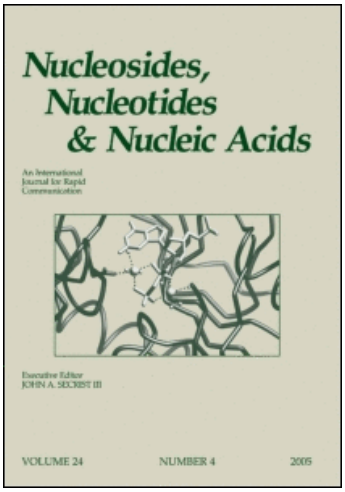

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Nhat Quang Nguyen Trung[a]; Peter Strazewski[a]; Martin Olsson[b]; Måns Ehrenberg[b]
[a] Institute of Organic Chemistry, University of Basel, Basel, Switzerland [b] University of Uppsala, Sweden

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THE CONFORMATIONAL SPACE OF NASCENT PEPTIDE-ACCEPTING 3′-AMINOACYL RIBONUCLEOS(T)IDES: ^{1}H NMR DATA AND *AB INITIO* CALCULATIONS OF PUROMYCIN AND SOME SYNTHETIC ANALOGS

Nhat Quang Nguyen Trung,[1] Peter Strazewski,[1,*] Martin Olsson,[2] and Måns Ehrenberg[2]

[1]Institute of Organic Chemistry, University of Basel,
St. Johanns-Ring 19, CH–4056 Basel, Switzerland
http://www.chemie.unibas.ch/OC/Strazewski/strazewski.html
[2]Molecular Biology, Biomedical Centre,
University of Uppsala, Sweden

Puromycin is a codon-independent acceptor of nascent peptide chains in ribosomes and is widely used *in vitro* as protein growth terminator and, more recently, as the crucial 3′-terminus of synthetic combinatorial mRNA libraries for the *in vitro* synthesis and selection of covalent protein-mRNA fusion molecules [1].

Now that the structural details of a 50 S ribosomal subunit advanced to 2.4 Å resolution [2] a more reliable knowledge of the ribosomal peptidyl transfer reaction seems within close reach. Studies on the intrinsic conformations of the peptide-accepting 3′-terminus of aminoacyl-tRNA (aa-tRNA) and puromycin using modern spectroscopic and computational techniques should allow for a better understanding of the 3D course of this reaction.

New puromycin analogs were synthesised[1] and tested[2] for *in vitro* peptide release activity. pH- and T-dependent ^{1}H NMR spectra[1] in H_2O let us gain insight into the conformational preferences of 3′-aminoacylamino-3′-deoxyadenosine (3′-aa-NH-3′-dA) derivatives. The experimental data was supplemented with a systematic *ab initio* study on 8 conformers of 3′-Ala-NH-3′-dA and on related 3′-amide and 3′-ester variants including 5′-O- and/or 2′-O-methyl, 5′-O-methylphosphate, and

*Corresponding author. E-mail: peter.strazewski@unibas.ch

2′-fluoro groups (42–49 atoms, 24–29 non-H, calculated with *Gaussian 98* using HF, B3LYP, MP2 methods and 6-31G**, 6-31 + G** and 6-311 ++ G** basis sets).

Consistent with the NMR experiments, the calculations suggest that 3′-aminoacyl *amides* with free 5′-hydroxyls as well as the 2′-fluoro-2′-deoxypuromycin analogs prefer a ribofuranose pucker bearing a Ψ-equatorial extension of the aminoacyl moiety (North type sugar pucker) and *syn* periplanar orientation of C=O and α-NH_2 rel. to H-C3′, while in *esters* such as 3′-O-alanyladenosine-5′-O-methylphosphate the competing (South type) pucker bearing a Ψ-axial extension is of similar stability.

Since the governing stabilising interactions in all found conformers are intramolecular H-bridges, we conclude that the present understanding of ribonucleoside conformation equilibria through the balancing effect between the X3′/C5′ *gauche* effect and the N9 anomeric effect needs to be reconsidered. The preference for intra- *vs*. intermolecular H-bridges is not only a possible competing phenomenon, but also a likely means of control by the ribosomal peptidyl transferase pocket. A 3D reactional pathway of the aa-tRNA=>pept-tRNA addition begins to emerge.

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