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Synthesis of homo and heteroleptic Ag(I) complexes based on N and P donor ligands

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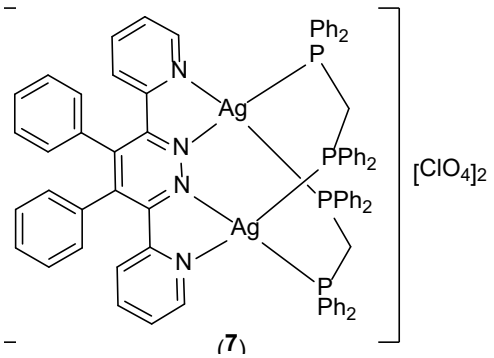
Silver has been known to possess antimicrobial properties for more than two thousand years and is considered as an antimicrobial agent. Pharmaceutical application of silver was first recognized with the use of silver nitrate in early 1800s for the treatment of ulcers. Water-soluble homoleptic Ag(I) complexes of the type $[Ag(N\hat{}N)_2](CF_3SO_3)$ based on adamantylamines have shown antibacterial properties. Recently, fluorescence emission in mononuclear heteroleptic trigonal Ag(I) complexes with the molecular formula $[Ag(N\hat{}N)(PR_3)](NO_3)$; PR_3 = PPh_3, PMe_2Ph, $PMePh_2$, $P(p\text{-}tolyl)_3$, $P(nBu)_3$, $P(OPh)_3$, and $P(OEt)_3$) has been studied. Therefore, it is of interest to investigate the chemistry of Ag(I) centres with chelating (N^N), (P^P), and mixed (N^N) and (P^P) donors. In this communication we report the preliminary studies carried out to devise synthetic routes to such complexes.

First, the coordination chemistry of the Ag(I) centre with the bulky bidentate nitrogen-donor ligand 3,4,5,6-tetraphenyl-2,2′-bipyridine (tpbpy) was studied. The two-coordinate Ag(I) complex of the type $[Ag(tpbpy)]^+$ (1) was prepared by treating $AgClO_4$ or $AgBF_4$ with one equivalent of the ligand. This complex and other Ag(I) complexes were characterized by IR, Mass and NMR spectroscopy. The four-coordinate Ag(I) complex $[Ag(tpbpy)_2]ClO_4$ (2) was isolated in 88% yield by reacting $AgClO_4$ with two equivalents of tpbpy in acetonitrile. Formation of (2) was supported by microanalytical data and the presence of the mass profile for $[M\text{-}ClO]^+$ ion.

Treatment of one equivalent of 4,5-bis(diphenylphosphino)-9,9′-dimethyl xanthene (Xantphos) with $AgClO_4$ in acetonitrile gave the complex $[Ag(Xantphos)(MeCN)]ClO_4$ (3) as a white solid in 83% yield. The $^{31}P\text{-}\{^1H\}$ spectrum of (3) showed a doublet of doublets at -5.3 ppm with $1J(^{109,107}AgP)$ = 461 Hz and 532 Hz.

The four-coordinate heteroleptic complex [Ag(Xantphos)(tpbpy)]ClO_4 (4) was prepared in 80% yield by treating (3) with one equivalent of tpbpy in dichloromethane. The complex (4) can also be prepared by treating $AgClO_4$ with a mixture of tpbpy and Xantphos in (1:1) ratio in acetonitrile. The phosphorus resonance of (4) appeared as a doublet of doublets at -5.4 ppm with $1J(^{109,107}AgP)$ = 384 Hz and 444 Hz. Similarly, the complex $[Ag(Xantphos)(dmbpy)]ClO_4$ (5) (dmbpy = 6,6′-dimethyl-2,2′-bipyridine) was isolated as a white solid with over 80% yield. It showed a doublet of doublets at -6.2 ppm with $1J(^{109,107}AgP)$ = 357 Hz and 412 Hz in its $^{31}P\text{-}\{^1H\}$ spectrum.

The chemistry of $AgClO_4$ with the diphosphine, bis(diphenylphosphino) methane (dppm) which is known to bridge two metal centres, was also studied. Treatment of $AgClO_4$ with one equivalent of dppm in acetonitrile gave a white solid in good yield. The $^{31}P\text{-}\{^1H\}$ NMR spectrum showed a broad spin system centred at 6.9 ppm with 1J(AgP) = 512 Hz suggesting that it is a fluxional molecule. It can be tentatively suggested that it has the molecular formula $[Ag_2(\mu\text{-}dppm)_2][ClO_4]_2$ (6) with two bridging dppm ligands. Complex (6) was reacted with 3,6-di(2-pyridyl)-4,5-diphenyl-pyridazine (dppz) which has the capability to bind two metal centres. Treatment of (6) with one equivalent of dppz gave a white solid $[Ag_2(\mu\text{-}dppm)_2\{\mu\text{-}dppz\}][ClO_4]_2$ (7) in 87% yield.



(7)

In conclusion, synthetic routes to homoleptic Ag(I) complexes of the type $[Ag(N\hat{}N)]^+$ and $[Ag(N\hat{}N)_2]^+$ were developed. Heteroleptic complexes such as $[Ag(N\hat{}N)(P\hat{}P)]^+$ can be prepared by adding both P^P and N^N ligands to $AgClO_4$ in acetonitrile or by adding one equivalent of N^N ligand to a solution of $[Ag(P\hat{}P)]^+$. A binuclear heteroleptic Ag(I) complex containing bridging

ligands 3,6-di(2-pyridyl)-4,5-diphenyl-pyridazine and dppm was also prepared.

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Guest Article

Natural product driven drug discovery

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The success stories reveal that the world's biodiversity offer human society with various pharmaceuticals, agrochemicals and research biochemicals. Various methods such as isolation of compounds from plants, microorganisms and other sources; synthetic chemistry, combinatorial chemistry and molecular modeling are being used for obtaining compounds for drug discovery. According to the most recent review of Newman and Cragg natural product driven drug discovery is still alive and going well. For an example, in the area of cancer, out of the 175 small molecules approved as drugs during 1940-2014, 75 % are non-synthetics, of which 49% is either natural products or directly derived from natural products.

Although there are numerous success stories of natural product driven drug discovery, the process of drug development from natural products are faced with frequent challenges. The path to the success of drug discovery using natural products is through a lot of obstacles. While most of the drugs such as antibiotics become obsolete with time due to the resistivity developed by the pathogenic bacteria, the natural products scientists and pharmaceutical industries continuously need to look into lead substances with novel structures and novel mechanisms of action or improve the quality of the existing ones through modifications to suit the needs.

Drug discovery process consists of several steps (Figure 1) which expands for an average period of 10 years and the estimated cost per drug development in average will reach up to $800 million or more. The first step in the process, which is identifying a drug lead, is also a tedious course. From the step of identifying an active extract to activity guided isolation of bioactive compounds take a substantial time limit. In addition to lead identification, lead optimization which involves medicinal and combinatorial chemistry, lead development using pharmacology, toxicology, pharmacokinetics and drug delivery and finally clinical trials prolong the drug discovery process.

Active compound isolation procedures coupled with the bioassays take weeks or months. This is simply too sluggish to complete with the screening of pure compounds. Nevertheless, with only microgram quantities of the active compound being isolated is not sufficient to drive the meaningful biological evaluation or clinical trials. In such situations re-isolation of the active compounds, i.e. if it is from a microbial source re-culturing, extraction, and isolation need to be carried out which makes this time-consuming process. Unfortunately, during some of these occasions some microorganisms under long term storage and growing on artificial media may have stopped producing the bioactive compounds. This has become one of the major challenges in microbial natural product drug discovery route.

On the other hand, to collect the active compound sufficient for the structure elucidation process large biological samples (plant, animal or microorganism) need to be utilized. Obtaining large biological samples such as a plant or an animal draw various issues related to conservation and ethics. In contrast, obtaining large

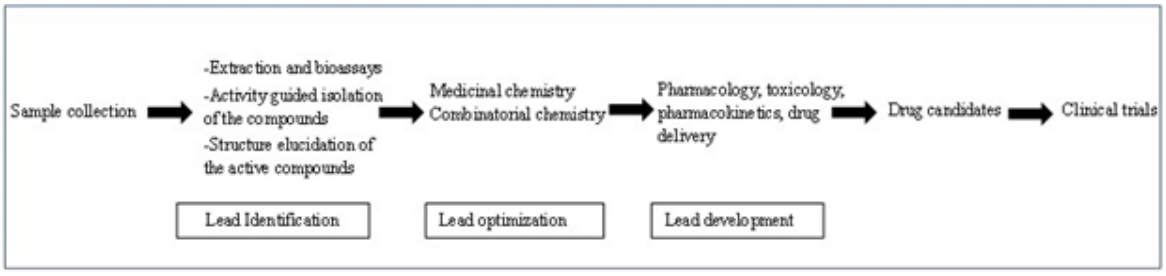

Figure 1: Drug discovery process
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