Polyamines in chemistry, biochemistry, and organic material science

Masaaki Iwata
Biopolymer Physics Laboratory

We summarize the results of our studies on the design and synthesis of polyamines to meet the development of methods for on-demand supply of polyamine building blocks required in chemistry, biochemistry, and organic material science. The feasibilitiy of our synthetic methods has been shown by the synthesis of many designed molecules, such as macromonocyclic polyamines, differentially protected acyclic natural polyamines, and multi-layered polyamines. All syntheses were carried out efficiently by taking advantage of the flow of a "reaction network" of serial transformation of nitrogen functional groups.

Polyamines did not receive much attention before 1970, although spermine, one of the prevalent natural polyamines, was isolated as a phosphate salt from human sperm by van Leewenhoek in 1674. Polyamines, however, have recently been recognized as key compounds in various fields. In the field of chemistry, Lehn *et al.*[1] demonstrated the molecular recognition of ATP and its hydrolysis by macromonocyclic polyamines. In the field of biochemistry, Russell *et al.*[2] reported on the sensitive response of the urinary polyamine levels of cancer patients before and after surgical removal of tumor cells. In human brain, polyamines are reported to be agonists[3] which stimulate the NMDA subtype glutamate receptor in cortical and hippocampal tissue. In the field of organic material science, polyamine-based dendrimers have recently been synthesized,[4] which are a new category of globular tree-like polymers and expected to possess a wide spectrum of properties. The above-mentioned types of research in various fields have been intensifying the requirement for on-demand supply of polyamines and their derivatives. We have engaged in the development of new methods for free-hand synthesis of open-chain and cyclic polyamines for the past ten years. The purpose of the present report is to summarize the results of our studies on the design and synthesis of polyamines.

Development of new elemental reactions

Figure 1 shows the flow of a "reaction network" of the serial transformation of functional groups related to a primary amine (**A**), which profiles new elemental reactions developed by us. Several features should be noticed: (1) the nucleophilic nitrogen atom in a tosylamide (**B**) is converted to an electrophilic sulfonate (**D**) through thermal rearrangement of the nitrosated compound (**C**); (2) phthalimide (**E**), which is used conventionally to protect the primary amino group, is converted in a single step to formamide (**F**), which is easily hydrolyzed to **A** with acid; (3) **F** can be a source of the corresponding alcohol (**I**) when **F** is converted first to formate (**H**) through thermal transformation of the nitrosated intermediate (**G**) and then by hydrolysis of **H**. In the reaction of a nucleophile (**B**) with an electrophile (**D**), chain elongation

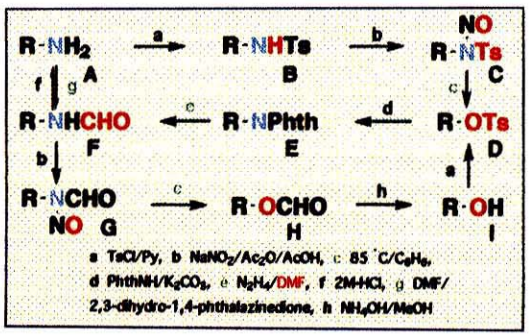

Fig. 1. Flow of a "reaction network" of the serial transformation of nitrogen functional groups.

should occur when point-to-point reaction occurs, or cyclization should occur when there are two reactive centers in each reagent. Considering the above, the design and synthesis of polyamines were started.

Design and synthesis of macromonocyclic compounds[5]

We have designed twelve macromonocyclic polyamines (**1** to **12**, Fig. 2) generated logically by setting of three criteria. Analysis of the common elements of the defined target

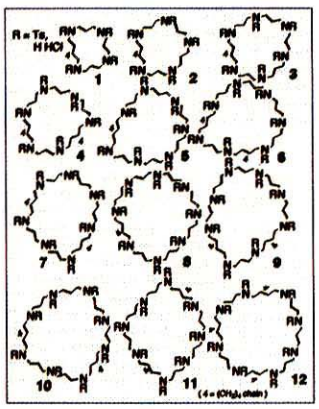

Fig. 2. Chemical structures of targeted macromonocyclic polyamines.

molecules for minimization of the numbers of synthetic steps suggested that 1,3-propanediamine, 1,4-butanediamine, and 4-azaheptane-1,7-diamine are requisite minimum starting units for the total synthesis of all compounds (R = Ts). Nitrogen contents were repeatedly increased symmetrically at both terminals of the chain in consideration of the reactivity of **B** and **D** (chain elongation). The transformation of **E** to **F**, utilized repeatedly, proceeded invariably well even for molecules with high nitrogen content and, at the final step, macrocyclization was carried out by the reaction of symmetrically functionalized long **B** and short **D**. We believe that synthesis on demand utilizing the flow of a "reaction network" is one of the best methods to provide long chains of symmetrically reactive polyamine blocks.

Unsymmetrization in diamine formation for polyamine-conjugate synthesis[6]

Feasible synthetic methods for differentially protected natural acyclic polyamines play a crucial role in the total synthesis of polyamine conjugates since the polyamine moiety has to be introduced regiospecifically at the appropriate step in the total synthesis. Practical methods hitherto devised for discrimination of amino groups have relied on stoichiometric control of reactants in the formation of triamine derivatives, and the extension of the subtle reactivity difference in the formation of diamine derivatives. We have found a novel transformation reaction specific for *N,N;N',N'*-diphthaloyl-1,3- propanediamine (**13**) to give the fused heterocycle (**14**) with an imine moiety in a single step (Fig. 3). Since the imino group is hydrolyzed quantitatively to the *N,N*-phthaloyl-1,3-propanediamine (**15**) HCl salt, the transformation reaction provides an excellent unsymmetrization method in the propanediamine formation. Since propanediamine is a common component of natural polyamines, we planned to synthesize threefold *N*-protected (by phthaloyl, tosyl, and formyl groups) natural triamines (spermidine) and tetramines (spermine, thermine, and thermospermine) by amplifying the unsymmetrical functionality of the diamine. Although results are not given here due to space limitations, differential protection has been achieved by use of the flow of a "reaction network".

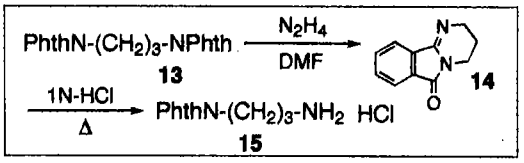

Fig. 3. Single-step unsymmetrization method.

Design and synthesis of multi-layered macromonocyclic polyamines[7]

Morphism of a systematic combination of sticks and circles as shown in Fig. 4 inspired a new molecular design of polyamines. We thought that this "multi-morphism" could be organized, assembled, and controlled by the interaction of small molecules and/or metal ions because single host molecules might be flexibly interactive with small guest molecules of various sizes, geometries, and charges by switchable morphism of host molecules. We then started synthesis of "muti-layered molecules" by considering the circles as macromonocyclic polyamines, the sticks as alkylene chains, and the joining points as nitrogen atoms. We have already achieved synthesis of several sets of multi-layered molecules by tactical use of the flow of a "reaction network" and soon we should be able to describe the unique intrinsic natures of multi-layered molecules. It was surprising to discover that considerable numbers of multi-layered molecules are anti-HIV active when these unique molecules were used in biological assays to determine anti-viral activity against human T-lymphotropic virus type III (HTLV-IIIb) infection of MT-4 cells. The chemical structures of anti-HIV active compounds are partly illustrated in Fig. 5 (**16** through **28**). In consideration of the structural variety of compounds with potent inhibitory effects on the infection of HIV, the present molecular design of macrocyclic polyamines appears to be promising for the development of a new class of compounds with anti-viral activity.

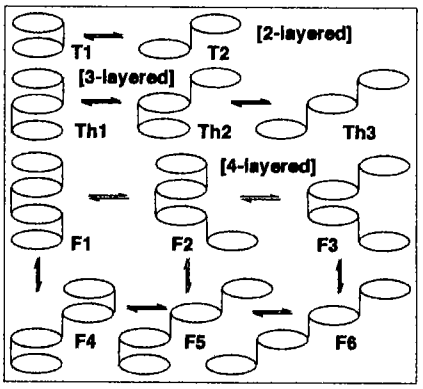

Fig. 4. Multi-morphism of layered molecules.

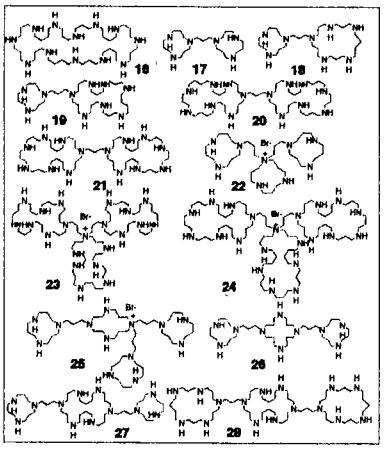

Fig. 5. Chemical structures of compounds with anti-HIV activity.

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