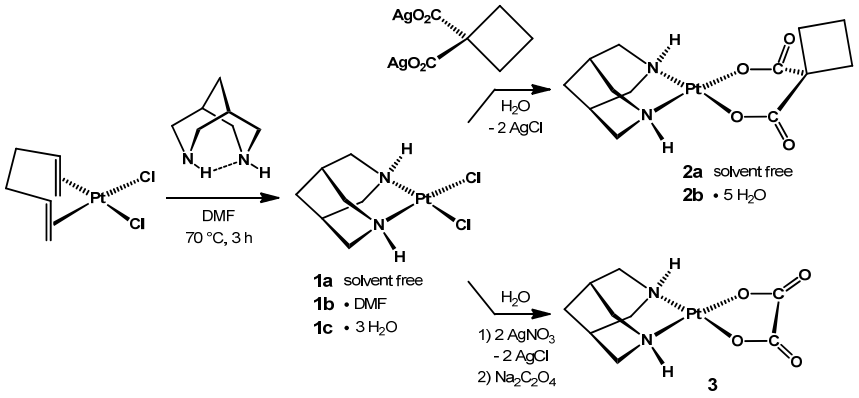
2.2.12 Research area "Bispidine Analogs of Cisplatin, Carboplatin, and Oxaliplatin" (K.-R. Pörschke)

Involved: H. Cui, W. Gamrad, R. Goddard

Objective: Cisplatin is the leading antitumor drug. There are, however, substantial side-effects associated with its administration. Additional major problems are an inherent platinum resistance (esp., toward colon cancer) and the development of an acquired platinum resistance of refractory tumors. Related developments are carboplatin and oxaliplatin. Present research on platinum-based drugs is directed at the reduction of side-effects and the enlargement of the spectrum of activity. Since the parent bispidine (3,7-diazabicyclo[3.3.1]nonane) has become available to us from previous work, we have used it as a possible "carrier ligand" and synthesized the corresponding analogs of cisplatin, carboplatin, and oxaliplatin.

Results: Reaction of (1,5-hexadiene)$PtCl_2$ with bispidine ($C_7H_{14}N_2$) in DMF afforded large pale yellow crystals of the DMF adduct ($C_7H_{14}N_2$)$PtCl_2$·DMF (**1b**) in 87% yield. Recrystallization from the less basic *N*-methyl formamide gave solvent free ($C_7H_{14}N_2$)$PtCl_2$ (**1a**) and from water the trishydrate ($C_7H_{14}N_2$)$PtCl_2$·$3H_2O$ (**1c**) was obtained. Similarly, the Pt–bispidine analogs of carboplatin, both solvent-free ($C_7H_{14}N_2$)Pt{$(O_2C)_2C_4H_6$} (**2a**) and the pentahydrate ($C_7H_{14}N_2$)Pt{$(O_2C)_2C_4H_6$}·$5H_2O$ (**2b**), and the analog of oxaliplatin, solvent-free ($C_7H_{14}N_2$)Pt(C_2O_4) (**3**), were prepared.



Of particular interest are the structures of the hydrates **1c** and **2b**. In the solid chloride **1c** the complex molecules are linked by parallel N–H···Cl hydrogen bonds to give infinite bands, which are accompanied on both sides by zigzag-shaped strings of water molecules (Figure 1). In contrast, in crystals of the 1,1′-cyclobutanedicarboxylate **2b** the

complex molecules are monomeric and completely surrounded by a shell of water molecules, easily explaining the enhanced water solubility of this complex (Figure 2).

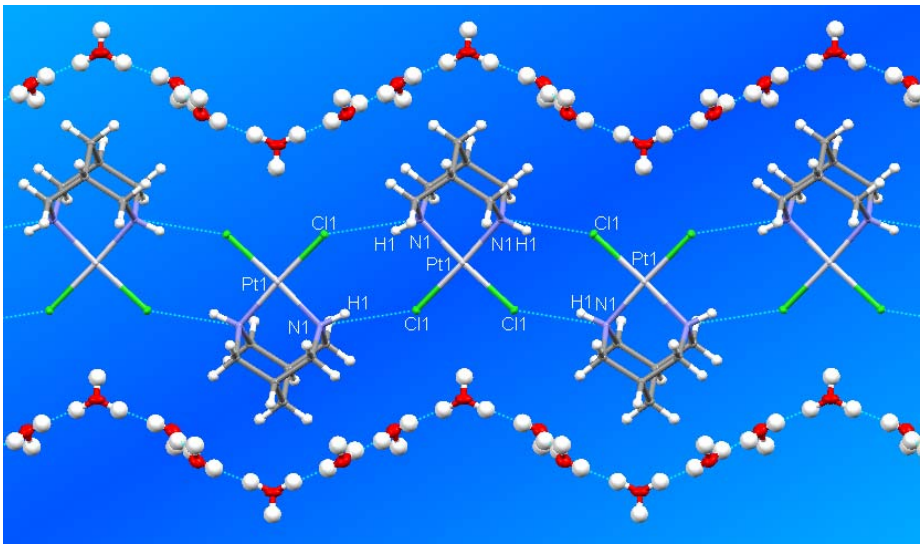


Figure 1. Crystal structure of $(C_7H_{14}N_2)PtCl_2 \cdot 3H_2O$ (**1c**).

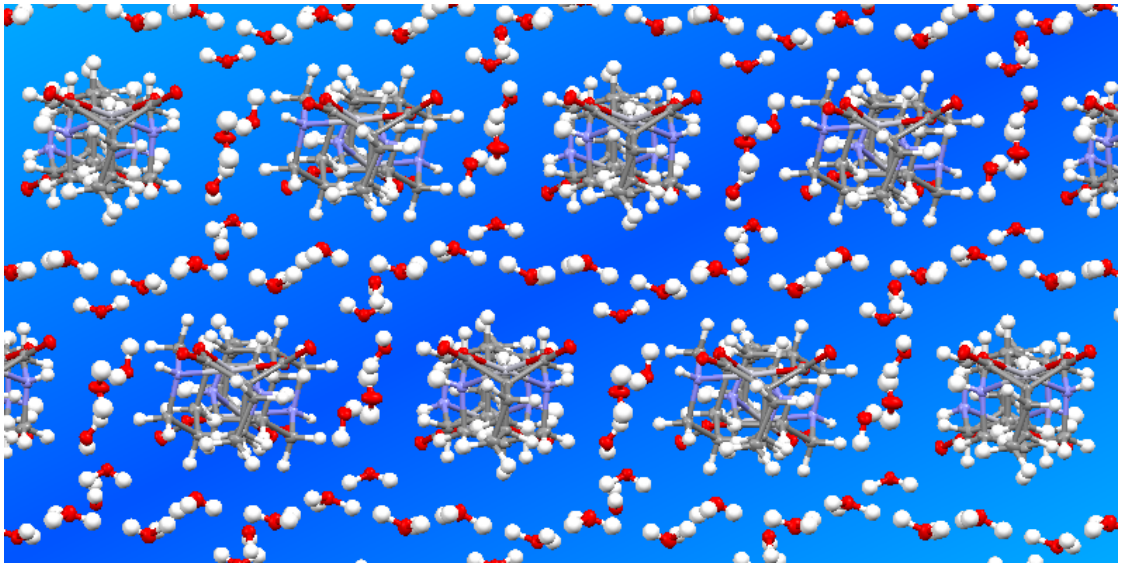
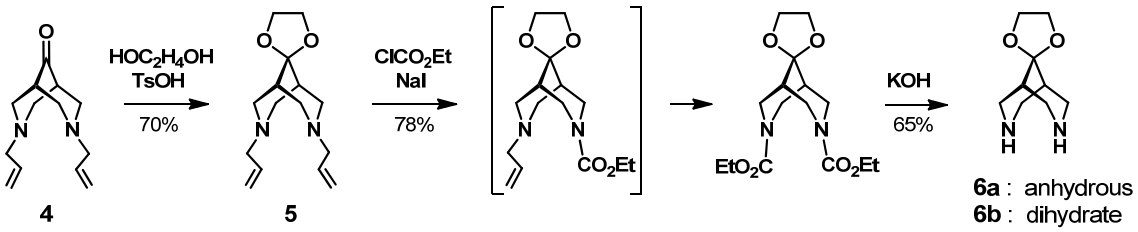


Figure 2. Crystal structure of $(C_7H_{14}N_2)Pt\{(O_2C)_2C_4H_6\} \cdot 5H_2O$ (**2b**).

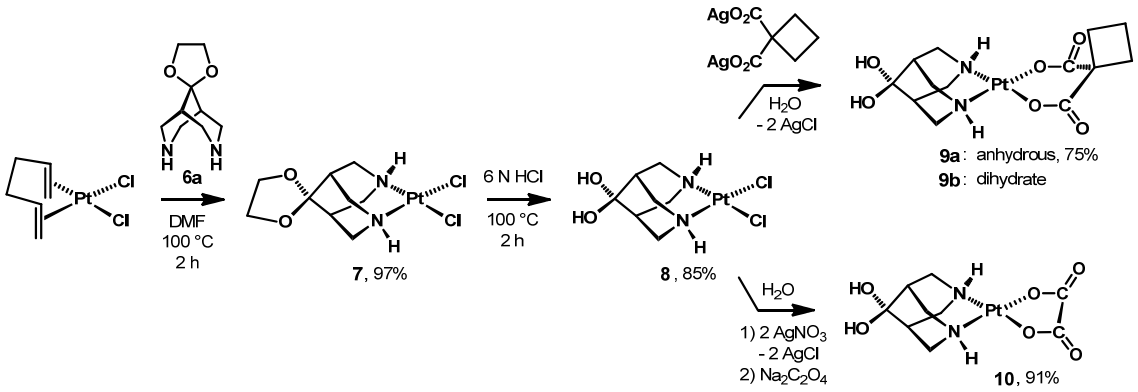
Cytotoxicity of **1**, **2**, and **3** was tested against human cancer cell lines K562 (chronic myeloid leukemia), A2780 (ovarian cancer), and its cisplatin-resistant subline A2780 CisR. All bispidine–Pt complexes showed significant cytotoxic activity in the μM range. While the cytotoxic potency compared to their parent analogs was somewhat reduced, except for **1** toward A2780 CisR, the resistance factor of **1** for A2780 and its subline

A2780 CisR was significantly smaller (more favorable) than for cisplatin. This appears relevant to the problem of platinum resistance and encourages further studies.

Subsequently, two hydroxy groups were introduced as substituents in 9-position of the bispidine to improve solubility. This was achieved by converting the bispidin-9-one **4** with glycol into spiro[3,7-diallylbispidin-9,2′-[1,3]dioxolane] (**5**) and cleavage of the substituents at N to give crystalline spiro[bispidin-9,2′-[1,3]dioxolane] dihydrate (**6b**), which was dehydrated to anhydrous crystalline **6a**.



The ketal **6a** was reacted with (1,5-hexadiene)$PtCl_2$ to form water-insoluble **7**, which excludes its application as a possible antitumor drug. Hydrolytic cleavage of the glycolic protecting group in **7** gave yellow needles of anhydrous (bispidin-9,9-diol)-platinum(II)dichloride (**8**) which dissolves moderately in water. From **8** the carboplatin derivative **9a**, forming dihydrate **9b**, and the oxaliplatin derivative **10** are accessible.



In the crystal, the molecules of **8** are pairwise associated by twofold OH···O* hydrogen bonds between the geminal diol groups (Figure 3). These dimeric entities are further associated by hydrogen bonds to form infinite strands. A similar association is found in crystals of the dihydrate **9b**, whose water molecules are clustered in pockets (Figure 4).

While **10** is virtually insoluble in water, precluding biological studies, the possible anticancer potency of **8** and **9b** is presently under investigation.

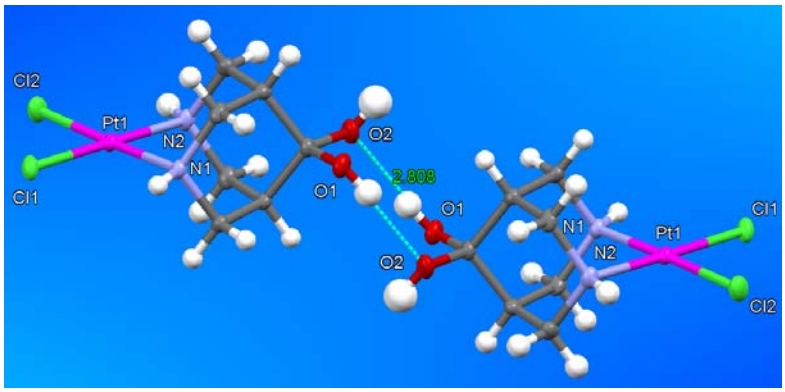


Figure 3. Crystal structure of $\{(HO)_2C_7H_{10}(NH)_2\}PtCl_2$ (**8**)
(shown is the dimerization *via* twofold OH···O* hydrogen bonds).

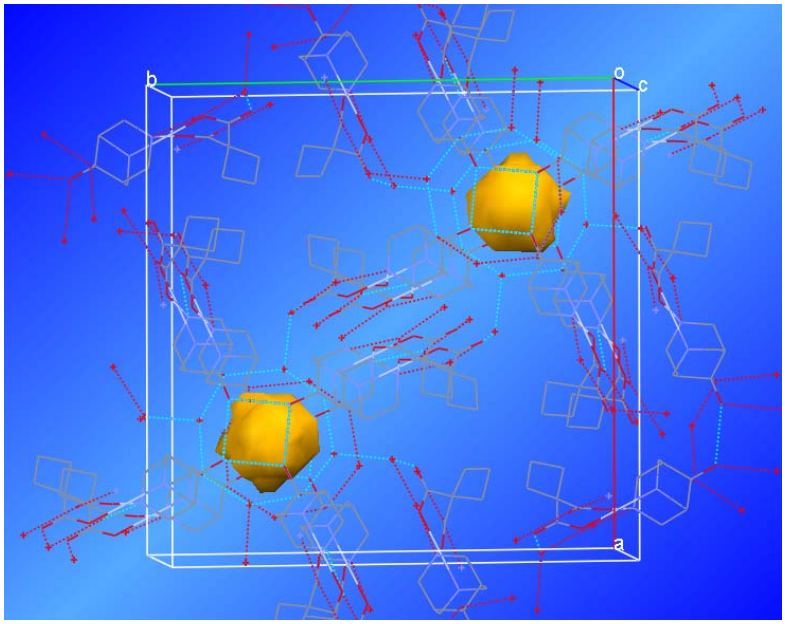


Figure 4. Crystal structure of $\{(HO)_2C_7H_{10}(NH)_2\}Pt\{(O_2C)_2C_4H_6\}\cdot 2H_2O$ (**9b**)
(shown is the association of complex molecules around the water pockets).

2.2.13 Research area "Structure and Solubility of 4-Oxopiperidinium Salts" (K.-R. Pörschke)

Involved: A. Dreier, W. Gamrad, R. Goddard

Objective: 9-Bispidinone, which contains two fused 4-piperidone rings, easily undergoes hydration to form 9,9-bispidindiol. In order to better understand this ketone hydration, we turned our attention to "4-piperidinone hydrate hydrochloride", which is a chemical feedstock in the pharmaceutical industry. We anticipated that this compound is actually 4,4-dihydroxypiperidinium chloride and became interested in the factors which render this quite simple geminal diol stable.

Results: Commercial "4-piperidinone hydrate hydrochloride" (**A**) is extremely soluble in water, but insoluble in all organic solvents. From DMF/water or acetone/water mixtures single-crystals of **A** have been obtained. X-ray structure analysis proved **A** to be 4,4-dihydroxypiperidinium chloride in which the cations are fourfold NH···Cl and OH···Cl hydrogen bonded to chloride anions in a 3D network (Figure 1). Dehydration with $SOCl_2$ afforded the ketone 4-oxopiperidinium chloride (**B**), which gave single-crystals from anhydrous DMF. Crystalline **B** forms infinite double-strands of molecules which are associated *via* NH···Cl···HN bridges, whereas the keto functions are not involved (Figure 2). Solid **B** is strongly hygroscopic and the hydration reaction **B**→**A** of the single-crystals can be followed under a microscope in a short time. Intriguingly, in a solution of either **A** or **B** in pure water (where chloride becomes hydrated) the ketone is only partially hydrated to give an about 9:1 geminal-diol/ketone mixture. This indicates that it is essentially the OH···Cl hydrogen bonds which stabilize crystalline **A**.

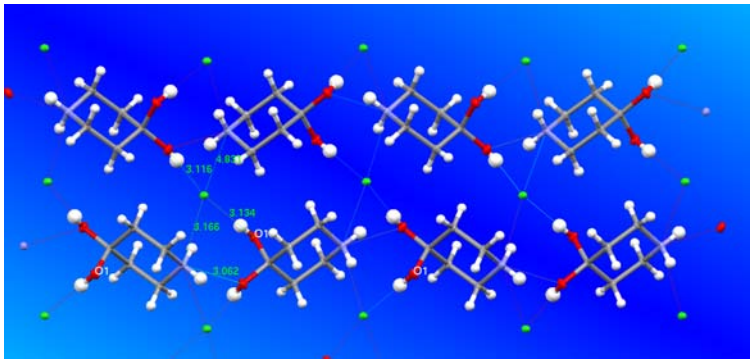


Figure 1. 3D-Structure of the diol **A**.

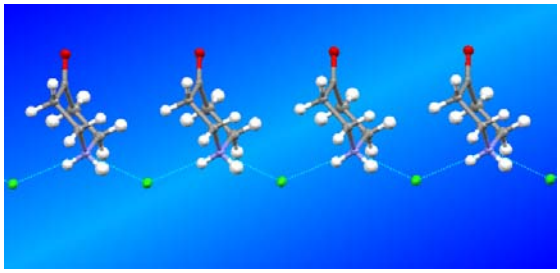


Figure 2. Linear association of the ketone **B**.

By anion exchange the 4-oxopiperidinium salts $[(O=)C_5H_8NH_2]X$ with weakly coordinating anions X = BF_4, ClO_4, OTf, and NTf_2 have been prepared. These solids are non-hygroscopic and their properties in aqueous solution are the same as for **A** and **B**. For $[(O=)C_5H_8NH_2]$OTf (**C**) and $[(O=)C_5H_8NH_2]NTf_2$ (**D**) chain structures similar to that of **B** have been determined. Thus, in these compounds the anions X bridge the ammonium groups by acting as "hydrogen bond acceptors" toward the ammonium protons (NH···X hydrogen bonds). The anions are apparently not basic enough to stabilize also the corresponding geminal diols by OH···X hydrogen bonds, which therefore are not formed.

The anion X = $Al\{OC(CF_3)_3\}_4$ is even less basic. When the anion exchange is carried out in either diethyl ether or CH_2Cl_2 as a solvent, the solute complexes $[(O=)C_5H_8NH_2(OEt_2)_2][Al\{OC(CF_3)_3\}_4]$ (**E**) and $[(O=)C_5H_8NH_2(CH_2Cl_2)]$-$[Al\{OC(CF_3)_3\}_4]$ (**F**) can be crystallized. The cocrystals of **E** consists of separate cations and aluminate anions, and two ether molecules are bound to the ammonium group *via* NH···O(ether) hydrogen bonds. Interestingly, pairs of piperidinium cations appear to be stabilized by N–CH···O(ketone) hydrogen bonds (Figure 3).

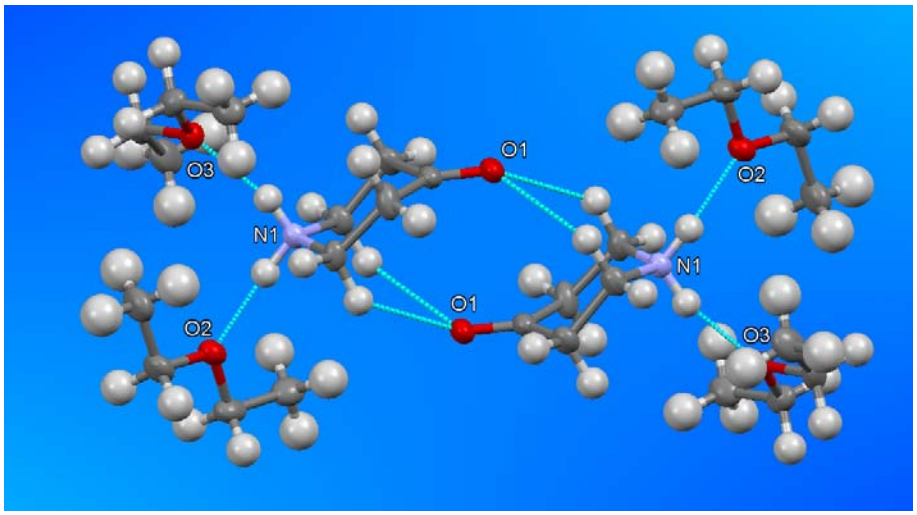


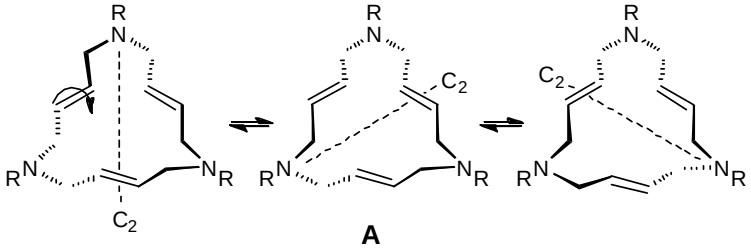
Figure 3. Structure of the piperidinium bis(etherate) **E** (shown are two cations).

2.2.14 Research area "Ni(0) Complexes of Polyunsaturated Aza Ligands" (K.-R. Pörschke)

Involved: W. Gamrad, R. Goddard

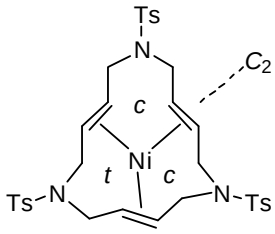
Objective: There is an enduring interest in zero-valent Ni(0), Pd(0), and Pt(0) complexes, since these are active precursor complexes for catalytic reactions. While typical ligands (e.g. COD) have ene functions in 1,5-sequence, we have studied cyclic and acyclic polyunsaturated aza molecules having two ene and one yne function in 1,6,11-sequences and used them as ligands for nickel(0). Mixing alkene and alkyne functions will introduce different carbon hybridization states into the ligands and should induce different conformations of the chain, together with associated variable donor–acceptor properties. A detailed conformational analysis was performed on the resulting product complexes.

Results: In the first part of the project (*E*,*E*,*E*)-1,6,11-tris(4-tosyl)-1,6,11-triazacyclopentadeca-3,8,13-triene (**A**) was coordinated to Ni(0), supplementing previous studies for Pd(0) and Pt(0) by A. Roglans. The structure of the uncoordinated macrocycle **A** can be thought of as (idealized) C_2-symmetrical, with the C_2-axis passing through the center of one C=C bond and the opposite N-atom. The NMR spectra indicate rotations of the C=C moieties about their vinylic C–C bonds, resulting in 60° jumps of the C_2-axis.



A

When **A** is coordinated to a metal center such as Ni(0), rotations about the vinylic C–C bonds are no longer possible. The triazacyclotriene ligand in **B** forms three formal azanickelacyclohexanic rings with the metal in a chair–chair–twist (c,c,t) conformational combination, resulting in an overall rigid C_2 symmetrical structure and the presence of a pair of enantiomers.



B

Reacting (*E*,*E*)-1,6,11-tris(4-tosyl)-1,6,11-triazacyclopentadeca-3,8-diene-13-yne (**C**) with Ni(0) affords mononuclear **D**, which can accept a further Ni(0) to give the dinuclear **E**. The structure of **D** is C_S-symmetrical and resembles a chair, with the 15-membered ring providing the seat, the two tosyl groups at $NCH_2C{\equiv}CCH_2N$ representing the front legs, and the other tosyl group forming the back rest (Figure 1).

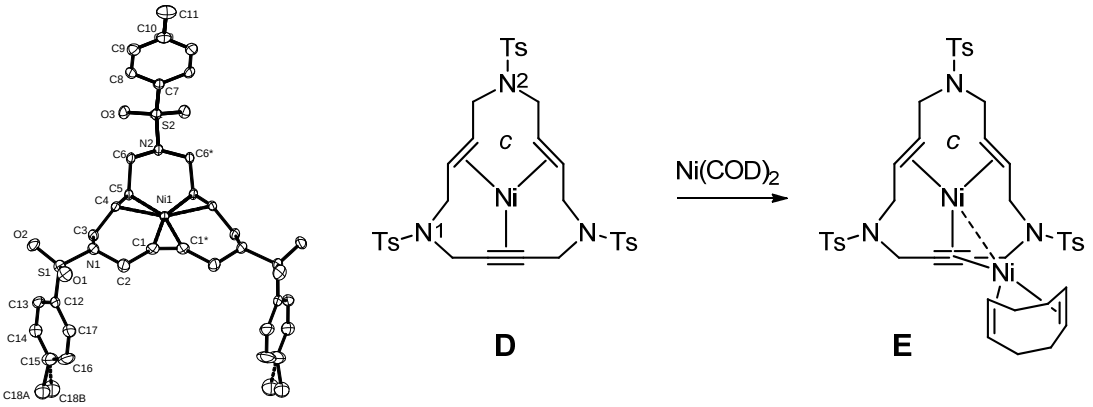
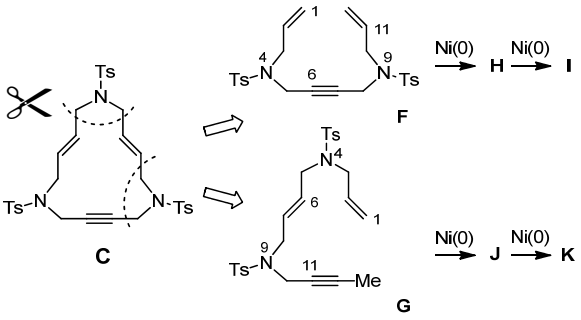


Figure 1. Structure of **D**.

Isolation of **D** and **E** raised the question as to how the structure and properties of these complexes are affected by replacing the cyclic ligand by *acyclic* analogs. Formal excision of a $CH_2N(TS)CH_2$ entity can occur at two sites to give ligands **F** and **G**, for which complexes **H–K** have been synthesized.



Complex **H** shows a C_2-symmetrical structure and packs in parallel columns, made up of identical C_2 symmetrical molecules having the same chirality and orientation (Figure 2). These are stacked such that the phenyl groups of adjacent molecules lie almost parallel to one another. The dinuclear **K** (Figure 3) crystallizes in well-formed spherulites (Figure 4).

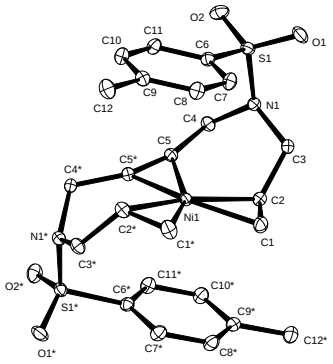


Figure 2. Structure of **H**.

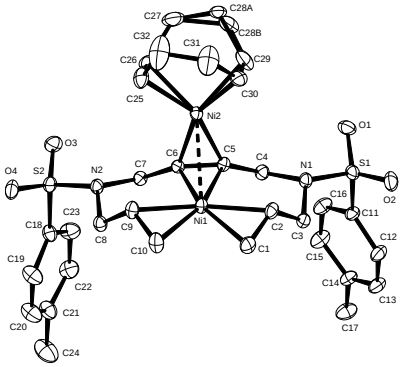


Figure 3. Structure of **K**.

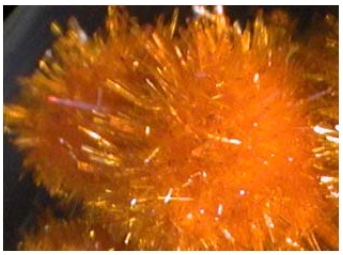


Figure 4. Spherulites of **K**.