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THE CONFORMATIONAL HOMOGENEITY OF CYCLOPOLYSARCOSINES

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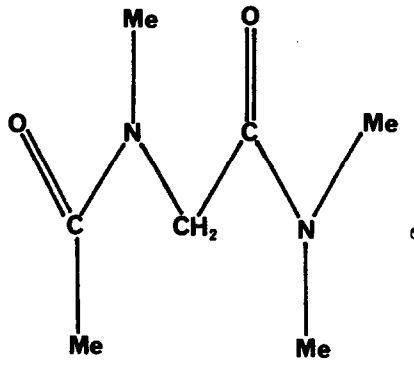
The study of polypeptide and protein conformation by means of empirical force-field (EFF) calculations is an important and rapidly expanding area of research. Empirical techniques necessitate the availability of adequate experimental data on which subsequent extrapolations may be based, and this is a particular difficulty with EFF calculations because most oligopeptides exist as conformational mixtures which are difficult, if not impossible to characterise experimentally.

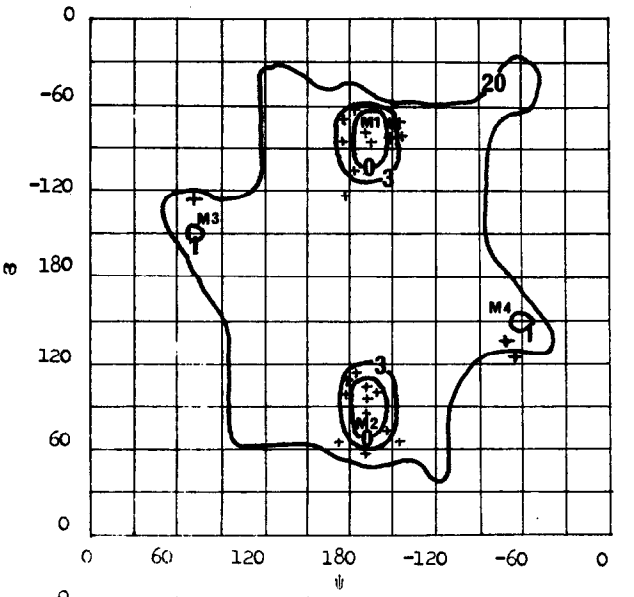
In contrast to cyclic oligopeptides composed of naturally occurring amino-acids[1,2], those consisting of sarcosyl residues are remarkable for their conformational definition. It was predicted, on the basis of NMR studies[3], that this was a consequence of attractive transannular forces, but subsequent X-ray crystal structure analyses invalidated this hypothesis[4]. These results lead to the conclusion that the homogeneity arises from intrinsic properties of the polypeptide chain[4]; a proposal which can be investigated by means of molecular mechanics calculations.

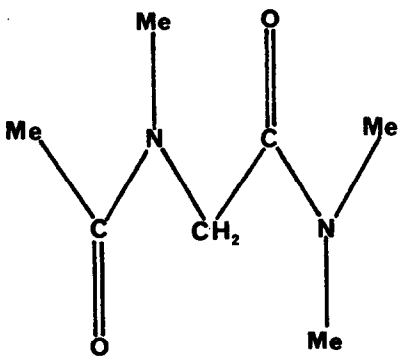
Ramachandran plots (Energy in k.cal.mole^{-1}, φ and ψ as defined in Ref 5) for N-acetyl N'N'-dimethyl cis- and trans-sarcosyl amide are shown below, with the observed (φ,ψ) pairs indicated by crosses on the first map. The most striking feature of these maps is the restricted area of low-energy conformational space available compared with the glycyl analogue of these dipeptides[6]. The two maps are identical to a first approximation and consist of a pair of centrosymmetrically related minima of high statistical weights (M1,M2) around which most of the experimental points are clustered, together with a similarly related pair of minima having low statistical weight (M3,M4) which are sparsely populated with experimental points. The fact that these latter pairs of minima have a slightly higher statistical weight in the trans-isomer has some interesting ramifications which are discussed later.

There are six possible combinations of cis- and trans-amide configurations for cyclotetrasarcosyl (N-methylation obscures the usual preference for trans-amide groups[7]) which taken together with the 64 possible combinations of (ϕ,ψ) values for M1-M4 leads to 384 low energy conformers, a proportion of which will effect ring closure with favourable (ϕ,ψ) values at the junction. Of these 384 combinations five unique conformers which resulted in an end-to-end distance < 3Å were used as starting points for full relaxation molecular mechanics calculations; with a previously defined force field[8] and minimisation procedure[9].

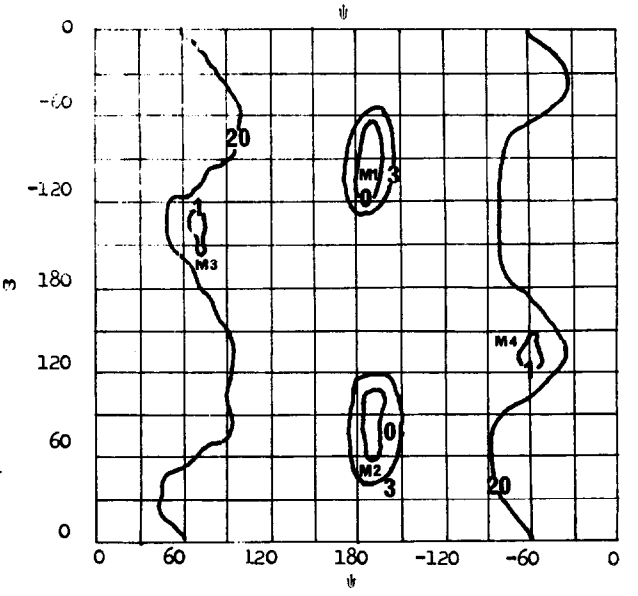


N-acetyl N'N'-dimethyl cis-sarcosyl amide

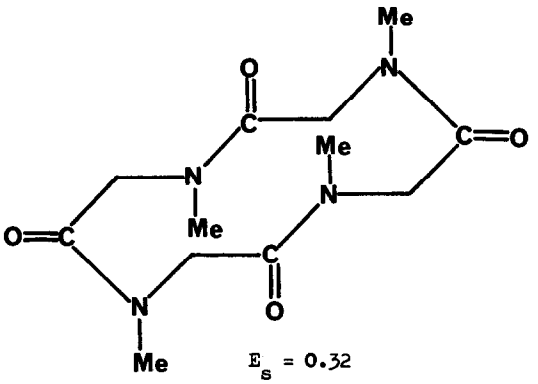




N-acetyl N'N'-dimethyl trans-sarcosyl amide

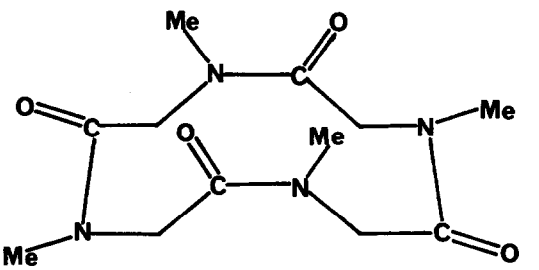


The results are shown in schematic form below with the steric energies in k.cal.mole^{-1}. The global minimum I corresponds to the conformation observed in the crystalline state which is identical with the only detectable solution conformer. All of the other low energy minima are at least 3 k.cal.mole^{-1} (steric energy) higher than I and represent conformers which should be unobservable by NMR experiments; a prediction in excellent agreement with the experimental facts. This statement will almost certainly still be true when statistical weights are calculated taking cognizance of symmetry, chirality and vibrational free energy.



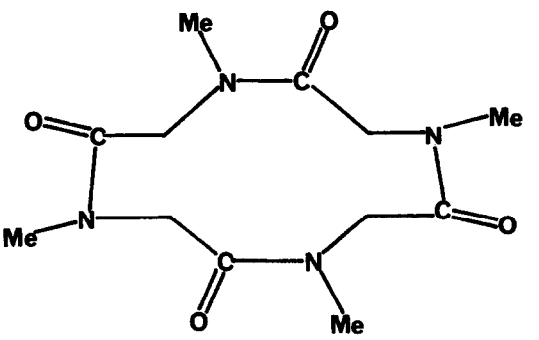
E_s = 0.32

I



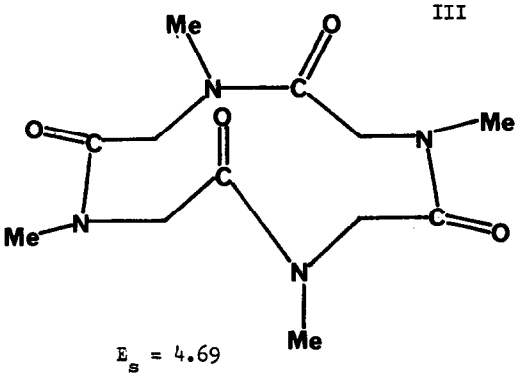
E_s = 3.27

II



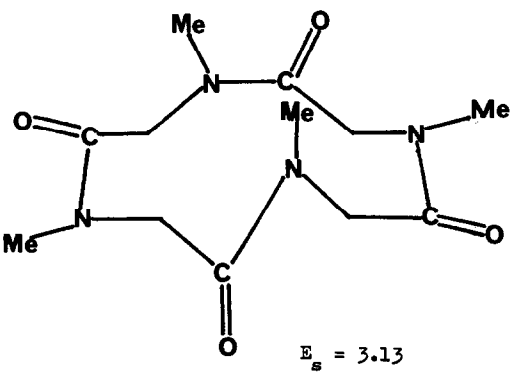
E_s = 3.95

III



E_s = 4.69

IV



E_s = 3.13

V

The X-ray results indicate that the first oligopeptide which can effect ring closure by making exclusive use of M1 and M2 occurs at eight residues; in the smaller oligomers at least one (φ,ψ) pair must occupy M3 or M4 and obviously the pair with the highest statistical weight will be preferred. These (φ,ψ) pairs would therefore be expected to occur at the junction of cis- and trans- or trans- and trans-amides. (The dimethyl N' terminus of N-acetyl N'N'-dimethyl trans-sarcosyl amide does not allow a distinction to be made between the cis-, trans- and trans-, trans-configurations). In fact without exception they are located at a cis-, trans- junction and this observation together with the conformations of higher oligomers are the subject of continuing investigation[10].

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