

THE CONCEPT OF STRAIN DELOCALISATION: MACROCYCLIC AND BIOLOGICAL SYSTEMS. ENZYME CATALYSIS

SOSALE CHANDRASEKHAR

Department of Organic Chemistry, Indian Institute of Science, Bangalore 560 012, India (E-mail: sosale@iisc.ac.in; sosalechandra@hotmail.com)

Abstract—The titled concept has not been broached so far, and arises from the fact that bond angle strain increases as the square of the concerned angle (torsional strain also behaving similarly). Macrocyclic systems can thus accumulate less overall strain than smaller systems, whether in the ground state or transition state. Although strain delocalisation is generally overridden by forbidding entropic barriers in macrocyclization reactions, strain delocalisation may well be important in enzyme catalysis. This is because entropic effects are largely minimised within the organized interior of an enzyme molecule, so that preferred reaction trajectories are more easily achieved. (Strain delocalisation would also play a role in duplex formation in nucleic acids.)

INTRODUCTION

The concept of electron delocalisation is well established in the case of molecules with extended π -conjugation. Thus, α,β -unsaturated carbonyl systems are known to be thermodynamically stabilized by the delocalisation of the electrons of the conjugated π system. The key concept of aromaticity, of course, is derived from the idea of cyclic π -conjugation, which determines the stability and reactivity of an enormous range of organic compounds.

The intriguing concept of strain delocalisation, however, has apparently not been broached so far. In fact, strain delocalisation is possible because bond angle strain—as measured by the deviation of a bond angle from an ideal unstrained value—increases as the square of the deviation [1]. Although not as apparent or widespread as electron delocalisation, strain delocalisation nevertheless may well play a critical role in determining stability and reactivity in certain macromolecular systems, as elaborated below. (Torsional strain apparently behaves analogously to bond angle strain [1], so torsional strain delocalisation may act in tandem with bond angle strain delocalisation.)

DISCUSSION

General considerations

The idea of strain delocalisation is best explained with a specific numerical example, bearing in mind that bond angle strain is proportional to the square of the deviation from an ideal angle. Thus, a deviation of (say) 50° in a single angle would correspond to a strain of 2500 (50^2); however, if this angle deviation were to be equally distributed among 5 angles (10° each), the total strain would correspond only to 500 (5×10^2). (Strain energy units have been omitted as a comparison is being made between the two cases, the same proportionality constant being assumed.)

Indeed, both long chain and macrocyclic systems may manifest the strain delocalisation phenomenon. Thus, the folding of a long chain molecule into a U-shaped conformer may entail a certain amount of bond angle strain, because of possible steric interactions involving substituent groups, that would force the chain into a conformer with considerable bond angle strain at various centres. In such a case, longer chains would be less strained than shorter ones, as the bond angle strain can be distributed among a greater number of bond angles. (This analysis ignores entropic and torsional effects, although the latter behave analogously to the bond angle effect.)

Similarly, larger macrocyclic systems would generally be more flexible and more stable than smaller macrocyclic systems. Interestingly, the resulting thermodynamic stability may be responsible for the prevalence of macrocyclic molecules in nature, despite their formation being entropically disfavoured.

Biological macromolecules and enzyme catalysis

An intriguing application of strain delocalisation concerns large enzyme molecules and the reactions involved in their catalytic functions. Thus, the binding of a substrate molecule at the active site of the enzyme is followed by a series of reactions involving both enzyme-linked catalytic groups and other molecules (co-enzymes, etc.). Interestingly, strain delocalisation would enable reaction trajectories within the enzyme interior to achieve optimum geometrical requirements, by virtue of the large size of the enzyme molecule. This may well explain, to a considerable extent, the need for a large, flexible enzyme molecule to perform the various catalytic functions upon which life depends.

In fact, strain delocalisation is likely to be generally important to the interaction of biological macromolecules between themselves, *e.g.* leading to protein quaternary structures. Similarly,

duplex formation (both inter- and intramolecular) in nucleic acids would also benefit from strain delocalisation. In all these cases, a large, flexible macromolecule enables steric interactions between relatively bulky groups to be minimized via appropriate changes in the backbone structure and conformation.

It is noteworthy that the highly organized structures of biological macromolecules minimize entropic effects, which otherwise tend to complicate macrocyclization reactions in particular. Thus, strain delocalisation would be particularly manifest in the case of biological macromolecules.

CONCLUSIONS

The concept of strain delocalisation is derived from the fact that bond angle strain is proportional to the square of the deviation from an ideal angle. Thus, the total strain in a molecule would be smaller if the strain in a particular angle were to be distributed among a larger number of bond angles. This would be feasible particularly in macrocyclic systems, as also U-shaped conformers of long chain systems.

Thus, the prevalence of macrocyclic molecules in nature may well reflect this increased stability. Strain delocalisation is also likely to be important in several biological macromolecular interactions. In particular, reactions within the interiors of enzymes may achieve optimum trajectories by virtue of the large and flexible enzyme molecule. Duplex formation in nucleic acids would also benefit from strain delocalisation. (Entropic effects are minimized in these cases by virtue of their highly organized structures.)

In summary, strain delocalisation promises to be a novel concept that is fundamentally valid and of wide importance, particularly in a range of phenomena involving biological macromolecules.

REFERENCES

[1] Allinger, N.L. *Molecular structure: understanding steric and electronic effects from molecular mechanics*; Wiley and Sons: Hoboken NJ, **2010**.