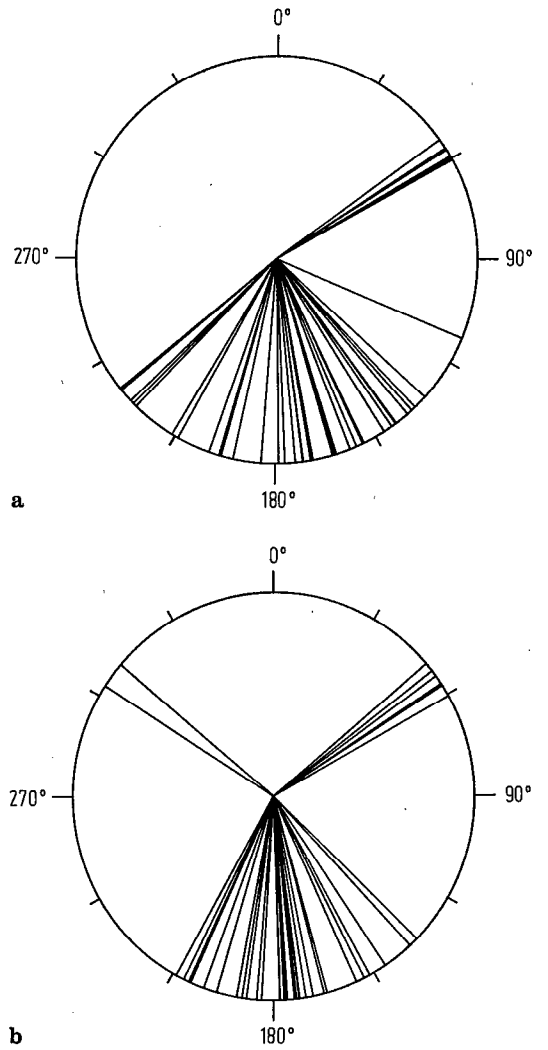

Fig. 5a, b. Torsion angle β (C4′–C5′–O5′–P5′) for (a) purine nucleotides, (b) pyrimidine nucleotides.

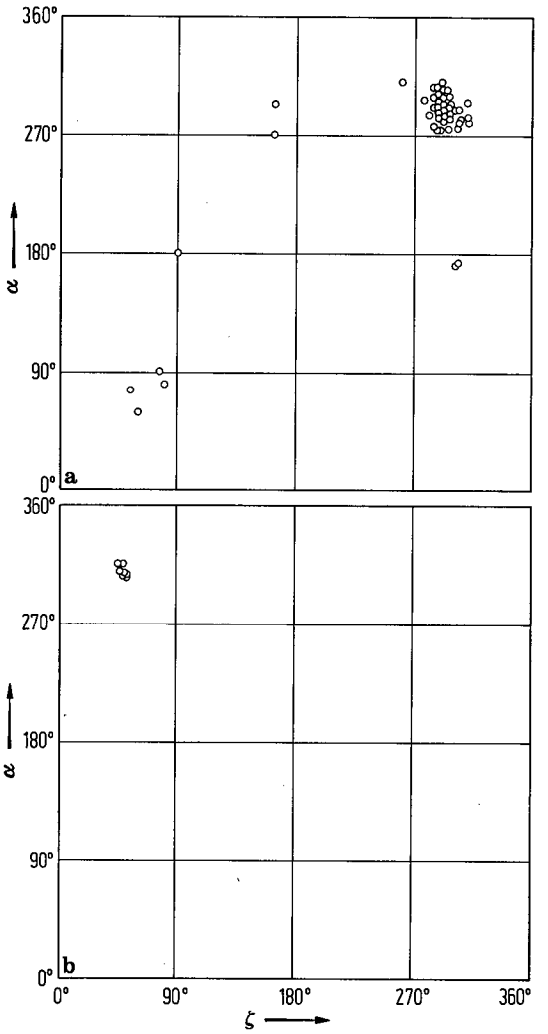

Fig. 6a, b. Torsion angle α (O3′–P–O5′–C5′) (vertical axis) vs. torsion angle ζ, (C3′–O3′–P–O5′) (horizontal axis) for (a) di(tri)nucleotides and (b) 3′,5′-cyclic nucleotides.

2.1.1.5 Analog structures

Most of crystal structures which have been reported are analogs of the naturally occurring bases, nucleosides, and nucleotides. Some of these analogs are found in nature, however, most of them have been synthesized to further our understanding of various enzyme mechanisms and structure-function relationships. These analogs have been used to study DNA, RNA, and protein synthesis, as well as to study the precursors in nucleic acid biosynthesis. They have also been used as substrate probes in numerous enzyme systems, many of which display some degree of biological activity, with a few analogs reacting even faster than the standard substrate. They have also furthered our understanding of various aspects of intermediary metabolism, subcellular organization, and certain hormone systems. Usually, the biological activities of the analogs result from their structural similarity with the corresponding natural enzyme substrates. Many analogs function as enzyme inhibitors, thereby interfering with nucleic acid or protein synthesis, a function which proves useful for the design of various antibiotic drugs. The analogs can be divided into the following general categories: minor substitutions, ring skeleton substitutions, cyclization, and major substitution or rearrangement.

Minor substitutions: There are numerous minor substituents which are primarily found at the base moiety. Among the possibilities are addition of methyl, ethyl, amino, acetyl, oxo, fluoro, chloro, iodo, and thio groups. The addition of a minor base substituent may affect the conformation of the entire nucleoside or nucleotide molecule. For example, a substituent at the C8 position of purine bases will tend to make the usually preferred *anti* glycosyl conformation less favorable due to potentially unfavorable steric interactions between the substituent and the C5′ or O5′ atoms of the ribose moiety. Along similar lines of reasoning, the exocyclic C4′–C5′ torsion angle will be driven from the preferred +*gauche* to the *trans* or −*gauche* domains.

By far the most common minor substituent at the sugar moiety is the acetyl group which is chemically easy to add to any of the available ribose hydroxyl groups. Such substitutions may affect the ribose ring puckering parameters since the molecule will attempt to minimize the steric interactions introduced by the substituent atoms.

Although the naturally occurring ribose sugar is by far the most prevalent among the reported crystal structures, other sugars including hexoses have also been reported, with arabinose dominating. Some of the reported arabinose structures are cyclized between the sugar O2′ position and the base (see below). In the case of nucleotides, the phosphate oxygen atoms may also be substituted.

Ring skeleton substitutions: The normal purine base skeleton has nitrogen atoms at the 1, 3, 7, and 9 positions while the pyrimidine base has nitrogen atoms at positions 1 and 3. The substituted analogs involve the inclusion of additional ring nitrogen atoms (aza substitutions) or the replacement of positions normally occupied by nitrogen atoms with carbon atoms (deaza). There are structures with aza substitutions at the 2 and 8 positions for the purine series and at the 5 and 6 positions of pyrimidine. Although these aza nucleosides may have a pronounced effect on certain biochemical reactions, they have nearly the same geometry as their carbon counterparts and therefore would not be expected to significantly affect the nucleoside conformation except for the 8-aza purine and 6-aza pyrimidine analogs which can influence the position of the O5′ atom due to electrostatic repulsion.

Cyclized structures: Cyclization can be found at various positions of the nucleoside or nucleotide molecule. Biologically the most important class is the 3′,5′-cyclic phosphate group where 3′,5′-cAMP has a well known hormonal function. Another common cyclization is the isopropylidene addition between the 2′ and 3′ positions of the ribose moiety. In one such structure the sugar ring is almost perfectly planar, a condition which is strongly disfavored for standard nucleosides or nucleotides.

Another point of cyclization is between the base and the sugar. For purine bases one such link is between C8 and C5′. This link can either be direct or with an intervening atom. This type of cyclization severely constrains the entire molecule forcing the glycosyl torsion angle χ, and the sugar pucker into very narrow ranges. The C3′–C4′–C5′–O5′ torsion angle is also not free to rotate since the +*gauche* site is covalently linked to the base.

Another type of cyclization is found not with ribose nucleosides but with arabinose nucleosides where the O2′ atom is in very close proximity to the base. The most common form of cyclization in this group is between the arabinose O2′ atom and the C2 atom of a pyrimidine base.

Major substitution or rearrangement: For the most part these structures show relatively little resemblence to their biologically active parent compounds. Among these structures are nonstandard bases, linear sugars, sugars attached to positions other than N1 for pyrimidines or N9 for purines, and other unusual substitutions or cyclization which cannot be easily combined with other related structures. Some structures, such as cobalamin (vitamin B12) incorporate the nucleotide moiety as only a small fraction of the entire molecule. Thiamine (vitamin B1) incorporates a pyrimidine base with a large side-group which may itself be phosphorylated in the absence of a sugar moiety.

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