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CONNECTIONS BETWEEN COORDINATION, ORGANOMETALLIC, AND BIOINORGANIC CHEMISTRY

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In response to an invitation from the editors to contribute to this special volume, I have prepared the following reminscence of my scientific career. Within this account I shall describe the themes which have influenced and connected my research and the role played by historical opportunity, able coworkers, and serendipity. Perhaps this story will interest young chemists who are beginning their independent research.

My first contact with research subsequently influenced my first independent work, four years later. While a B.S. student at the University of Nebraska, I was encouraged by Henry Holtzclaw to investigate the polarographic reduction of some β-diketone complexes [1]. I remained at Nebraska for an M.S. degree and carried out spectroscopic studies of these transition metal chelates. I found this research less interesting because of my weak physical-chemical background and my greater interest in chemical reactions. At that time inorganic chemistry did not seem to me to be a comprehensible topic. About then Henry Baumgarten aroused my interest in organic chemistry, which seemed more rational because of the connections between reaction mechanism and synthesis. I began to wonder whether those coordination complexes I had previously worked with would undergo reactions without being degraded. A few reactions of metal acetylacetonates were already described in the literature, but I was then unaware of these examples.

Abandoning inorganic chemistry, in 1956 I went to the University of Illinois to study organic chemistry under the late R.C. Fuson. I proposed to study reactions of coordination complexes, but Fuson was reluctant to support such work, even though he gave me total independence and almost no advice on the Grignard chemistry project to which I was assigned. At that time ferrocene had just been discovered and Ken Rinehart at Illinois was already working on its reactions. I remember being very impressed by E.O. Fischer's seminar about bis-benzenechromium. However, the structures, bonding, and reactions of these organometallic systems were then quite mysterious to me. This was partly my fault, because a better than average performance on the entrance exams excused me from taking an inorganic course and, unwisely, I did not do so. I did, however, obtain a strong organic background, especially from N.J. Leonard and E.J. Corey.

In 1958 I was fortunate to secure a position as instructor at the University of North Carolina at Chapel Hill. In fact, I was surprised to receive offers to become a member of either the organic or the inorganic faculty, but not both! I chose the former offer, because organic positions were then so much more difficult to obtain, but I was not permitted to direct inorganic Ph.D. students, a situation which prevailed until about 1966. I therefore began to do inorganic research with organic graduate students. I have always disliked the compartmentalization of chemistry departments which still exists in many universities.

Upon gaining research freedom, I soon returned to metal acetylacetonates and began to study their electrophilic substitution reactions. We found that these substances undergo a wide range of quasi-aromatic reactions [2]. Proton NMR and chromatography were then rather new techniques which facilitated this research. At the same time, I was assigned to teach organic chemistry to premedical students and was thus forced to learn more about peptide chemistry, a subject I had disliked in graduate school. Research grants, which were rather new then, were far easier to obtain from NIH than from NSF. Thus, on purely avaricious grounds, I sat down to write an NIH proposal. This effort resulted in one of the best ideas I have ever had: that a class of bis-aquohydroxycobalt(III) tetramine complexes would rapidly cleave the N-terminal amino acid residues from peptides in aqueous solution at physiological pH and room temperature. They do, albeit stoichiometrically rather than catalytically. To conceive of this idea was one thing, but to carry it out was quite another. My students at the time were unable to cope with two such different areas—coordination chemistry and peptide chemistry. However, at an ICCC meeting in Detroit I again encountered the famous Australian chemist, Frank Dwyer, with whom I had discussed reactions of coordinated ligands during my undergraduate days at Nebraska. Brashly, I asked if Dwyer could recommend (provide) a postdoctoral. His New Zealand student, D.A. Buckinham, was supposed to study with Basolo; however, Basolo was scheduled to be on sabbatical. Thus Dave Buckingham joined me at Chapel Hill and successfully developed the chemistry in my proposal [3]. Later on, Buckingham worked out the mechanisms of these reactions jointly with Alan Sargeson in Canberra, Australia.

In 1962, on my way to another ICCC meeting in Sweden, I visited Jack Lewis and Ron Nyholm in London and was very impressed by their work concerning covalent metal—metal bonds. During the same trip I first met Oren Williams of the NSF, who was willing to take a chance on supporting a young chemist (he still is).

Back in Chapel Hill another New Zealand postdoctoral, Warren Roper, had arrived, having been recommended by Buckingham. Roper and I began to discuss the reactions of organotransition metal complexes, including L. Vaska's remarkable complex. We saw a pattern between these reactions and electrophilic additions to olefins, which we later wrote about in our review on "oxidative-additions" [4]. I was principally interested in such reactions as a method of forming metal—metal bonds. We also began to write a review of this subject, but we abandoned the effort, since in this, as in most of our initial experimental work, we were continually "scooped". We pushed on, however, with a broad study of oxidative-addition reactions and eventually developed a synthesis of some novel ruthenium(0) and osmium(0) complexes [5]. During this period Roper taught me a great deal about structural and synthetic transition metal chemistry and, in turn, I taught him some organic chemistry. It was obvious that there were many oxidative-addition reactions to try and we explored several of these [6]. There were experimental and intellectual limitations to our work. We lacked the equipment and expertise to work with air-sensitive substances, and at first we avoided doing so. We did employ medium pressure reaction vessels, obtained from a local industrial laboratory. We also shied away from kinetic studies, because of my inexperience. Other things also slipped by. For example, I discouraged my student, C. Sears, from exploring a ruthenium(0) oxo catalyst which he discovered, because we did not have our own gas chromatograph.

We became interested in the stereochemistry of oxidative-additions to Vaska's iridium complex. Another New Zealand chemist and a crystallographer, Ward Robinson, at the time a postdoctoral with Ibers, visited our lab. We discussed the possibility of employing X-ray diffraction to resolve this stereochemical problem, but our crystals proved too complex and we abandoned this approach. This problem was solved [7] using ^{1}H NMR and IR spectroscopy, along with the then new technique of thin layer chromatography, which we had been using in the final stages of our acetylacetonate chemistry [8]. It is interesting that we learned of this technique from a colleague just back from a Gordon conference. A grooved glass shower door was cut up at a local hardware store to make our first plates. Kinetically controlled, *trans* oxidative-addition of polar substrates was established using these techniques.

During this period I was becoming increasingly interested in the reactions of coordinated ligands and the mechanisms of homogeneous catalysis. With my colleague, W.F. Little, I studied the mechanism of acetylene cyclotrimerization [9] using the iridium dinitrogen complex which my postdoctoral Kang serendipitously discovered while examining some oxidative-additions of 1,3-dipoles [10].

At that point M. Kubota, whom I had known as a fellow student at Illinois, came to Chapel Hill on his sabbatical leave. Together we explored atom-transfer redox reactions between coordinated dioxygen and other coordinated substrates [11]. Thus began my long-standing interest in dioxygen.

About that time I took a sabbatical at Stanford, largely because of its pleasant climate and the presence of a famous inorganic chemist, Henry Taube, whose research interests were so different from my own that I thought the scientific community would not confuse our research. Retrospectively, I deplore this attitude. However, Taube's longstanding interest in dioxygen was eventually to influence my own work.

During this period my interest in metal—metal bonds had not diminished [12]. I was intrigued by the possibility that polymeric intermetallic chains might exhibit electrical conductivity. We explored this idea with some solid state physicists in the Research Triangle [13].

In 1967 I could not resist a call to Stanford and I brought along my interests in reactions of both organotransition metal compounds and dioxygen complexes, but little in the way of physical or human resources. My earlier interest in the electron-transport properties of metal—metal bonds was further stimulated by a colleague in Physics, W.A. Little, who had published a still controversial theory of achieving superconductivity at high temperature through an excitonic mechanism. Bill Little taught me something about solid state physics and I taught him some organic chemistry. Thus I continued my interest in synthesizing metal-bonded oligomers [14], but I eventually abandoned Little's elusive goal.

During this period I was still interested in organometallic reactions, but things were not going well. I was anxious to develop organotransition metal compounds which are catalysts or reagents useful for organic synthesis. However, our efforts on nitrosyl complexes [15] were abandoned, as were our interests in cluster catalysis, because the necessary mass spectrometry facilities were not accessible. Serendipity struck. During an attempted synthesis of metal—metal bonds in the physics project, a postdoctoral associate, M.P. Cooke, chanced upon some organic reactions of $Na_2Fe(CO)_4$ [16]. After developing a practical method for synthesizing this very air-sensitive substance (by now I had acquired a good inert atmosphere chamber), my students began to explore organic syntheses using this reagent [17]. In collaboration with my colleague, John Brauman, we began to explore the kinetics and mechanisms of these reactions. Our student, Rick Finke, thus explicated the diverse ion-pairing effects which these anionic reagents exhibit in these oxidative-addition [18] and migratory insertion reactions [19].

My long-standing interest in reactions of coordinated dioxygen [20] and my previous "bioinorganic" venture with peptide complexes led me to explore synthetic analogues of the cytochrome oxygenase P_{450} family. Barry Sharpless started this work as a postdoctoral, but he did not get very far, except to stimulate further his now celebrated interest in oxidation reactions. This problem was then taken up by another New Zealand postdoctoral, Chris Reed (a student of Roper's), who had just arrived in my lab. Reed and my student Bob Gagné eventually isolated stable iron-dioxygen complexes of the "picket-fence porphyrins" [21]. These compounds proved to be remarkably good synthetic and structural analogues of the oxygen binding sites in hemoglobin and myoglobin [22]. The initial structural work [23] was carried out by Ward Robinson, who happened to be on sabbatical in my lab when the dioxygen complex was isolated. This picket-fence porphyrin system was further refined by Tom Halbert [24] and Ken Doxsee [25] under the co-direction of Brauman.

As this work was progressing, Taube introduced me to the problem of catalyzing the 4-electron reduction of dioxygen. Such a catalyst is necessary at the oxygen cathode of a fuel cell. In acid media only platinum works adequately; cytochrome-c oxidase also catalyzes this 4-electron reduction of oxygen, employing two hemes and two copper centers in a still mysterious mechanism. I thus joined a team consisting of Henry Taube and Michel Boudart at Stanford, Fred Anson at Caltech, and Howard Tennent at Hercules to explore this general problem.

Starting from the picket-fence porphyrin concept, we planned the synthesis of "face-to-face" cyclophane porphyrins in the hope that two metal centers acting jointly on dioxygen might facilitate its reduction. After much travail, we eventually prepared some compounds of this type [26] and developed methods for characterizing their co-facial interaction. Our first face-to-face porphyrin derivatives were not effective catalysts for oxygen reduction (although they do catalyze N_2O reduction). Eventually we succeeded in finding a dicobalt face-to-face porphyrin which is a very efficient catalyst for oxygen reduction. At +0.72 V vs SHE this catalyst effects a 4-electron reduction of O_2 at a turnover of ~50 events per site per second, which is at least an order of magnitude faster than platinum at +0.6 V [27]! As this work has continued, it has become clear that we do not understand the role which the two metals play in the mechanism of this remarkable process. It is ironic that in this research I had come full circle back to electrochemistry after a lapse of 24 years.

At this point I shall turn to another theme which began soon after I came to Stanford, but which is just now beginning to show promise. Because of my long-standing interest in the role which coordinative unsaturation plays in catalysis [28], we had tethered both mononuclear and cluster complexes to cross-linked polystyrene and examined these substances as hydrogenation catalysts. I had hoped that such highly unsaturated, immobilized complexes would be very active catalysts; however, they proved to be disappointing on two grounds [29]. First, our solvent-swollen, cross-linked polystyrene was too mobile to achieve site isolation. Second, both the clusters and the highly unsaturated metal centers which we generated within these polymers exhibited a tendency to aggregate, forming metal particles similar to traditional heterogeneous catalysts. In view of the shortcomings of these polystyrene-bound ligands, we spent several years preparing a silica-bonded chelating phosphine; immobilized rhodium hydrogenation complexes derived from this system proved resistant to aggregation and behaved much like their homogeneous analogues. This work, therefore, seemed to be finished with a trivial result.

Reading my former student Jack Norton's [30] papers on binuclear reductive-elimination reactions, it occurred to me that certain homogeneously catalyzed reactions, such as the oxo process, may involve such a binuclear reductive-elimination step in the catalytic cycle. This idea had also occurred to Norton and, in fact, was already supported by some data in the literature [31]. I realized that our silica-bonded, site-isolated, bidentate phosphines are well-suited to probe the possible involvement of a binuclear step in various catalytic reactions. A Stanford undergraduate, Eric Moore, began to explore this question.

In fact, our silica-bonded rhodium complex barely catalyzes olefin hydroformylation, even though the analogous soluble complex by itself is an effective precatalyst for the oxo reaction [32]. Moreover, the combination of a small amount of the soluble analogue and the silica-bonded complex is a better catalyst! Even though the actual catalysts for these oxo reactions have not been well characterized, these preliminary results indicate that the dynamics of a catalytic reaction can be dramatically altered by site isolation and lend credence to the hypothesis that binuclear elimination sometimes plays an important role in homogeneously catalyzed reactions.

We are also employing cross-linked organic polymers as *substrates* for homogeneously catalyzed reactions. These systems are designed to distinguished a truly homogeneous catalyst from a heterogeneous catalyst. For example, ^{13}C labeled olefinic groups attached to 1% cross-linked polystyrene are readily hydrogenated in the presence of Wilkinson's catalyst, $RhCl(PPh_3)_3$; however, heterogeneous hydrogenation catalysts of all types, including metal sols, do not affect these polymeric substrates [33]! Using these systems we are in the process of studying some "homogeneous catalysts", which we suspect actually involve small metal particles as the active catalysts.

Looking back over my past research, I can see the threads which connect coordination chemistry, organometallic chemistry, and bioinorganic chemistry. I tend to think of this sort of chemistry as "molecular engineering". It is clear that past experience, scientific opportunity, but most importantly, the creative talent of students, co-workers, and able collaborators, are essential to the kind of research I have engaged in.

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