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Synthetic and bioorganic chemistry

Organic chemistry — the chemistry of carbon compounds — underlies all of biochemistry and, therefore, life itself. Roman Dembinski is an organic chemist who specializes in combining organic molecules with metals to form unique compounds called metal coordination complexes. These compounds have fascinating properties and important biomedical applications.

For instance, Dembinski's group is pursuing the synthesis of nucleoside analogues — drugs that inhibit the replication of a virus — along with their metal coordination complexes. The abundance of various metal ions with different coordination numbers, geometry and redox potentials makes their combination with natural molecules a powerful tool for the construction and modification of biomolecules. The ultimate goal is to synthesize compounds that exhibit anticancer or antiviral properties or serve as bio-probes, as well as to develop new methods for manufacturing these molecules.

The development of simple and inexpensive procedures for the preparation of diverse classes of molecules, like halogenated heterocycles (ring-like organic molecules containing a halogen such as chlorine, fluorine, iodine or bromine) and their derivatives, is an important area of research. Recently, Dembinski's group described a novel electrophilic halocyclization reaction that represents an efficient and potent methodology. The process leads to functionalized heterocycles and modified nucleosides, by tandem cycloisomerization-halogenation processes. The electrophilic (attracted to electrons) component serves as both a cycloisomerization catalyst to form a ring and as a halogen donor, thus creating a very effective process from the standpoint of material economy. In this way, chlorofuropyrimidine nucleosides were obtained. Despite the fact that useful compounds such as iodo- or bromo-derivatives can be relatively easily produced with the use of halogen or pseudohalogen reagents, chlorocyclization reactions remain largely unexplored due in part to the diminished electrophilic character of chlorine, as compared to iodine or bromine.

The importance of the presence of an appropriate metallic fragment may be underlined by results obtained with different organometallic nucleoside derivatives. In Dembinski's research, active hexacarbonyl dicobalt complexes were obtained with nucleoside alkyne ligands (an alkyne is an organic molecule containing triple carbon bonds, and a ligand is a molecule that binds to a central metal ion to produce a coordination complex). The $Co_2(CO)_6$ derivatization induced different effects for this class of ligands. In the case of compounds with substituents on both sides of the triple bond, antiproliferative activity (important in the treatment of cancer) of the complexes exceeded that of the uncomplexed ligands. The opposite effect was noted for derivatives with a hydrogen or silicon atom at one end of the alkyne group. These results demonstrated that the $Co_2(CO)_6$ unit is a useful tool for the modification of existing biological properties.

Recently the group investigated alkyne-tethered dinucleosides that have been shown to display two distinct behaviors. When reduced, the electron is localized on only one ring (nucleobase), whereas if they are oxidized, the electron is delocalized across both rings. This effect could be used as a gate that separates hole and electron transport between strands in DNA systems.

Representative Recent Publications

1. Sniady A, Sevilla MD, Meneni S, Lis T, Szafert S, Khanduri D, Finke JM, Dembinski R. 2009. Synthesis and ESR studies of 2'-deoxyuridines tethered with alkynyl, rod-like linkages. *Chemistry – A European Journal* 15:7569-7577.

2. Wyrbek P, Sniady A, Bewick N, Li Y, Mikus A, Wheeler KA, Dembinski R. 2009. Microwave-assisted zinc chloride-catalyzed synthesis of substituted pyrroles from homopropargyl azides. *Tetrahedron* 65:1268–1275.

3. Sniady A, Morreale MS, Wheeler KA, Dembinski R. 2008. Room temperature electrophilic 5-endo-dig chlorocyclization of alk-3-yn-1-ones with the use of pool sanitizer: Synthesis of 3-chlorofurans and 5-chlorofuropyrimidine nucleosides. *Eur J Org Chem* 2008:3449-3452.

4. Sniady A, Durham A, Morreale MS, Marcinek A, Szafert S, Lis T, Brzezinska KR, Iwasaki T, Ohshima T, Mashima K, Dembinski R. 2008. Zinc-catalyzed cycloisomerizations. Synthesis of substituted furans and furopyrimidine nucleosides. *J Org Chem* 73:5881–5889.

5. Sergeant CD, Ott I, Sniady A, Meneni S, Gust R, Rheingold AL, Dembinski R. 2008. Metallo-nucleosides: Synthesis and biological evaluation of hexacarbonyl dicobalt 5-alkynyl-2'-deoxyuridines. *Org Biomol Chem* 6:73–80.

6. Ott I, Kircher B, Dembinski R, Gust R. 2008. Alkyne hexacarbonyl dicobalt complexes in medicinal chemistry and drug development. *Expert Opin Ther Pat* 18:327–336.

7. Sniady A, Durham A, Morreale MS, Wheeler KA, Dembinski R. 2007. Room temperature zinc chloride-catalyzed cycloisomerization of alk-3-yn-1-ones: Synthesis of substituted furans. *Org Lett* 9:1175-1178.