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# This Week's Citation Classic™

**Moffatt J G & Khorana H G.** Nucleoside polyphosphates. X. The synthesis and some reactions of nucleoside-5′ phosphoromorpholidates and related compounds. Improved methods for the preparation of nucleoside-5′ polyphosphates. *J. Amer. Chem. Soc.* **83**:649-58, 1961.
[Chemistry Division, British Columbia Research Council, Vancouver, Canada]

Reactions of adenosine-5′ phosphate with various amines and dicyclohexylcarbodiimide give N-substituted phosphoramidates. These compounds react with phosphate dianions to form pyrophosphates. The best compromise between ease of formation and reactivity is found with the nucleoside-5′ phosphoromorpholidates, which are versatile intermediates for the synthesis of nucleoside-5′ polyphosphates. [The *SCI*® indicates that this paper has been cited in over 415 publications since 1961.]

John G. Moffatt
Institute of Bio-Organic Chemistry
Syntex Research
Palo Alto, CA 94304

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"Between 1954 and 1960 I had the unique opportunity of working, first as a graduate student and later as a staff researcher, in the laboratory of H. Gobind Khorana in Vancouver. These were exciting years since the fundamentals of nucleotide chemistry were being established in several laboratories and our group was in the thick of it. I have been asked why it took close to 15 years before Gobind took on a second graduate student, but I suppose that only he knows the answer and I probably don't want to!

"At any rate, my project for several years was to examine routes for the synthesis of unsymmetrical pyrophosphates such as those found in nucleoside polyphosphates and nucleotide coenzymes. Until that time, the only available methods relied upon random couplings of the 5′-nucleotides with the other phosphate component or cumbersome couplings of fully protected silver salts and phosphorochloridates. It was known that certain compounds, such as creatine phosphate, containing phosphoramidate linkages could serve as phosphate donors in enzymatic pyrophosphate forming reactions. This led Bob Chambers, then a postdoctoral fellow in our group, to investigate the synthesis of adenosine-5′ phosphoramidate via a rather cumbersome six-step synthesis.[1] Bob and I then jointly developed a convenient synthesis of nucleoside-5′ phosphoramidates via direct condensation of 5′-nucleotides and ammonia in the presence of dicyclohexylcarbodiimide,[2] and these compounds were shown to react with orthophosphate[3] or with phosphate monoesters[3] to form nucleoside-5′ diphosphates and nucleotide coenzymes, respectively.

"The phosphoramidates were, however, often poorly soluble in suitable anhydrous solvents, and hence I turned to a study of the DCC mediated reactions of adenosine-5′ phosphate with a variety of substituted amines leading to the respective N-substituted phosphoramidates. These products were, in turn, examined for their stability and reactivity with phosphate monoesters. The best compromise between ease of synthesis and reactivity in pyrophosphate forming reactions was found with the nucleoside-5′ phosphoromorpholidates, which could be isolated in almost quantitative yield as their highly soluble 4-morpholino-N,N′-dicyclohexylcarboxamidine salts. These compounds were then shown to react readily with ortho- and pyrophosphate salts to form nucleoside-5′ di- and triphosphates and with a variety of phosphate monoesters to form nucleotide coenzymes.[4,5] Subsequent work further improved the conditions for synthesis of nucleoside-5′ triphosphates.[6]

"While other methods have evolved over the years for the preparation of unsymmetrical pyrophosphates, the phosphoromorpholidate route still remains one of the most reliable and has been quite widely used in many laboratories, thus ensuring frequent citations."

1. **Chambers R W & Khorana H G.** Nucleoside polyphosphates. VII. The use of phosphoroamidic acids in the synthesis of nucleoside-5′ pyrophosphates. *J. Amer. Chem. Soc.* **80**:3749-52, 1958.
2. **Chambers R W & Moffatt J G.** The synthesis of adenosine-5′ and uridine-5′ phosphoramidates. *J. Amer. Chem. Soc.* **80**:3752-6, 1958.
3. **Moffatt J G & Khorana H G.** Nucleoside polyphosphates. VIII. New and improved syntheses of UDPG and FAD using nucleoside-5′ phosphoramidates. *J. Amer. Chem. Soc.* **80**:3756-61, 1958. (Cited 85 times since 1958.)
4. **Roseman S, Distler J J, Moffatt J G & Khorana H G.** Nucleoside polyphosphates. XI. An improved general method for the synthesis of nucleotide coenzymes. Synthesis of uridine-5′, cytidine-5′ and guanosine-5′ diphosphate derivatives. *J. Amer. Chem. Soc.* **83**:659-63, 1961. (Cited 205 times.)
5. **Moffatt J G & Khorana H G.** Nucleoside polyphosphates. XII. The total synthesis of coenzyme A. *J. Amer. Chem. Soc.* **83**:663-75, 1961. (Cited 140 times.)
6. **Moffatt J G.** A general synthesis of nucleoside-5′ triphosphates. *Can. J. Chem.* **42**:599-603, 1964. (Cited 105 times.)

 