Overlooked opportunities in stereochemistry: neglected connection between Werner's metal-ammines and Pope's organic onium compounds

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Abstract – One of the intriguing but unanswered questions in the history
of coordination chemistry is why it took so long for Alfred Werner (1866-
1919) and his students to resolve coordination compounds and thus prove
the correctness of both his concept of the octahedral configuration for
cobalt(III) and his coordination theory. In view of Werner's expertise in
both organic and inorganic stereochemistry, especially of nitrogen com-
pounds, and his documented familiarity with the work of Sir William
Jackson Pope (1870-1939), it is surprising that he did not immediately
avail himself of the new and versatile resolving agents introduced by that
famous English stereochemist. Similarly, it is surprising that Pope did
not make use of Werner's theoretical views to interpret the configurations
of the unusual compounds which he had synthesized and resolved for the
first time. The contributions of both chemists to the field of stereo-
chemistry are examined, and possible reasons why they failed to use each
other's work to solve their respective stereochemical problems are dis-
cussed. In doing so, some light may be shed on the relations between
scientists of different nationalities working in the same area and on the
blind spots which are sometimes exhibited in dealing with and evaluating
the works of rivals.

WERNER'S INTEREST IN ORGANIC CHEMISTRY

Alfred Werner (1866-1919)(ref. 1) is best known as the undisputed founder of coordination
chemistry and the great systematizer of structural inorganic chemistry, which earned him the
epithet of the inorganic Kekulé. Yet many chemists fail to realize that he was trained pri-
marily as an organic chemist at the Eidgenössisches Polytechnikum (now the Eidgenössische
Technische Hochschule) in Zürich, and despite his later preoccupation with coordination com-
pounds, his interest in organic chemistry continued throughout the entire thirty years of his
scientific career (ref. 2).

Werner's first publication, "Über räumliche Anordnung der Atome in stickstoffhaltigen
Molekülen" (ref. 3), excerpted from his doctoral dissertation, remains his most popular and
important work in the organic field. With this paper, co-authored with his teacher Arthur
Hantzsch (1857-1935), one of the most important organic chemists of the time, the 23-year-old
Werner entered into one of the most exciting disputes in the history of organic chemistry,
which in this case centered around the oximes (ref. 4), which constitute the classic example
of geometric isomerism among trivalent nitrogen compounds.

In contrast to the more conventional views of their predecessors, Werner and Hantzsch attri-
buted the stereoisomerism not to the carbon atom but to the nitrogen atom. They transfered
van't Hoff and Le Bel's spatial concepts from the carbon atom to the nitrogen atom:

> In certain compounds, the three valences of the nitrogen atom
> are directed toward the corners of a (in any case irregular)
> tetrahedron whose fourth corner is occupied by the nitrogen
> atom itself (ref. 3a, p. 18; ref. 3b, p. 159).

Thus Werner played a central role in the elucidation of the stereochemistry of nitrogen just
as he was later to do in that of cobalt, platinum, chromium, and other transition metals.

"QUINQUEVALENT" NITROGEN COMPOUNDS

An area of research in which both Werner and Pope made valuable contributions yet apparently
did not make use of each other's results was the stereochemistry of what was then called
quinquevalent (fünfwertig) nitrogen and is now known as tetracovalent nitrogen (refs. 5 & 6).

Metal-ammonia salts (now called metal-ammines) are the prototypes of coordination compounds and the ones most extensively investigated by Werner. Just as Werner first approached the unexplained metal-ammines in terms of their analogy with the better known ammonium salts, he later (1903) applied his coordination theory to the ammonium salts (ref. 7). Thus ammonium salts, like metal-ammines, occupied a central position in Werner's work.

Three contending constitutional formulas for ammonium salts were proposed: (1) the molecular formula (Molekülformel) defended by August Kekulé and the adherents to his principle of constant valence (ref. 8), (2) the valence formula (Valenzformel) proposed by Edward Frankland and the advocates of variable valence (ref. 8), and (3) Werner's auxiliary valence formula (Nebenvalenzformel), in which the nitrogen atom was assumed to have a tetrahedral configuration and which is universally accepted today.

The first generally accepted resolution of a substituted ammonium compound was accomplished by the eminent English stereochemist, William Jackson Pope (1870-1939), who, by use of the silver salt of the strong acid, d-bromocamphorsulfonic acid, succeeded, in collaboration with Stanley John Peachey, in resolving methylallylbenzylphenylammonium iodide (ref. 9). This was soon followed by numerous resolutions, which were evidence for Werner's tetrahedral configuration but were still compatible with the tetragonal pyramidal configuration. In 1928 Wyckoff examined the crystal structure of tetramethyl- and tetraethylammonium halides and found that each nitrogen atom was surrounded tetrahedrally by four methyl or ethyl groups (ref. 10). Werner's prediction of almost forty years earlier had at last received its most direct confirmation.
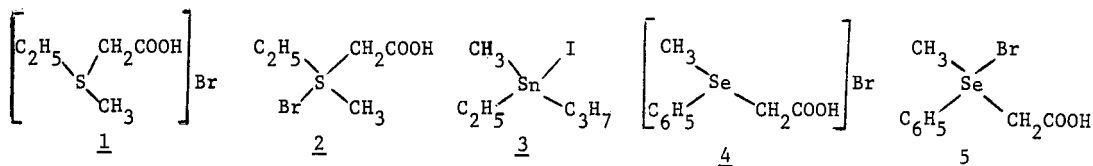
POPE'S CONTRIBUTIONS

Of Pope's numerous contributions to the resolution of optically active isomers only those directly relevant to Werner's work will be considered. In 1893, the very year that Werner published his coordination theory (ref. 11), Pope, together with Frederic Stanley Kipping, found that camphor can be sulfonated by fuming sulfuric acid and that the sulfochlorides, sulfobromides, and their derivatives were compounds of exceptional crystallizing power (ref. 12).

Until 1899 compounds that exhibited optical activity all contained one or more asymmetric carbon atoms, and it was widely believed that the presence of an asymmetric carbon atom was a necessary condition for optical activity. Shortly after recognizing the superiority of the camphorsulfonates and bromocamphorsulfonates over other resolving agents, Pope "lost no time in applying them to one of the outstanding problems of the time--the resolution of symmetrically substituted ammonium salts" (ref. 13, p. 260).

As we have already seen in our discussion of "quinquevalent" nitrogen compounds, in 1899, by the use of silver (+)-3-bromocamphor-9-sulfonate Pope and Peachey succeeded in resolving methylallylbenzylammonium iodide (ref. 9). This resolution not only furnished evidence for Werner's postulated tetrahedral configuration for nitrogen, but for the first time an optically active compound which owed its activity to an asymmetric atom other than carbon had been prepared, showing that the valence bonds of an element other than carbon had sufficient stability to give rise to optical activity in an asymmetric configuration. Unfortunately, Pope interpreted his resolution in terms of "quinquevalent" nitrogen rather than Werner's tetrahedral nitrogen. This discovery attracted wide attention. It was immediately recognized as a stereochemical contribution of the first magnitude, and it opened a wide field to be exploited by Pope and others.

Once he had shown that the carbon atom had no monopoly on optical activity, Pope followed this resolution of an asymmetric nitrogen compound in rapid succession with resolutions of asymmetric compounds of other elements. The following year he and Peachey resolved an asymmetric compound of sulfur, methylethylthetine bromide (1) (which they formulated as (2)), with (+)-3-bromocamphor-9-sulfonate (ref. 14). That same year Pope and Peachey resolved an asymmetric tin compound, methylethyl-n-propyltin(IV) iodide (3) (which they formulated correctly) (ref. 15), and in 1902 Pope and Allen Neville resolved an asymmetric selenium compound, methylphenylselenetine bromide (4), (which they formulated as (5)) (ref. 16), in both

$$
\left[\begin{array}{c} C_2H_5 \diagdown \diagup CH_2COOH \\ S \\ CH_3 \end{array} \right] Br \qquad \begin{array}{c} C_2H_5 \diagdown \diagup CH_2COOH \\ S \\ Br \diagup \diagdown CH_3 \end{array} \qquad \begin{array}{c} CH_3 \diagdown \diagup I \\ Sn \\ C_2H_5 \diagup \diagdown C_3H_7 \end{array} \qquad \left[\begin{array}{c} CH_3 \diagdown \diagup \\ Se \\ C_6H_5 \diagup \diagdown CH_2COOH \end{array} \right] Br \qquad \begin{array}{c} CH_3 \diagdown \diagup Br \\ Se \\ C_6H_5 \diagup \diagdown CH_2COOH \end{array}
$$

$$\underline{1} \qquad\qquad \underline{2} \qquad\qquad \underline{3} \qquad\qquad \underline{4} \qquad\qquad \underline{5}$$

cases through the precipitation of the (+)-3-bromocamphor-9-sulfonates. Pope later (1912) unsuccessfully attempted to resolve asymmetric phosphonium compounds (with Charles Stanley Gibson) and asymmetric arsonium compounds (with T. F. Winmill).

ALFRED WERNER
(1866 - 1919)

Sir WILLIAM JACKSON POPE
(1870 - 1939)

IUPAC President : 1923-1925

ARTURO MIOLOTI AND ALFRED WERNER
(left)   (right)

photograph 1893

ALFRED WERNER (left) and ARTHUR HANTZSCH (right)
(1866-1919)   (1857-1935)

photograph 1910

According to Gibson,

> The experimental proofs that nitrogen, sulfur, selenium and tin
> could, like carbon, be centres of asymmetry and give rise to
> optically active compounds constituted the greatest advance in
> stereochemistry since the work of Pasteur, van't Hoff and Le Bel
> (ref. 17, p. 307).

However, as in his interpretation of "quinquevalent" nitrogen compounds, Pope was incorrect in his assignment of constitution to the optically active compounds of tetravalent sulfur and selenium, which he regarded as formally analogous to compounds of asymmetric tetravalent carbon. Yet, even at a time when the distinction between what we now call electrovalence and covalence was imperfectly understood, when the role of electron pairs and empty orbitals in bonding was unknown, and before Max von Laue and W. H. and W. L. Bragg had used X-ray diffraction to demonstrate the existence of ions even in the solid state, Pope pointed out that the compounds in question were salts, which ionized in solution, and that in the optically active ions only three groups were bonded to the asymmetric atom (ref. 13, p. 260; ref. 18).

THE NEGLECTED CONNECTION

The results of Pope's research should have been of great interest and significance to Werner and his work and vice versa. Two coordination chemists who have been active in the field since the 1930s, K. A. Jensen of the University of Copenhagen, and Joseph Chatt, who was a student at Cambridge University during the latter time of Pope's tenure there, are fairly certain that there was no <u>direct</u> contact between Pope and Werner. They base their supposition largely on the fact that Pope was a "classical organic chemist" (Jensen), while "Werner was an inorganic chemist, and...the gulf between the disciplines was wider in the early part of this century even than it is now" (Chatt). Also Prof. Chatt's research supervisor, Frederick G. Mann, never mentioned any such contact. An examination of Werner's correspondence for the period October 8, 1896 to April 6, 1909 reveals a few letters to English chemists but none to Pope, while among the few surviving letters of Pope's none to Werner could be found. However, Werner was active in organic chemistry throughout his career and did not believe in the customary divisions between the different branches of chemistry, while much of Pope's research dealt with inorganic or organometallic compounds. Therefore, as productive, internationally known stereochemists conversant with the literature of both organic and inorganic chemistry, they were undoubtedly well acquainted with each other's work.

Pope's awareness of Werner's work

Although most of Werner's work appeared in German, this should have presented no obstacle for Pope, who learned foreign languages readily and became proficient in both German and French in his teens, and "his fluent French and German proved invaluable in later years and singled him out to represent [England] with significant success at international conferences" (ref. 19, p. 698). Pope translated Andreas Ludwig Fock's <u>Einleitung in die chemische Kystallographie</u> (W. Engelmann: Leipzig, 1888) into English. Also, although there seems to have been some mutual rivalry and jealousy between British and continental chemists, Pope was an internationally oriented scholar who became the first president of the IUPAC (1922-1925). Also, any possible competition did not prevent him from collaborating with the German chemist Otto Wallach on the resolution of a centroasymmetric compound, published simultaneously in English and German (ref. 20).

Also, even if Pope had not been fluent in German, most of Werner's articles were almost immediately abstracted in the <u>Journal of the Chemical Society (London),</u> and a few were later available in English translation, including his book <u>Neuere Anschauungen auf dem Gebiete der anorganischen Chemie.</u> Furthermore, by the closing years of the nineteenth century Werner was sufficiently well known in England as to attract graduate students from that country. Direct evidence of Pope's acquaintance with Werner's work and of the manner in which it was then viewed by British chemists is provided by John Read, who returned to England in the autumn of 1907 after receiving his doctorate under Werner and began a fruitful eight-year collaboration with Pope:

> When he [Pope] had shaken hands he asked: "Well, and what do you
> think of Werner's Co-ordination Theory?" Evidently he was unable
> at that time to share to the full the opinion of an ardent disci-
> ple; but British chemists in general were not disposed to regard
> Werner's views with the attention they deserved until he achieved
> the first resolution of a co-ordination compound in 1911 (ref. 21,
> p. 284).

Pope and other British chemists finally became convinced of the validity of Werner's views, and by 1932 in a lecture entitled "Forty Years of Stereochemistry," Pope paid tribute to Werner both for his coordination theory and for his postulation of a tetrahedral configuration of the nitrogen atom in oximes, which "have given a stereochemical aspect to the whole of chemistry" (ref. 22).

Werner's awareness of Pope's work
Since lack of definitive proofs for both his ammonium theory and his coordination theory
prevented their acceptance by the chemical community, it is surprising that Werner did not
make use of Pope's work. Today, of course, we recognize in Werner's remarkably modern view-
point the genesis of what was later to become the Lewis octet theory and a precursor of
Lewis' generalized theory of acids and bases. Werner was no narrowly sectarian inorganic or
organic chemist; he viewed the formation of a fourth bond by the nitrogen atom of the ammonia
molecule by reaction with methyl iodide, hydrochloric acid, or a cobalt salt as essentially
the same type of reaction. In modern terms, the unshared pair of electrons on the nitrogen
atom forms a coordinate covalent bond.

Although Werner was not proficient in English, the language in which Pope's works appeared,
he undoubtedly followed Pope's research, either in the original publications or in German or
French abstracts, for in his <u>Lehrbuch der Stereochemie</u> (1904), but not in any editions of his
<u>Neuere Anschauungen auf dem Gebiete der anorganischen Chemie</u>, he cited Pope's resolutions of
various organic compounds (pp. 68, 81) and of asymmetric nitrogen (p. 304), sulfur (pp. 7,
312-313), selenium (p. 314), and tin (pp. 7, 314-315) compounds and interpreted the constitu-
tion of the sulfur, selenium, and tin compounds (pp. 316-317) in terms of extensions of his
ammonium theory (ref. 23). However, he made no reference to the fact that Pope and Peachey's
resolution of methylallylbenzylphenylammonium iodide (ref. 9) was evidence in favor of his
own tetrahedral configuration for nitrogen.

Werner recognized that optical resolution of asymmetric coordination compounds would provide
an elegant and definitive proof of his postulated octahedral configuration for cobalt(III),
one of the most basic tenets of his coordination theory, and he was actively seeking
suitable candidates for resolution as early as February 1897 (ref. 24). Yet although he was
aware of Pope's use of the powerful resolving agents, the (+)-3-bromocamphor-9-sulfonates, as
evidenced by his citation of the resolutions mentioned in the last paragraph, and although he
corresponded with John Read and followed his work while Read was working with Pope at Cam-
bridge (ref. 21, p. 296), nevertheless, he did not avail himself of their use until his
classic resolution of <u>cis</u>-bromo- and chloroamminebis(ethylenediamine)cobalt(III) salts in
1911 (ref. 25; ref. 11b, pp. 159-173), which led to his being awarded the Nobel Prize in
Chemistry in 1913. It was apparently Werner's American student Victor L. King rather than
Werner himself who chose the successful resolving agent (ref. 26).

A dozen years earlier, with his resolution of the first asymmetric nitrogen compound
(ref. 9), Pope had forced the carbon atom to relinquish its apparent monopoly on optical iso-
merism. Now, with the first resolution of an octahedral complex, accomplished with the aid
of Pope's resolving agent, Werner had similarly forced the tetrahedron to relinquish its
apparent monopoly on optical isomerism.

CONCLUSION

We have shown how the work of each of two of the greatest stereochemists of all time could
have mutually enriched, reinforced, and accelerated the contributions of each to science.
Both men were familiar with each other's work but apparently chose not to make use of it for
reasons of rivalry, jealousy, or motives unknown to us. Werner failed to recognize in Pope's
(+)-3-bromo-camphor-9-sulfonic acid the long-sought resolving agent that would provide the
key to the riddle of resolving optically active coordination compounds needed to prove the
octahedral configuration of cobalt(III) and his coordination theory. He also failed to
recognize in Pope's resolution of an asymmetric nitrogen compound strong evidence for his
assignment of a tetrahedral configuration to the nitrogen atom. Pope likewise failed to
recognize in Werner's views a simple explanation for the constitution and configuration of
the unusual compounds that he was the first to resolve. Pope eventually accepted Werner's
views, but by this time Werner had already died. Had they chosen to collaborate during the
1890s or even the first ten or fifteen years of the twentieth century, they would have made
a formidable team that might have accomplished much more than they did by working separately.
All that we can do is to lament with John Greenleaf Whittier:

> For of all sad words of tongue or pen,
> The saddest are these: "It might have been!"

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