

ChemLife meeting

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Innovative Cyclic Nucleotides are Easy Peasy to make.

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Naturally abundant cyclic nucleotides play numerous roles in all kingdoms of life. Two well-known members of this family are nucleoside -2',3'-cyclophosphate, **1**, and -3',5'-cyclophosphate, **2**, containing 5- and 6- membered rings, respectively. Isosteres of natural and non-natural cyclic nucleotides are needed for pharmacological uses as well as biochemical tools. In my talk I will describe a rapid, stereo- and regio-selective one-pot synthesis of nucleoside-2',3'-*O,O*-phosphoro -thioate and -selenoate analogs. This method avoids the need for protection strategies and chiral reagents, chiral metal catalysts, or chiral separations, and has been applied to all natural ribonucleosides (U/A/G/C/T). Unlike naturally abundant 5- or 6-membered cyclic phosphates, **1**, or **2**, neither natural nor synthetic *7-membered* cyclic nucleotides are known. I will describe a facile synthesis of the first ribonucleotide derivatives containing a 7-membered 2',3'-*O,O*- tetrathio-diphosphonate/ diphosphonate ring, **3** and **4**. A protection-free, regio-selective, rapid, one-step reaction of methylene-bis(1,3,2-dithiaphospholane-2-sulfide), MDPS, with U/A/C/I/G, successfully resulted in analogs **3**. Additionally, we have developed a facile oxidation of tetrathio-diphosphonate analogs **3** to obtain diphosphonate analogs **4**. ΔG^\ddagger DFT calculations supported the observed preference for formation of 2',3'-tetrathio-diphosphonate 7-membered ring rather than 3',5'-8-membered ring- or 5'-linear- tetrathiodiphosphonate analogs. Furthermore, we have deciphered the origin of regio- and stereo- selectivity of the reactions leading to 5- and 7-membered cyclic-thiophosphate and cyclic-(tetrathio)-diphosphonate, respectively. These new cyclic nucleotides exhibited unexpected chemical stability, acidity, and rigid conformation in solution. The unique cyclic nucleotides are potential tools for biochemical and pharmacological studies and open new synthetic avenues in the chemistry of nucleotides.