protein–protein interactions, substrate binding, and residue modification can be fruitfully studied by MD, both in terms of structural characterization and dynamic properties. While a lot of work has been done and valuable experience has been gained with DNA and "organic" proteins [26], much less has been done with metalloproteins and other systems containing metal ions. This is due to the intrinsic difficulty in determining good metal ion force field parameters, especially for open shell ions.

Recently, parameters for the d^{10} zinc ion have been reported [28,29], permitting MD calculations on a large variety of zinc enzymes [30,31]. The power of these calculations in predicting the structural modifications as determined by substrate and inhibitor binding is illustrated nicely in MD calculations of inhibitor adducts with carboxypeptidase A (CPA), a zinc enzyme catalysing the breaking of the peptide bond [31]. Indeed, these results predicted the correct structure as determined by X-ray diffraction.

The perspectives and the frontiers in this area of research are the computation of force field parameters for d^n ($n<10$) ions, thus opening the possibilities to study and characterise the dynamic properties of a large class of metalloproteins.

B. MEDICAL AND CLINICAL OPPORTUNITIES

A decade from now should find us having a much better idea of how Ca and Mg ions are absorbed from food, how these ions are translocated through the brush border epithelial cells without perturbing the low intracellular concentrations of Ca^{2+}, how they are then pumped into our body, and how all this is controlled by Vitamin D. One might also resolve questions such as, "why is the dietary intake of Ca^{2+}, for most mammals, normalised to size, some 8–10 times higher than that for

the average adult human?" Are we Ca^{2+}-undernourished [32]? This is obviously related to bone growth, about which little is known, and is relevant to the problems of bone embrittlement faced by post-menopausal women. Progress in this field has been stimulated by the design of ion-selective chromophoric chelators, available for Ca^{2+} [33] and much needed for Mg^{2+} [34], whose regulatory role is poorly understood [35]. A better understanding of the molecular events which mediate the free energy of interaction between Ca^{2+} sites in regulatory proteins such as calmodulin should emerge fairly shortly [36,37].

Ehrlich first postulated the existence of "chemoreceptors", being vulnerable targets in living cells, which, if inactivated, could alter the course of an otherwise deadly condition. He then began to search for "magic bullets", being pharmaceuticals which could affect such inactivation. Penicillin is an early example of such a "bullet". Similar strategies are adopted in the search for anti-cancer drugs. Metal ion chemistry plays a central role in this endeavour [38–41]. Cisplatin (*cis*-$[Pt(NH_3)_2Cl_2]$) is a leading chemotherapeutic agent for certain types of cancer but has relatively serious side effects. The development of future less toxic anti-cancer drugs involves, inter alia, understanding in detail the mechanism by which cisplatin functions. It binds to DNA and locally modifies (damages) it. A human protein has recently been identified which recognises the structural modifications induced by cisplatin [41,42]. Its function is not yet known, but such understanding should lead to more rational design of reactive drugs. An interesting strategy for future investigation involves the application of two small molecules in solution which can migrate along the DNA chain, or similar biopolymer. Reaction between them and the target biopolymer can be facilitated by entropic factors. If the product affords a lethal lesion at a DNA site, a powerful basis for chemotherapy obtains. Such chemistry has already been observed with cisplatin and ethidium bromide [43] and may account, at least in part, for the synergism seen in the use of cisplatin in combination chemotherapy with intercalating drugs [40] for the treatment of human malignancies.

This leads on to the idea that biological functions are extremely complex multicomponent systems. Even "simple" processes such as iron storage and transport are poorly understood. The future should consider a more holistically oriented approach to such understanding.

Magnetic resonance imaging (MRI) has become an important tool in the arsenal of physicians. It is a powerful, non-invasive procedure for "looking" at various parts of the anatomy, including the brain. A commonly used contrast-enhancing agent is $[Gd(DTPA)]^{2-}$ (DTPA = diethylenetriaminepentaacetic acid), used intravenously to generate a better image. However, there is an explosive demand for new contrast reagents which will selectively bind to organs and tissues and expand the capabilities of this important clinical tool, and, in parallel, a demand for a deeper understanding of the electronic relaxation mechanisms of metal ions [44], which in turn will lead to the design of better contrast agents. Future research in this area will recognise (a) that many of the important parameters which determine the

relaxivity of MRI contrast agents are tensor quantities, and that advantages can be gained by manipulation of only some of their tensor elements, (b) that much may be gained by defining the structure of the ligand more critcally, e.g. using a planar macrocycle [45,46] with heavy moities, having a longer rotational relaxation time, and (c) that multicentre paramagnetic ions, ferromagnetically coupled, even in a small complex, can be of tremendous import.

Other uses for the macrocycles alluded to above include the modification of antibodies for radiolabelling, and studies in selective ion and molecule recognition (sensors), transport processes, and host–guest chemistry, etc. Indeed, the entire research frontier dealing with electrodes modified by biologically active species to detect highly specifically their appropriate biological partner is ready for rapid development [47–49].

Photodynamic therapy involves the activation by light inside the body of a photochemical process having clinical utility. The use of luminescent or photoreactive complexes as labels, probes and reactants in biological systems, and their use in medical treatment, will develop steadily in the coming years.

C. SUPRAMOLECULAR CHEMISTRY AND MICROELECTRONICS (MATERIALS SCIENCE)

These are rapidly expanding areas [50–52] which can be expected to produce significant new chemistry in the coming years [52,53]. Attention will be addressed to

(a) *binding and recognition of metal ions*, including selective ligand design, complexation selectivity control, and the generation of sophisticated modified electrodes;

(b) *structural components*, where the traditional chemistry of organic fragments with most bonds occurring about tetrahedral or trigonal sites can be replaced by metal ions and coordination fragments for the architectural design of planar, octahedral, and right-angle features;

(c) *multielectron transfer and multielectron catalysis* for polyelectronic processes such as water splitting, nitrogen and carbon dioxide fixation, etc. This includes catalytic processes on multimetallic sites and coordination centres, and also has obvious relevance to energy storage;

(d) *photochemical molecular devices* (PMD) for charge separation, light conversion, energy transfer, etc. in applications such as artificial photosynthesis and photoelectronic signal generation [52,54]. Supramolecular ionic devices can be designed for processes such as the pulsed generation of ions upon a light stimulus. Such ionic devices may involve signal carriers, ion channels, ionic signal transfer through membranes, e.g. photocontrolled membrane permeability, etc. PMDs, of course, already exist in nature, e.g. in photosystem I and II, and in the biochemistry of vision. PMDs require the development of chemical systems which are suitably organised in the

dimensions of space, energy and time but they need not be, and are unlikely to be, as complex as the natural systems [52];

(e) *non-linear optical* devices based upon supermolecules will play a role in the manipulation of light, as will

(f) *switching units* capable of the redox switching of optical properties or of ion-binding properties, etc.

Examples (d–f) are domains of a new field which might be called *semiochemistry* [50,55], being the chemistry of signal generation, transfer, modulation and detection. The development of such systems may permit new approaches to information processing, based upon molecular systems incorporated into microelectronic devices.

Supermolecules may also be involved, though not exclusively, in areas such as

(g) *molecular batteries*, including polyelectronic storage;

(h) *amplifying devices* for the cooperative binding or release of metal ions;

(i) *self-organising systems* for multinuclear, multimetallic complexes which may come together spontaneously [56–58] from components fabricated in a controlled directed fashion. These systems are the forerunners of the *nanostructures* to be used in molecular electronic devices. In most cases, the utilization of these nanostructures [59] will require the scaling-up by several orders of magnitude to pass from supermolecules to the dimensions of microdevices of the macroscopic world [52]. Current approaches to macro-to-molecular connections, which will undoubtedly develop rapidly in the near future, include Langmuir–Blodgett films [60], the derivatization of electrodes and the direct fabrication of microelectrochemical devices [47,61].

Supramolecular chemistry also attempts to fill the gap between the usually poorly organised systems of chemistry, as it is currently practised, and the enormous complexity, yet organization, of biological functions.

Other fields of materials science where the role of metal-ion-based chemistry may produce exciting developments in the next years are: the use of metallo-organic precursors to advanced materials [62], the development of new classes of conductors [63] and of superconductors, either of the ionic or of the so-called organic type [64], the development of new magnetic materials based on molecular or polymeric rather than metallic or ionic lattices [65], and the development of new sensors [66]. Finally, larger and larger metal clusters will be assembled; they will attain the mesoscopic scale which is currently of such great interest in the physical literature. An obvious extension of the approach will be in the synthesis of magnetic clusters in which the metal ions will be bridged by suitable ligands in order to transmit exchange interactions.

D. CATALYSIS

Catalytic processes already play a critical role in the chemical industry. The main goal of research into *homogeneous catalysis* in the short-term future is improved chemoselectivity, regioselectivity and stereoselectivity. One approach to controlling

stereochemistry involves the use of tripodal ligands such as the polyphosphines. These provide a rigorous and unique control on the stereochemistry of the resulting complexes [67,68]. Hybrid polydentate (tripodal) ligands, containing donors such as nitrogen as well as phosphorus, have great potential in the further development of this area since they have the ability to unfasten either of the two donor atoms during the catalytic cycle.

The use of chemical models based on metal porphyrins is a valuable means to gain more insight into the mechanism of enzyme catalysis, and to build up new efficient catalytic systems. Recent work has described a series of macrocyclic compounds, in solution as well as surface-bound, capable of efficiently photoinducing different redox processes on organic and inorganic substrates (photocatalysis). Examples include the monooxygenation of alkenes by molecular oxygen [69,70] and the reduction of halogenated alkanes [71].

Among interesting photochemical catalysts, inorganic semiconductors have proven quite promising either alone or when modified with metals. Semiconductor modification with macrocyclic compounds is currently under investigation (photoelectrocatalysis) [72].

Great progress should be made in *heterogeneous catalysis* in the short-term future, especially involving catalysts laid down on surfaces in an organised fashion. Needed in this field are improved procedures for characterising and modelling surfaces, and here the recent advent of *scanning tunnelling microscopy* (STM) [73] is especially important. The direct observation of surface features by STM is likely to provide us, in the coming years, with a much greater appreciation of surface structure and dynamics. These features may be physical structures or regions of charge density or energy [74–76]. Indeed, STM may also be used to "cut" or "draw" directly onto surfaces with nanometer precision [77].

Many techniques are available for the study of surfaces (electron spectroscopy for chemical analysis (ESCA), Auger, secondary ion mass spectrometry (SIMS), energy loss spectroscopy (ELS), etc.). In the coming years, photoelectron spectroscopy with angular resolution will be used to determine the composition of the surface overlayer non-destructively, perhaps with monolayer resolution. This progress will enable greater insight into adsorption phenomena. Greater use of modern computational techniques can be expected [78].

New procedures will be developed to tailor-make catalyst molecules of increasing complexity, likely utilising organometallic fragments and having the capability to form chiral products. A major problem to be solved is how to stabilise such tailor-made systems either as molecular complexes, or as small metallic assemblies, against fragmentation, nucleation, and deactivation, etc.

The controlled preparation of ultra-pure and ultra-small particle metallic catalysts, of uniform properties, is desirable. The inclusion of such micro-particles, of nanometer dimensions, into polymer supports provides an extremely active catalytic system, due partially to the very large effective surface areas [79]. Intermediate

between surfaces and individual molecules lie the clusters, an area of intense current research activity [80]. These will be used extensively as models for surfaces, and for improving our understanding of anchoring of catalysts, and of the nucleation and disruption of metal particles.

E. COMPUTING

Computers grow ever larger in memory and storage, ever smaller in volume, and ever cheaper in price. They are finding their way into research laboratory and finally into the undergraduate laboratories. The ability to carry out quite complex calculations, even with a home microcomputer, must stimulate a great deal of activity using these machines.

Activity in the coming years [81] will be centered around the use of artificial intelligence in analytical chemistry [82,83], in structure/property relationships [84–86], especially in connection with developing new drugs and insecticides [87,88], and in modelling a wide variety of complex systems, including proteins and carbohydrates [89,90]. Computers will also be used to tackle current problems such as the mechanism of odor [91], leading, no doubt, to the greater use of smell in our entertainment and advertising industries!

The facile access to computers will stimulate the further development of simple models which can predict large areas of chemistry. These currently include the many solvent parameters, the E and C parameters [92] and their more recent developments [93], recent contributions to the concept of hardness and softness [94], and the very recently introduced electrochemical parameters for predicting metal-centered redox potentials [95].

F. THE ENVIRONMENT

Governments around the world are increasingly turning their attention to funding targeted research of more "obvious", relatively short-term, benefit to society. One may anticipate, therefore, continued and perhaps growing funding for environmentally related projects (which is not to understate their importance). A great deal more needs to be known about the relationships between the structures of molecules and their toxicity towards a wide variety of living organisms [96]. Current research fronts include (a) interactions between metal ions and humic or fulvic substances, and the study of metal ions in soil and the chemical forms in which they appear, (b) transformation reactions, distribution and the fate of metallorganic compounds in different environmental compartments, and (c) the recycling of waste and the study of degradative biotechnologies using metalloenzymes directly or via microorganisms. Certainly nature has provided microorganisms which can metabolise much of man's waste, but, in general, such processes are slow. The study of the mechanism of action of the enzymes employed by the microorganisms is vital for degradative biotech-

nology. Furthermore, bacteria can express different enzymes, depending upon the substrate upon which they are forced to grow. The isolation of the gene responsible for the expression of the enzyme could then permit the design of new bacteria that can metabolise predetermined substrates.

Because of the non-standard nature of the biological substrate under study, the reproducibility of such studies between different laboratories has been poor; therefore new and standard procedures need to be developed for sampling and sample analysis.

Just as the best course for solving our energy problems is not larger power stations but conservation, so the best course to solve our environmental problems lies in preventing them as well as dealing with them after the fact. Efforts will be made to replace dangerous chemicals with benign chemicals which can supply the same needs.

G. TEACHING UNDERGRADUATE CHEMISTRY

A final word, on teaching. Introductory chemistry courses have not changed much during the past 30 years. Students seem more reluctant to take chemistry than in the past. Certainly chemistry has a bad public image which exacerbates this problem. Changes in chemistry teaching have always lagged behind the realignment of research frontiers but the current situation is beginning to hurt badly in the critical area of student recruitment. We will have to think about a total overhaul of the curriculum to provide a programme which will attract and challenge the students of the next century. The barriers between inorganic, organic and physical chemistry need to be broken down. A new curriculum might start with experimental organic and inorganic chemistry with computer-aided design [97,98] in the first year, with chemical biology and materials science in the second year, and theoretical chemistry and experimental chemical physics in the third. We must aim to transfer the excitement of modern chemical research to the students if chemistry is to flourish in the 21st century.

ACKNOWLEDGEMENTS

The reporter thanks all the contributors for their input in the construction of this document. He has distilled their comments and is hopeful that the result is not too disjointed. The following individuals, listed in alphabetical order, contributed: R. Amadelli, M. Aresta, V. Balzani, L. Banci, I. Bertini, C. Bianchini, V. Carassiti, J. Cowan, R.S. Drago, S. Forsen, D. Gatteschi, H.B. Gray, S.H. Koenig, J.-M. Lehn, A. Liberatori, S.J. Lippard, C. Luchinat, A. Maldotti, S. Mangani, L. Messori, M. Micheloni, V.I. Nefedov, T. O'Halloran, P. Paoletti, H. Ruterjans, W. Schneider, A. Scozzafava, A. Sgamellotti, H. Sigel, O. Tubertini, R. Ugo, A. Vigato, and A.V. Xavier.

REFERENCES

1 K.M. Merz, J. Am. Chem. Soc., 113 (1991) 406.
2 K.M. Merz, M. Murcko and P.A. Kollman, J. Am. Chem. Soc., 113 (1991) 4484.
3 J.Y. Liang and W.N. Lipscomb, Proc. Natl. Acad. Sci., U.S.A., 87 (1990) 3675.
4 P. Carloni, E. Clementi and G. Corongiu, in preparation.
5 D.L. Oxender and C.F. Fox (Eds.), Protein Engineering, Liss, New York, 1987.
6 T.J. Meade, H.B. Gray and J.R. Winkler, J. Am. Chem. Soc., 111 (1989) 4353.
7 M.J. Therien, M.A. Selman, H.B. Gray, I.J. Chang and J.R. Winkler, J. Am. Chem. Soc., 112 (1990) 2420.
8 H.B. Gray and B.G. Malmstrom, Biochemistry, 28 (1989) 7499.
9 H. Sigel and A. Sigel (Eds.), Metal Ions in Biological Systems, Vol. 27, Dekker, New York, 1991.
10 J.A. Cowan, R.K. Upmacis, D.N. Beratan, J.N. Onuchic and H.B. Gray, Ann. N.Y. Acad. Sci., 550 (1989) 68.
11 J.N. Onuchic and D.N. Beratan, J. Chem. Phys., 92 (1990) 722.
12 M. Aresta and J.V. Schloss (Eds.), Enzymatic and Model Carboxylation and Reduction Reactions for Carbon Dioxide Utilization, Kluwer, Dordrecht, The Netherlands, 1990.
13 M. Aresta, E. Quaranta and I. Tommasi, J. Chem. Soc. Chem. Commun., (1988) 450.
14 A. Lack, I. Tommasi, M. Aresta and G. Fuchs, Eur. J. Biochem., in press.
15 M. Aresta, E. Quaranta and I. Tommasi, in E. Pellizzetti and M. Schiavello (Eds.) Photochemical Conversion and Storage of Solar Energy, Kluwer, Dordrecht, The Netherlands, 1991, pp. 517–550.
16 M. Mitchell-Waldrop, Science, 246 (1989) 1248.
17 H. Sigel, Coord. Chem. Rev., 100 (1990) 453.
18 H. Sigel and R. Tribolet, J. Inorg. Biochem., 40 (1990) 163.
19 (a) H. Sigel, Biol. Trace Element Res., 21 (1989) 49.
(b) H. Sigel, Chimia, 41 (1987) 11.
(c) K.H. Scheller and H. Sigel, J. Am. Chem. Soc., 105 (1983) 5891.
20 H. Sigel, Pure Appl. Chem., 61 (1989) 923.
21 S.S. Massoud, R. Tribolet and H. Sigel, Eur. J. Biochem., 187 (1990) 387.
22 (a) G. Liang and H. Sigel, Inorg. Chem., 29 (1990) 3631.
(b) H. Sigel, S.S. Massoud and R. Tribolet, J. Am. Chem. Soc., 110 (1988) 6857.
(c) H. Sigel, Eur. J. Biochem., 165 (1987) 65.
23 H. Sigel, ACS Symp. Ser., 402, American Chemical Society, Washington, DC, 1989, pp. 159–204.
24 L. Banci, I. Bertini, C. Luchinat and M. Piccioli, Coord. Chem. Rev., 100 (1990) 67.
25 I. Bertini, F. Briganti, C. Luchinat and M. Sola, J. Am. Chem. Soc., 113 (1991) 1237.
26 A. McCammon and S. Harvey, Molecular Dynamics of Proteins and Nucleic Acids, Cambridge University Press, New York, 1987.
27 P.A. Kollman and K.M. Merz, Acc. Chem. Res., 23 (1990) 246.
28 M.J.S. Dewar and K.M. Merz, Organometallics, 5 (1986) 1494.
29 A. Vedani and D.W. Huhta, J. Am. Chem. Soc., 112 (1990) 4759.
30 K.M. Merz, M. Murcko and M. Kollman, J. Am. Chem. Soc., 113 (1991) 4484.
31 L. Banci, P.A. Kollman and S. Schroeder, submitted for publication.
32 R.P. Heaney, Prog. Basic Clin. Pharmacol., (1990) 28.
33 R.Y. Tsien and M. Poenie, Trends Biochem. Sci., 11 (1990) 611.
34 R.R. Preston, Science, 250 (1990) 285.
35 H. Sigel and A. Sigel, Metal Ions in Biological Systems, Vol. 26, Dekker, New York, 1990.

36 R.H. Kretsinger, Cold Spring Harbour Symposium on Quantitative Biology, Vol. LII (1987) p. 499.
37 S. Linse, A. Helmersson and S. Forsen, J. Biol. Chem., 266 (1991) 8050.
38 W.I. Sundquist and S.J. Lippard, Coord. Chem. Rev., 100 (1990) 293.
39 M. Coll, S.E. Sherman, D. Gibson, S.J. Lippard and A.H.-J. Wang, J. Biomol. Struct. Dynam., 8 (1990) 315.
40 J.M. Malinge, M. Sip, A.J. Blacker, J.-M. Lehn and M. Leng, Nucleic Acids Res., 18 (1990) 3887.
41 W.J. Heiger-Bernays, J.M. Essigmann and S.J. Lippard, Biochemistry, 29 (1990) 8461.
42 B.A. Donahue, M. Augot, S.F. Bellon, D.K. Treiber, J.H. Toney, S.J. Lippard and J.M. Essigmann, Biochemistry, 29 (1990) 5872.
43 W.I. Sundquist, D.P. Bancroft, L. Chassot and S.J. Lippard, J. Am. Chem. Soc., 110 (1988) 8559.
44 L. Banci, I. Bertini and C. Luchinat, Nuclear and Electron Relaxation, VCH, Weinheim, 1991.
45 C.F.G.C. Geraldes, A.D. Sherry, R.D. Brown III and S.H. Koenig, Magnet. Reson. Med., 3 (1986) 242.
46 A.D. Sherry, R.D. Brown III, C.F.G.C. Geraldes, S.H. Koenig, K.T. Kuan and M. Spiller, Inorg. Chem., 28 (1989) 620.
47 N. Leventis, M.O. Schloh, M.J. Natan, J.J. Hickman and M.S. Wrighton, Chem. Mater., 2 (1990) 568.
48 A.P.F. Turner, I. Karube and G.S. Wilson, Biosensors: Fundamentals and Applications, Oxford University Press, Oxford, 1987.
49 J. Janata, Chem. Rev., 90 (1990) 689.
50 J.-M. Lehn, Angew. Chem., 100 (1988) 91; 102 (1990) 1347. See also Angew. Chem., Int. Ed. Engl., 27 (1988) 89; 29 (1990) 1304.
51 J.-M. Lehn, M. Mascal, A. DeCian and J. Fischer, J. Chem. Soc., Chem. Commun., (1990) 479.
52 V. Balzani and F. Scandola, Supramolecular Photochemistry, Horwood, Chichester, 1991.
53 H. Fuchs, H. Ohst and W. Prass, Adv. Mater., 3 (1991) 10.
54 V. Balzani and L. Moggi, Coord. Chem. Rev., 97 (1990) 313.
55 J.-M. Lehn et al., 1991, research in progress.
56 T.M. Garrett, U. Koert, J.-M. Lehn, A. Rigault, D. Meyer and J. Fischer, J. Chem. Soc. Chem. Commun., 557 (1990).
57 J.-M. Lehn, A. Rigault, J. Siegel, J. Harrowfield, B. Chevrier and D. Moras, Proc. Natl. Acad. Sci. U.S.A., 84 (1987) 2565.
58 J.-M. Lehn and A. Rigault, Angew. Chem. Int. Ed. Engl., 27 (1988) 1095.
59 M. Baba and S. Matsui, Jpn. J. Appl. Phys. Part 1, 29 (1990) 2854.
60 T.M. Ginnal, Ind. Eng. Chem. Prod. Res. Dev., 24 (1985) 188.
61 C.A. Mirkin and M.S. Wrighton, J. Am. Chem. Soc., 112 (1990) 8596.
62 D.C. Bradley, Chem. Rev., 89 (1989) 1317.
63 T.J. Marks, Angew. Chem. Int. Ed. Engl., 29 (1990) 587.
64 J.M. Williams, H.H. Wang, T.J. Emge, U. Geiser, M.A. Beno, P.C. Leung, K.D. Carlson, R.J. Thorn, A.J. Schultz, M.H. Whangbo, Prog. Inorg. Chem., 35 (1990) 51.
65 D. Gatteschi, O. Kahn, J.S. Miller and F. Palacio (Eds.), Magnetic Molecular Materials, Kluwer, Dordrecht, The Netherlands, in press.
66 W. Gopel, J. Hesse and J.N. Zemel, Sensors, A Comprehensive Survey, VCH, Weinheim, 1989.
67 C. Bianchini, E. Farnetti, M. Graziani, G. Nardin, A. Vacca and F. Zanobini, J. Am. Chem. Soc., 112 (1990) 9190.

68 C. Bianchini, P. Innocenti, A. Meli, M. Peruzzini, F. Zanobini and P. Zanello, Organometallics, 9 (1990) 2514.
69 K.S. Suslick and R.A. Watson, Inorg. Chem., 30 (1991) 912.
70 A. Maldotti, C. Bartocci, R. Amadelli, G. Varani, E. Polo and V. Carassiti, in E. Rizzarelli and T. Theophanides (Eds.), Chemistry and Properties of Biomolecular Systems, Kluwer, Dordrecht, The Netherlands, 1991.
71 C. Bartocci, A. Maldotti, G. Varani, P. Battioni, V. Carassiti and D. Mansuy, Inorg. Chem., 30 (1991) 1255.
72 A.P. Hong, D.W. Bahnemann and M.R. Hoffmann, J. Phys. Chem., 91 (1987) 6245.
73 T. Ohmori, K. Sakamaki and K. Fujishima, Boshoku Gijutsu, 39 (1990) 564.
74 R.J. Wilson, G. Meijer, D.S. Bethune, R.D. Johnson, D.D. Chambliss, M.S. De Vries, H.E. Hunziker and H.R. Wendt, Nature, 348 (1990) 621.
75 W. Schmickler, J. Electroanal. Chem. Interfacial Electrochem., 296 (1990) 283.
76 R. Wiesendanger, H.J. Guentherodt, G. Guentherodt, R. Gambino and R. Ruf, Helv. Phys. Acta, 63 (1990) 778.
77 C.Y. Liu and A.J. Bard, Chem. Phys. Lett., 174 (1990) 162.
78 W.G. Johnson, V. Buch and M. Trenary, J. Chem. Phys., 93 (1990) 9167.
79 W.J. Halperin, Rev. Mod. Phys., 58 (1986) 533.
80 R.J. Puddephatt, L. Manojlovic-Muir and K. Muir, Polyhedron, 9 (1990) 2767.
81 A.M. Stoneham, J. Comput. Aided Mol. Des., 3 (1989) 355.
82 J.P. Gastmans, M. Furlan, M. Lopes, J.H. Borges and V. de P. Emerenciano, Quim. Nova, 13 (1990) 10.
83 K. Schumnig and G. Wuensch, Labor Praxis, 14 (1990) 699.
84 H. Boegel, Wiss. Z. Tech. Hochsch. Carl Schorlemmer Leuna-Merseburg, 30 (1988) 579.
85 P.A. Wender, Pure Appl. Chem., 61 (1989) 469.
86 F. Schwaab, Stud. Phys. Theor. Chem., 71 (1990) 777.
87 N.C. Cohen, J.M. Blaney, C. Humblet, P. Gund and D.C. Barry, J. Med. Chem., 33 (1990) 883.
88 M.G. Ford, R. Greenwood, C.H. Turner, B. Hudson and D.J. Livingstone, Pestic. Sci., 27 (1989) 305.
89 M. Vihinen, Kem. Kemi., 16 (1989) 243.
90 A.D. French and J.W. Brady (Eds.), Computer Modeling of Carbohydrate Molecules, ACS Symp. Ser. 430, American Chemical Society, Washington, DC, 1990, 406 pp. Developed from a Symposium by the ACS Divisions of Carbohydrate Chemistry, Cellulose, Paper, and Textile Chemistry and Computers in Chemistry, at the 197th National Meeting, Dallas, Texas, April 9–14 1989.
91 K. Lipkowitz, J. Chem. Educ., 66 (1989) 275.
92 R.S. Drago, Coord. Chem. Rev., 33 (1980) 251.
93 R.S. Drago, D.C. Ferris and N. Wong, J. Am. Chem. Soc., 112 (1990) 8953.
94 (a) R.G. Parr and P.K. Chattaraj, J. Am. Chem. Soc., 113 (1991) 1854.
(b) P.K. Chataraj, H. Lee and R.G. Parr, J. Am. Chem. Soc., 113 (1991) 1855.
95 A.B.P. Lever, Inorg. Chem., 29 (1990) 1271.
96 H.G. Seiler, H. Sigel and A. Sigel (Eds.), Handbook on Toxicity of Inorganic Compounds, Dekker, New York, 1988.
97 J.A. Tanner, J. Chem. Educ., 67 (1990) 917.
98 R.M. Jarret and Ny Sin, J. Chem. Educ., 67 (1990) 153.