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LETTER TO THE EDITOR

Peptide Models for the Study of Coupled Conformational Properties of Protein Secondary Structures

This letter describes the construction and use of molecular models designed for the investigation of the coupled conformational properties of polypeptide structures. The models incorporate several degrees of conformational freedom that are not present in other varieties of models, and are in addition furnished with angle dials so that changes in torsional bond angles accompanying motion of the structure may be read out directly. The models are particularly useful in establishing the qualitative mechanical behavior of coupled structures. Once the mechanical behavior of the system is known, it becomes relatively straightforward to compute the energetics of the system under study.

Owing to the time-averaged nature of the X-ray experiment, relatively little information concerning the dynamic properties of proteins has been gained from their crystallographically determined structures. Indeed, crystallographic studies of some proteins have failed to reveal structural differences which phenomenologically manifest themselves in a variety of solution studies (Salemme, 1977). Although proteins show dynamic activity virtually throughout the spectroscopically accessible frequency range, there is little available information concerning the manner in which coherent motion might propagate throughout a protein structure, although such processes have occasionally been invoked in mechanisms of allostery and energy transduction. However, many proteins are in large part composed of regular, periodic secondary structural elements such as α-helices and β-pleated sheets. Such structures would appear to be natural candidates for the propagation of coherent, dynamic structural changes in proteins owing to their regular, periodic nature (Brillouin, 1946).

This letter describes molecular models that have been specifically designed for the examination of the coupled conformational properties of polypeptide secondary structures. The models are constructed of brass at the scale of 10 cm = 1 Å, and consist of individual atoms and their associated half-bonds. The bond angles and lengths incorporated in the models (Ramachandran *et al.*, 1974) are shown in Figure 1. Fixed bond angles were machined using an indexing head and are accurate to at least 0·1°. The measured error in built up bond length is typically 0·5 mm, corresponding to 0·005 Å on the atomic scale. The conformational degrees of freedom incorporated in the models are shown in Figure 2.

For the most part, the allowed degrees of freedom correspond to conformational alterations which are governed by slowly varying and low energy potential functions. Mechanical features include: (1) free or adjustably restricted torsional rotation about all bond axes, which was accomplished by means of the bond connections shown in Figure 3(a). All torsional bond angles (ϕ, ψ, ω) are furnished with dials and pointers for direct readout of torsional bond angles. (2) The nitrogen atoms are provided with

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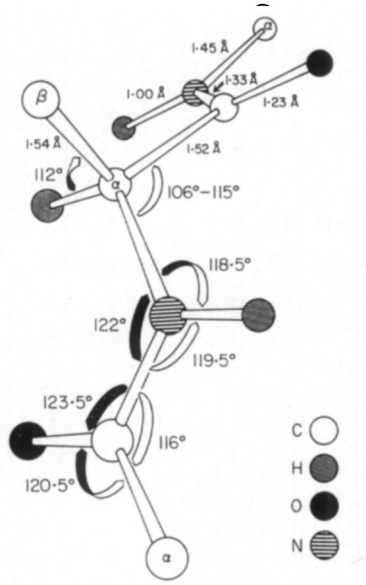

FIG. 1. Dimensions used in model construction, which are essentially those of Ramachandran *et al.* (1974).

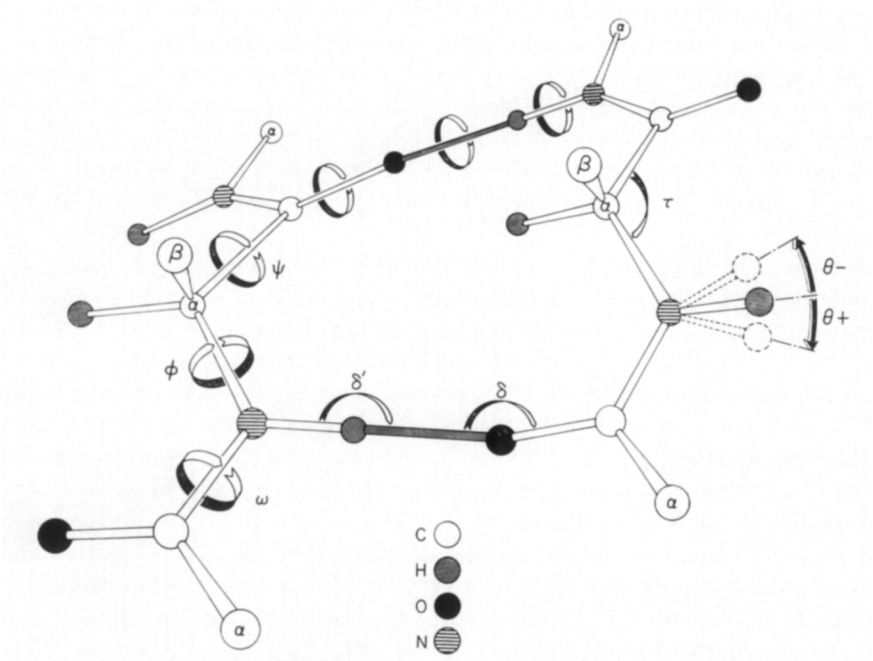

FIG. 2. A section of parallel β-sheet illustrating degrees of fixed or variable conformational freedom incorporated in the models.

a swivel on the N—H bond to allow the incorporation of tetrahedral character into the peptide nitrogen atom (Ramachandran, 1974) (Fig. 3(b)). (3) Carbonyl oxygen, amide hydrogen, and α-carbon atoms are swivel atoms with adjustable drag (Fig. 3(c)). The angle at $C_\alpha(\tau)$ is adjustable, since it is significantly more acute in glycine than in substituted amino acids. Figure 4 shows the models built up as a small peptide unit.

In use, the desired structure is built up from the model parts and suspended by wires from a system of levers. After the introduction of the desired fixed geometrical features (e.g. τ, peptide bond non-planarity, and hydrogen bond length or geometry), the structure is twisted or otherwise distorted in a continuous manner and the torsional angles read off and/or atomic co-ordinates measured (Salemme & Fehr, 1972). The resulting data provide a complete picture of the coupled motional properties of the structure which are governed by low energy potential functions. The largest structures studied thus far have been β-sheet structures (four residues by three strands), which are approximately 1·5 metres on a side. Although there are gravitational and edge termination effects in the models, they are nevertheless extremely useful in establishing the coupled motional properties of such structures. Once the general behavior is known, it is subsequently possible to design computational algorithms for further analysis of the motion which are of optimal efficiency. Indeed, by selectively locking down various degrees of freedom, while leaving others

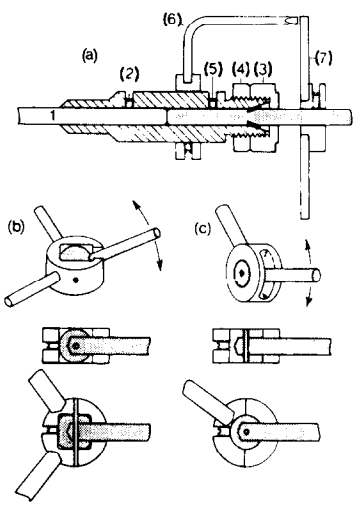

FIG. 3. Mechanical features of the models.

(a) A section of the rotating bond coupling. The design objective of the coupling is to provide smooth rotation about an accurately colinear bond axis with fixed length. The body of the clamp (diagonal hatching) is fixed to the non-rotating bond (1) by means of a set screw (2). One end of the bond clamp is furnished with a Swagelok fitting composed of a cap nut (3) which compresses a Teflon ferrule (black) into a circumferential groove on the rotating bond (shaded). The degree of rotating resistance is adjusted by the force applied to the cap nut (3), which may be locked by a jam nut (4). Rotation is locked by a set screw (5). The pointer assembly (6) is fixed to the body of the clamp, while the dial assembly (7) is fixed to the rotating bond.

(b) The swivel nitrogen atom, showing a perspective view, and vertical and horizontal sections through the assembly (below).

(c) Swivel atom used for C_α, O, and H, in perspective and in section. Shaded parts in (b) and (c) are rotating components.

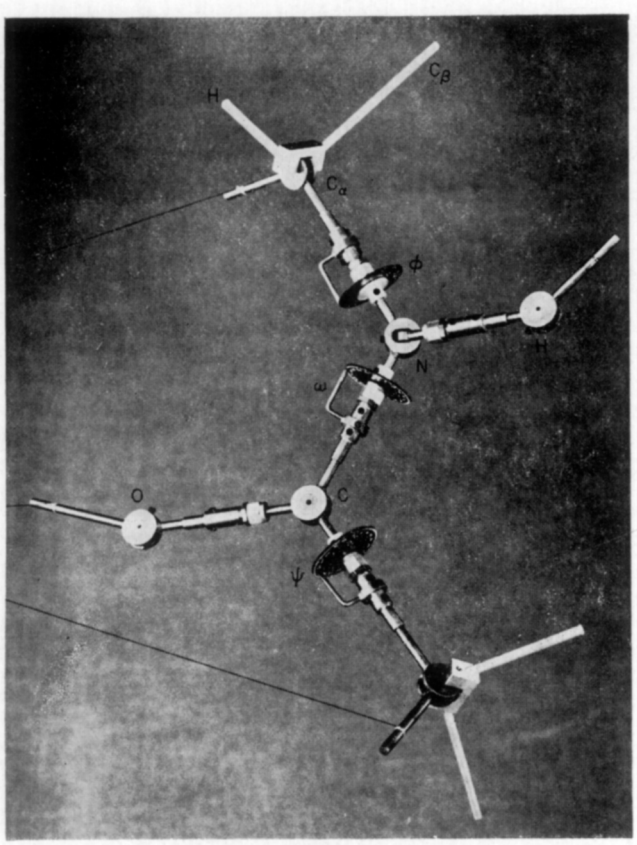

FIG. 4. A photograph of the model parts showing features described in Fig. 3 and clip-on (C_β—H units for co-ordinate measurements. Photograph by D. P. Bourque.

unconstrained, it is possible to establish which degrees of conformational freedom are coupled, and which are not. Those sets of independently coupled conformational alterations which do exist define the fundamental librational modes of the structure as a whole (Weatherford & Salemme, manuscript in preparation). It is not, in contrast, a trivial task to obtain such information by purely computational means, since there is *a priori* little way of knowing which of the large number of conformational variables in a large structure may be correlated.

Although the models have thus far been utilized for the study of coupled motional properties of protein secondary structural elements, they are also likely to be useful in the characterization of the librational properties of small cyclic polypeptide systems. In either case, the mechanical models provide a fairly accurate, though qualitative, picture of the behavior of the system under study. Most importantly, however, they show which conformational events are temporally correlated, and the way in which various conformational states may be interconverted by the path of least resistance. This information is valuable as a starting point for full-scale energy refinement procedures.

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REFERENCES

Brillouin, L. (1946). *Wave Propagation in Periodic Structures*, McGraw-Hill, New York.

Ramachandran, G. N. (1974). In *Peptides, Polypeptides and Proteins* (Blout, E. R., Bovey, F. A., Goodman, M. & Lotan, N., eds), pp. 14–34, Wiley Interscience, New York.

Ramachandran, G. N., Kolaskar, A. S., Ramakrishnan, C. & Sasisekharan, V. (1974). *Biochim. Biophys. Acta*, **359**, 298–302.

Salemme, F. R. (1977). *Annu. Rev. Biochem.* **46**, 299–329.

Salemme, F. R. & Fehr, D. G. (1972). *J. Mol. Biol.* **70**, 697–700.