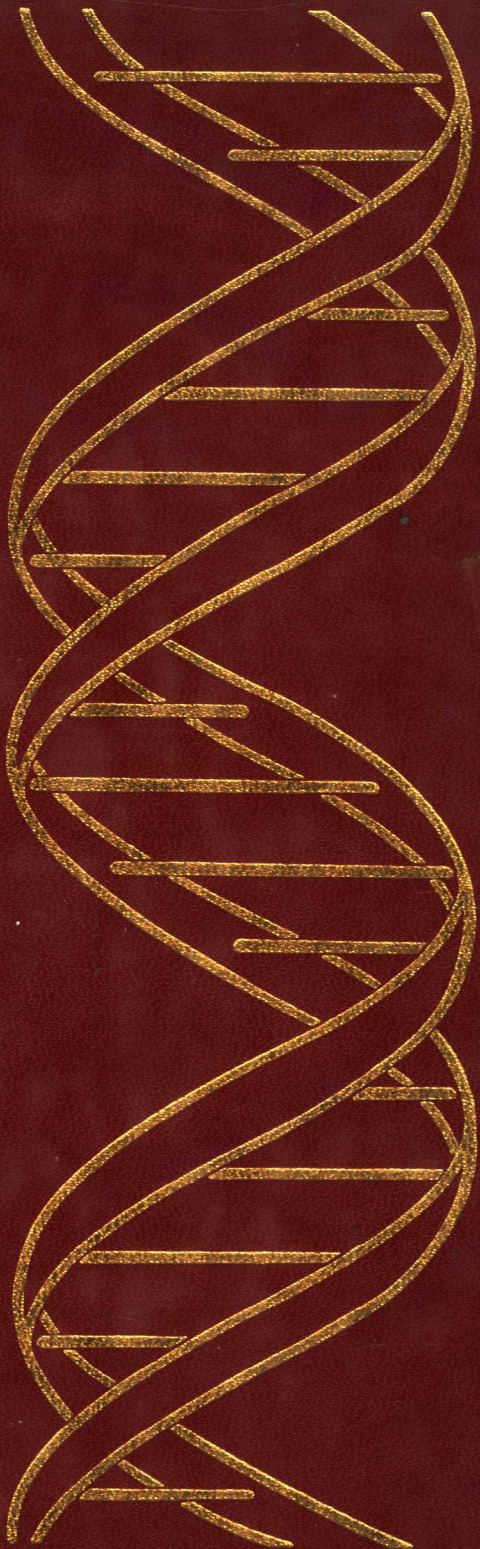
Topics in Nucleic Acid Structure

PART 2

EDITED BY

Stephen Neidle



TOPICS IN MOLECULAR AND STRUCTURAL BIOLOGY

2

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PART 2

Edited by

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Preface

The relatively short time since the conception of this series has witnessed a remarkable growth in the development of structural studies on nucleic acids. There have been numerous advances not only in our knowledge of the fine details of structure, but also in the analysis of the relationships between form and structure and biological function. This volume explores a number of these areas that are of especial current interest and activity. It is perhaps of some significance (and a portent of future directions) that the historical categorisations of nucleic acid structural studies, into either biological or physical ones, are becoming increasingly out-moded. It is left to the reader to discern and perhaps even make use of the common threads linking these areas.

In any rapidly-evolving field, the selection of topics for review has invariably an element of subjectivity and it is thus inevitable that an editor's choice will be subject to cries of outrage from one quarter or another. It is to be hoped that some of the areas not receiving full coverage in this volume, especially those that are in particularly rapid development at present, will receive more extensive appraisal in a subsequent one.

I am most grateful to the contributors for their painstaking and thorough efforts, to many colleagues for their advice and help and to Harry Holt and Peter Clarke of Macmillan Press for their infinite patience at all times.

London, 1982 S. N.

Contents

1

Theoretical studies of nucleic acid conformation: potential energies, chain statistics, and model building

Wilma K. Olson

INTRODUCTION

Theoretical investigations of nucleic acid conformation* attempt to find a rational connection between the chemical architecture of the polynucleotides and their macroscopic properties. The field involves conformational energy analyses, molecular model building schemes, and statistical mechanical treatments of polymer chain flexibility. As outlined below, the collected results provide considerable insight into the influence of primary covalent bond structure upon the three-dimensional geometry of these macromolecules and additionally clarify the relationship between the various spatial arrangements and the configuration-dependent properties of the polynucleotide as a whole.

Over the past decade theoretical understanding of nucleic acid conformation has evolved from simple phenomenological descriptions to detailed geometric characterisation. Short segments of double-stranded DNA were previously envisioned as rigid rods (see, for example, Bloomfield *et al.*, 1974). Very long chains were approximated by ideal Gaussian (freely-jointed polymer) models (Kuhn, 1936), while duplexes of intermediate sizes were described as worm-like coils (Kratky and Porod, 1949). Various other nucleic acid systems –

*The term conformation used in this chapter refers to the various three-dimensional spatial arrangements of a macromolecule generated by different combinations of its internal structural parameters. The configuration of a polymer, in contrast, reflects the additional influences of neighbouring molecules (solvent and other polymer molecules) upon its overall shape. We accordingly categorise the observable properties of a chain molecule in the condensed phase of configuration-dependent and the structures analysed in most theoretical studies as conformational.

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including short, single-stranded fragments and globular RNA structures – were not amenable to any simple representation. Moreover, none of the early mathematical models were directly related to the collection of atoms and bonds constituting the polynucleotide chain. Thus, no matter how faithfully such schemes might have reproduced experimental data, there was no possibility of understanding the observations in terms of chemical structure.

Recent theoretical treatments of polynucleotide structure, in contrast, are based upon mathematical schemes that relate the three-dimensional structure to the constituent bonds and atoms of the chain. Configuration-dependent physical properties of the system are based, in turn, upon the spatial geometry through straightforward application of classical statistical mechanics. Averages are evaluated over the numerous chain conformations with each state weighted by the Boltzmann factor of its potential energy. The energies, however, must be approximated by rough theoretical estimates of the various contributing factors or by inferences from available experimental studies on low molecular-weight analogues. Despite these limitations of accuracy, the computed potential energies, nevertheless, are useful in discriminating between the many possible arrangements of the polynucleotide chain and therefore in understanding the observed configuration-dependent properties.

This chapter deals with the methods of theoretical conformational analysis as they apply to polynucleotide chains. It includes a review of the progress to date and an assessment of the potential of these methods for illuminating the relationship of nucleic acid structure to properties of physical and biological interest.

STRUCTURAL GEOMETRY

Conformational analyses of the polynucleotides are normally conducted with respect to the set of chemical bond lengths, valence bond angles, and bond torsional angles that completely characterise the spatial geometry of the chain molecule. Although subject to minor ($< 5\%$) fluctuations that may sometimes be significant, the bond lengths and valence angles are usually treated as fixed variables. The variations in these parameters are more or less symmetric about their mean values so that effects of those of opposite sign tend to cancel one another. With few exceptions (see below), it is therefore permissible to assign each of these "structural" variables its mean value in the polynucleotide chain. The rotations about the skeletal bonds are then considered the principal determinants of nucleic acid conformation. Stated in alternate terms (Flory, 1974), the fluctuations of torsion angles are generally lower in energy than distortions of bond lengths or valence angles that produce comparable atomic displacements. Structural distortions are therefore less likely to occur than torsional changes except when they are coupled with other favourable interactions.

Detailed sets of internal coordinates are required to assess the potential energies and related spatial properties of the various configurations of the polynucleotide chain. These data may be obtained from the geometric variables

introduced above through simple application of matrix algebra (Flory, 1969). Since many different spatial arrangements are examined, it is convenient to assign a Cartesian coordinate frame to each chemical bond of the system and, after selection of the internal parameters describing the geometry of interest, to transform each chemical bond vector into a common chain coordinate system.

In order to obtain the atomic coordinates it is necessary to treat the polynucleotide chain as a sequence of concatenated bond vectors. The main chain backbone, for example, is described by regular repetition of the six-vector fragment

$$C4' \rightarrow C3' \rightarrow O3' \rightarrow P \rightarrow O5' \rightarrow C5' \rightarrow C4'$$

associated with each nucleotide repeating unit. For convenience the bonds along the main chain are assigned serial indices $i = 1 - 6x$ where x is the number of chain repeating units. In the example in figure 1 the first bond vector is chosen to lie along the C4′-C3′ bond of the 5′-terminal nucleotide with bonds successively nearer the 3′-end assigned increasingly higher values.

A Cartesian coordinate system is assigned to each bond vector so that its x axis lies in the direction of the given bond and its y axis is located in the plane defined by the bond and its predecessor. The positive direction of the y axis is chosen to make an acute angle with the preceding bond vector and the z axis is positioned to form a right-handed system. By premultiplication with the orthogonal matrix $\mathbf{T}_i$, the representation of a vector ℓ_{i+1} with components ℓ_x, ℓ_y, ℓ_z, expressed in reference frame $i + 1$ can be transformed to its representation in reference frame i. This matrix is a function of $\theta^{i,i+1}$, the supplement to the fixed valence angle between bonds i and $i + 1$, and of ξ_i, the angle of rotation about bond i. The matrix $\mathbf{T}_i(\theta^{i,i+1}, \xi_i)$ is simply expressed as the matrix product

$$\mathbf{T}_i(\theta^{i,i+1}, \xi_i) = \mathbf{X}(\xi_i)\mathbf{Z}(-\theta^{i,i+1}) \tag{1}$$

where

$$\mathbf{Z}(\theta) = \begin{bmatrix} \cos\theta & -\sin\theta & 0 \\ \sin\theta & \cos\theta & 0 \\ 0 & 0 & 1 \end{bmatrix} \tag{2}$$

and

$$\mathbf{X}(\xi) = \begin{bmatrix} 1 & 0 & 0 \\ 0 & \cos\xi & -\sin\xi \\ 0 & \sin\xi & \cos\xi \end{bmatrix} \tag{3}$$

The required transformation is achieved by a rotation of the $i + 1$ reference frame through an angle $-\theta^{i,i+1}$ about its z axis followed by a rotation of $-\xi_i$ about its x axis which then coincides with the x axis of vector ℓ_i. The angle of rotation is defined in the standard fashion of crystallographers by the relative orientations of bond vectors $i - 1$, i, and $i + 1$ with the parameter taken to be zero in the planar *cis* conformation and assigned positive values for right-handed

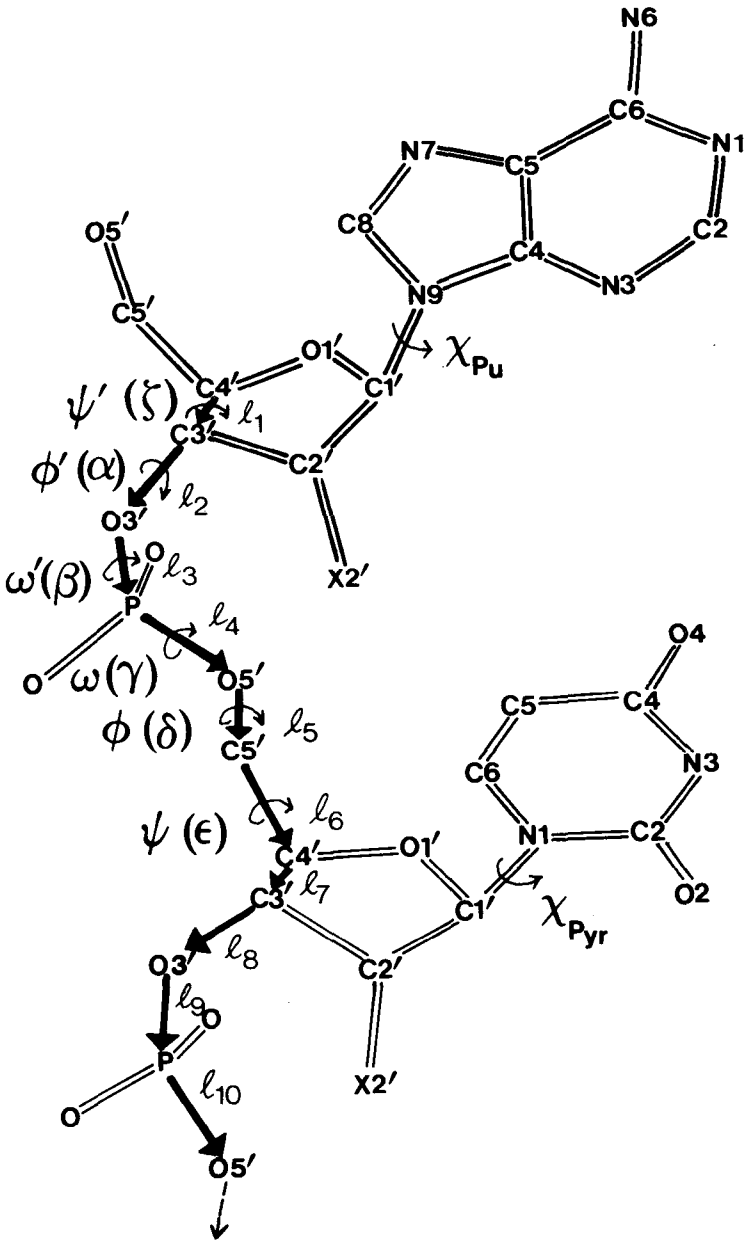

Figure 1

Figure 1 5′-Terminal section of a polynucleotide chain showing chain atoms, internal rotations, and skeletal bond vectors. Torsion angles are named, following Sundaralingam (1973), in terms of the types of chemical bonds with which they are associated (that is, ϕ' and ϕ for C–O, ψ' and ψ for C–C, ω' and ω for P–O). The $\alpha\beta\gamma\delta\epsilon\zeta$-angle nomenclature used in other chapters of this volume (and volume one) and noted in parentheses here is confusing in the context of theoretical conformational research where the same letters have well established alternate meanings (see text). Moreover, the logical repeating unit of a polynucleotide chain from the point of view of conformational theory is the C4′-to-C4′ segment illustrated here rather than the C3′-to-C3′ unit suggested by the $\alpha\beta\gamma\delta\epsilon\zeta$ designations. Backbone torsional angles are defined throughout with respect to the planar *cis* arrangement as 0° and the glycosyl torsion with respect to the *cis* orientations of the O1′–C1′–N9–C8 bond sequence in purines and the O1′–C1′–N1–C6 sequence in pyrimidines.

rotations. Formulations of $\mathbf{T}_i$ offered in previous studies of nucleic acid conformation (Olson and Flory, 1972*a*; Olson, 1975*d*, 1980*a*), however, are defined with respect to the planar *trans* conformation as reference. In general, the representation of any bond vector can be expressed in the coordinate frame of any other bond in the chain backbone by successive application of the appropriate transformation matrices. For example, when $j > i$ the transformed description of ℓ_j in the $x_i y_i z_i$ coordinate system is given by

$$\mathbf{T}_i \mathbf{T}_{i+1} \cdots \mathbf{T}_{j-1} \ell_j \tag{4}$$

The chemical bonds constituting the sugar-base side groups of the polynucleotide chain may be treated in terms of branch chains using the formalism introduced above. To facilitate mathematical representation of the side group atoms, the branches must be constructed to diverge away from the main chain backbone. As illustrated in figure 2, a hierarchy of side-group branches must be introduced to describe all the atoms in the chain repeating units. Before the sugar-base branches can be expressed in terms of the main chain backbone, the bond vectors along each branch must be converted in the above described fashion into the coordinate frame of the initial vector of the branch. The branch as a whole can then be transformed into the coordinate frame of the bond vector that terminates at the point in the main or higher-order branch chain where the branch originates. This transformation is accomplished by premultiplication with a matrix $\mathbf{T}(\theta^b, \xi + \Delta)$, where θ^b is the supplement to the valence angle formed by the initial bond of the branch with the preceding bond in the higher-order chain sequence and Δ is a phase angle shift that relates torsions describing the relative orientations of the main and branch chains. The parameter ξ is the torsion angle defined in terms of the main chain bond that radiates from the same atom as the branch chain together with the two main chain bonds that precede the branch point. In the case of the three-vector C3′ → C2′ → C1′ → O1′ furanose branch in figure 2, θ^b is the supplement to the valence angle formed by the C3′ → C2′ branch vector and the C4′ → C3′ main chain vector while Δ is the angular difference between the main chain C5′ → C4′ → C3′ → O3′ and related branch chain C5′ → C4′ → C3′ → C2′ torsions. The magnitude of Δ is determined by the supplements to the three valence angles formed at the intersection of the main and branch chains (Hendrickson, 1961)

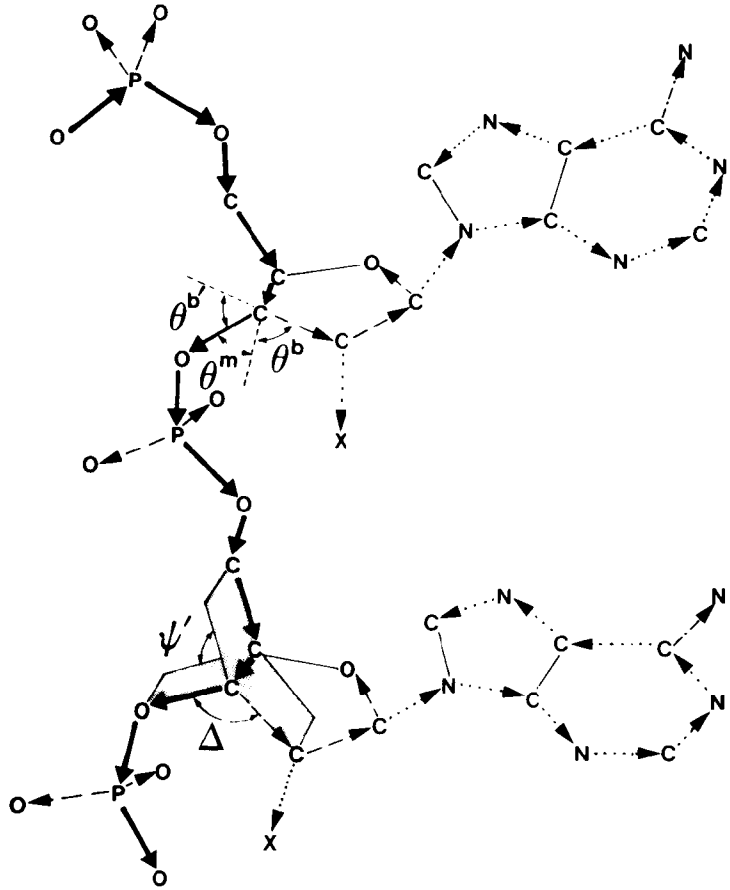

Figure 2 Schematic illustrating the hierarchy of chain branches used to generate internal coordinates of a polynucleotide. Skeletal backbone (—), first side-chain (----), second side-chain (· · · ·), third side-chain (–· –·). Valence angle supplements and torsion angles used to transform chain branches into the coordinate frame of the next higher-order branch are illustrated at the intersections of the skeletal backbone and the pentose branches of this example. See text for further explanation.

$$\cos \Delta = \frac{\cos \theta^{m} \cos \theta^{b} - \cos \theta^{b'}}{\sin \theta^{m} \sin \theta^{b}} \tag{5}$$

In the case of the furanose-main chain junction in figure 2, θ^{m} and $\theta^{b'}$ are the supplements to the C4′-C3′-O3′ and C2′-C3′-O3′ valence angles, respectively.

Because of cyclisation constraints, the sugar-base branches of the polynucleotide chain are conformationally less mobile than linear strands of the same chain length. The three-dimensional structure of the five-membered furanose ring is completely determined by nine of its fifteen geometric variables (the five bond

lengths, the five valence bond angles, and the five angles of internal rotation). As noted below, at least one of these conformational parameters must be a ring torsion angle. When bond lengths are assumed to be fixed, the number of independent variables is reduced to four. If the valence angles are further assumed to be constant, the furanose ring is restricted to two rigid forms differing only in the direction of the ring pucker (Olson, 1982). The choice of bond lengths and valence bond angles is responsible for the relative displacements of the five ring atoms but not for the directions of displacement. The conformational distinction between up (*endo*) and down (*exo*) ring puckering is based upon the absolute values of the ring torsion angles (Altona and Sundaralingam, 1972). Since only the magnitudes and relative signs of the ring torsions are determined by a given set of bond lengths and valence angles, at least one torsion angle must therefore be defined to describe a unique sugar puckering.

If the bond lengths and/or valence bond angles are permitted to undergo small, energetically inexpensive changes in value, the five-membered furanose ring is able to interconvert between a continuum of puckered forms along its so-called pseudorotational pathway of motion (Kilpatrick *et al.*, 1947). Until recently, theoretical ring puckering was described in terms of various artificial parameters, such as the rectilinear displacements of ring atoms from a suitably chosen mean plane (Cremer and Pople, 1975) or the curvilinear displacements of the atoms from a specific planar segment of the pentose (Sasisekharan, 1973), that only indirectly describe the geometrical features of the ring. The valence angle variations that result upon energy minimisation of these ring structures are usually widely discrepant from the observations of solid-state studies (Olson and Sussman, 1982). The well-characterised variations of endocyclic valence bond angles in differently puckered sugars (Murray-Rust and Motherwell, 1978; de Leeuw *et al.*, 1980; Westhof and Sundaralingam, 1980) can be better approximated using a model, like the one described above, based directly upon the geometrical parameters of the ring (Olson, 1982).

Structural parameters for use in the theoretical conformational analysis of the polynucleotides can be drawn from the crystallographic literature of model sugars, phosphates, bases, and low molecular weight nucleic acid fragments. Mean values and standard deviations of bond lengths and valence bond angles observed in the heterocyclic bases have been compiled by Arnott and coworkers (1976). Refined structural information on the phosphodiester linkage is limited to a few examples so that the reported average geometry (Arnott *et al.*, 1976) is subject to a high degree of uncertainty. The geometric parameters associated with the furanose have been analysed recently by various regression techniques (Murray-Rust and Motherwell, 1978; de Leeuw *et al.*, 1980; Westhof and Sundaralingam, 1980). The endocyclic valence angles are found to exhibit small sinusoidal fluctuations over the complete cycle of pentose pseudorotation. The internal bond lengths, however, are virtually independent of the ring puckering and can be assigned mean values. The observed variations of the exocyclic bond angles are not yet clearly understood. These parameters are expected to

respond to fluctuations in the endocyclic valence angles sharing common ring atoms. Increases in the exocyclic C–C–O valence angles, for example, have been noted to follow decreases in C–C–C endocyclic valence angles in certain C2′-*endo* and C3′-*endo* puckered sugars (Sundaralingam, 1965).

POTENTIAL ENERGIES

In principle, the polynucleotide is capable of adopting an essentially endless variety of three-dimensional spatial arrangements, each corresponding to a unique combination of geometric variables. Fortunately, many of these chain conformations are readily excluded on simple steric grounds. The nonbonded interatomic contacts observed in X-ray structures of nucleic acid models are generally restricted to certain lower limits below which steric overlaps are deemed to be excessive (Ramachandran *et al.*, 1963). A given chain conformation is therefore allowed only if all nonbonded distances of separation exceed these minimum values. Because of such factors, the rotational freedom of individual torsion angles in the polynucleotide chain is restricted to a few relatively narrow ranges (Morgan, 1958; Donohue and Trueblood, 1960; Haschemeyer and Rich, 1967; Sasisekharan *et al.*, 1967; Lakshminarayanan and Sasisekharan, 1970). Certain combinations of these allowed ranges can be additionally eliminated on the basis of higher-order steric interactions (Olson and Flory, 1972*a*). The sequences of torsional states that introduce long-range excluded volume effects between remote parts of the polynucleotide molecule, however, cannot be determined without complete specification of all chain coordinates. Because such steric conflicts are frequently brought about by unfavourable combinations of local torsions, many of these states can, nevertheless, be identified in simple model calculations on mono- and dinucleotides.

The conformational importance of the various arrangements of the polynucleotide chain cannot be determined on the basis of the above hard-core approach. In order to rank the sterically permissible regions of nucleic acid conformation space and to differentiate the relative severity of the various disallowed states, it is necessary to introduce a potential energy function that reflects the various interactions of the chain molecule. The construction of reliable force fields for the analysis of nucleic acid conformational energy has accordingly become a major focus of theoretical research activity.

With the advent of increasingly powerful computational systems, it has become possible, at least for isolated small nucleic acid analogues, to carry out *ab initio* quantum mechanical calculations that assume no more than the basic premises of the SCF-MO (self-consistent field molecular orbital) approach (Newton, 1973). *Ab initio* determination of the potential energy surface for molecular fragments large enough to be adequately representative of a polynucleotide chain segment, however, is yet an expensive undertaking in terms of both resources and time. Various approximate molecular orbital theories – including the extended Hückel, CNDO (complete neglect of differential overlap),

and PCILO (perturbative configuration interaction using localised orbitals) methods – have also been applied to the analysis of nucleic acid conformation. There is no clear evidence that these highly parameterised molecular theory methods provide estimates of potential energy surfaces that are more accurate or useful than the data generated by a still simpler method which has come to be known as the empirical or classical method. The decision to focus attention here on the simplest classical approach for estimation of the conformational energies of the nucleic acids, however, should not be construed as a denigration of the value of either *ab initio* or semiempirical molecular orbital calculations. Indeed, the fruitful use of such methods for the elucidation of certain features of the conformational energy will be described below.

Conformational energy analyses in the empirical or classical manner involve decomposition of the total potential energy of a molecule into a sum of additive contributions. The terms generally include (1) effects of bond length and valence angle strain associated with small molecular vibrations, (2) intrinsic torsional energies that arise at least in part from the electronic structure of the molecule (Epstein and Lipscomb, 1970; Jorgensen and Allen, 1971) and perhaps from 1,4 interactions of atoms separated by the three chemical bonds defining each rotation, and (3) pairwise interactions between atoms in the chain sequence that are not directly bonded by covalent linkages. The potential depends exclusively upon the internal structural parameters of the chain, and commonly takes the form:

$$V(\{\ell,\theta,\xi\}) = \sum_{\{\ell\}} K_\ell(\ell-\ell_0)^2 + \sum_{\{\theta\}} K_\theta(\theta-\theta_0)^2 + \sum_{\{\xi\}}\sum_{n=1}^{3} K_\xi^{(n)}(1+\cos n\xi) + \sum_{p\neq q} V_{NB}(r_{pq}) \tag{6}$$

This representation contains no cross terms (between different types of structural variables) although the set of structural variables does not constitute a proper set of normal coordinates. Coupling among members of the set of structural variables is routinely assumed to be negligible.

As evident from equation 6, the deviations of chemical bond lengths and valence bond angle supplements are taken to be quadratic in the displacements from their assumed strain-free values (ℓ_0 and θ_0, respectively). The torsional potentials are expressed by Fourier series with terms to the third harmonic ($n = 3$). A sum of terms is required to reproduce the peculiar *gauche* and anomeric effects associated with several torsions of the nucleic acid backbone (Il'icheva and Dashevskii, 1975; Govil, 1976; Hayes *et al.*, 1977; Olson, 1982). On the other hand, Tosi and coworkers (1978*a–c*, 1979) are able to reproduce *gauche* rotational preferences through judicious choice of nonbonded parameters. Alternate potentials that monitor the location of the lone-pair electrons on oxygen atoms have also been introduced to account for these effects (Tvaroška and Bleha, 1979; Srinivasan *et al.*, 1980; Platt *et al.*, 1981). When the latter approach is used, the torsional potential is treated as threefold symmetric with

only the $n = 3$ contribution of equation 6 considered. The stretching (K_ϱ) and bending (K_θ) force constants as well as the torsional barrier heights ($K_\xi^{(n)}$) are often assumed to be transferable to related species. That is, the parameters obtained by spectroscopic or thermodynamic analysis of model compounds are assumed to be directly applicable to the polynucleotide chain. Unfortunately, the library of experimental data on relevant nucleic acid models is limited. The necessary parameters are then estimated, if possible, on the basis of appropriate *ab initio* quantum mechanical determinations.

The nonbonded function $V_{NB}(r_{pq})$ in equation 6 includes the repulsive (steric) and attractive (London) forces between all atoms or groups separated by variable distances. The repulsive interactions dominate at short ranges where atoms approach one another too closely while the attractive interactions assume importance at slightly larger distances. Most treatments of polynucleotide conformational energy also include in $V_{NB}(r_{pq})$ the electrostatic interactions between charged or partially charged (dipolar) moieties and the hydrogen bonding interactions between suitably constituted groups. Charge-induced dipolar (inductive) effects between permanently or partially charged groups, while included in some studies (Olson and Flory, 1972*b*,*c*), usually have little influence upon the total nonbonded energy of a polynucleotide chain. Although there is no justification to the procedure, the classical approach ignores many-body interactions and assumes the total potential to be pairwise additive. That is, the summation over $V_{NB}(r_{pq})$ includes contributions only from pairs of atoms or groups p and q whose distance of separation r_{pq} varies with the choice of structural variables. The sum usually excludes all 1,2 and 1,3 atom pairs (separated by one and two chemical bonds, respectively) which presumably contribute to the bond stretching and valence angle bending terms. The total nonbonded energy, however, may reflect 1,4 pairwise contributions unless these effects are absorbed in the terms depending explicitly upon ξ. Provisions must be made to avoid double counting of the different contributions.

The van der Waals contributions may be estimated by various procedures. Most common in the treatment of polynucleotides are the Lennard-Jones 6-12 potential

$$V_{VDW}(r_{pq}) = A_{pq}/r_{pq}^{12} - B_{pq}/r_{pq}^{6} \tag{7}$$

and the Buckingham equation

$$V_{VDW}(r_{pq}) = a_{pq} \exp(-b_{pq} r_{pq}) - c_{pq}/r_{pq}^{6} \tag{8}$$

The latter function with three adjustable parameters (a_{pq}, b_{pq}, and c_{pq}) is more useful than the former (with only A_{pq} and B_{pq}) in attempting to fit theory to experimental data. Because the attractive term of the Buckingham potential dominates unrealistically at short distances of approach, the Lennard-Jones equation is generally favoured among theoretical researchers (Brant, 1976). While all workers have accepted the inverse sixth power dependence for the London attraction, the exponent of the repulsive term has been adjusted in