

Figure 1. a, b, Specimen preserved with phragmocone c, Another specimen showing the apex

for want of confirmation. Hence, the present find of species of *Peratobelus* Whitehouse of Aptian age is the first authentic report of belemnoid from the Upper Gondwana sediments occurring along the southeastern coast of India.

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'i's right!

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The interdigitated tetraplex model of DNA with cytosine repeats has recently received crystal structure confirmation^{1,2} from the group of Alexander Rich at the Massachusetts Institute of Technology.

This 'i' (for 'intercalated') motif consists of two pairs of oligocytosine strands. Each strand of a pair is hydrogen-bonded to the other, parallel, strand by means of C-C⁺ base pairing. The two pairs are intercalated to form the tetraplex (Figure 1). Since the base pairing scheme requires the cytosines to be hemi-protonated, the

structure is observed at low pH.

The first observation of the 'i' motif came from NMR studies³ on the oligonucleotide d(TCCCC) at pH 4.3. The structure consisted of twelve intercalated base pairs, including two possible T-T pairs. On the NMR time scale, a 222 symmetry was seen in the structure, which implied that the two interdigitated duplexes were anti-parallel to one another. The tetrad as a whole had a right-handed helical twist of about 16° between base pairs belonging to the same duplex. The

cytosine-cytosine base pairs were evidenced by lack of significant exchange broadening of the imino protons. Interpretation of the NOESY spectra led to the intercalated model for the base stacking. Similar results were reported by the same group for several other oligos with continuous stretches of cytosine bases.

Nothing under the sun, of course, is entirely new, and aspects of the 'i' motif have been suggested earlier. Parallel duplexes containing C-C⁺ base pairs were constructed to explain the fibre diffraction

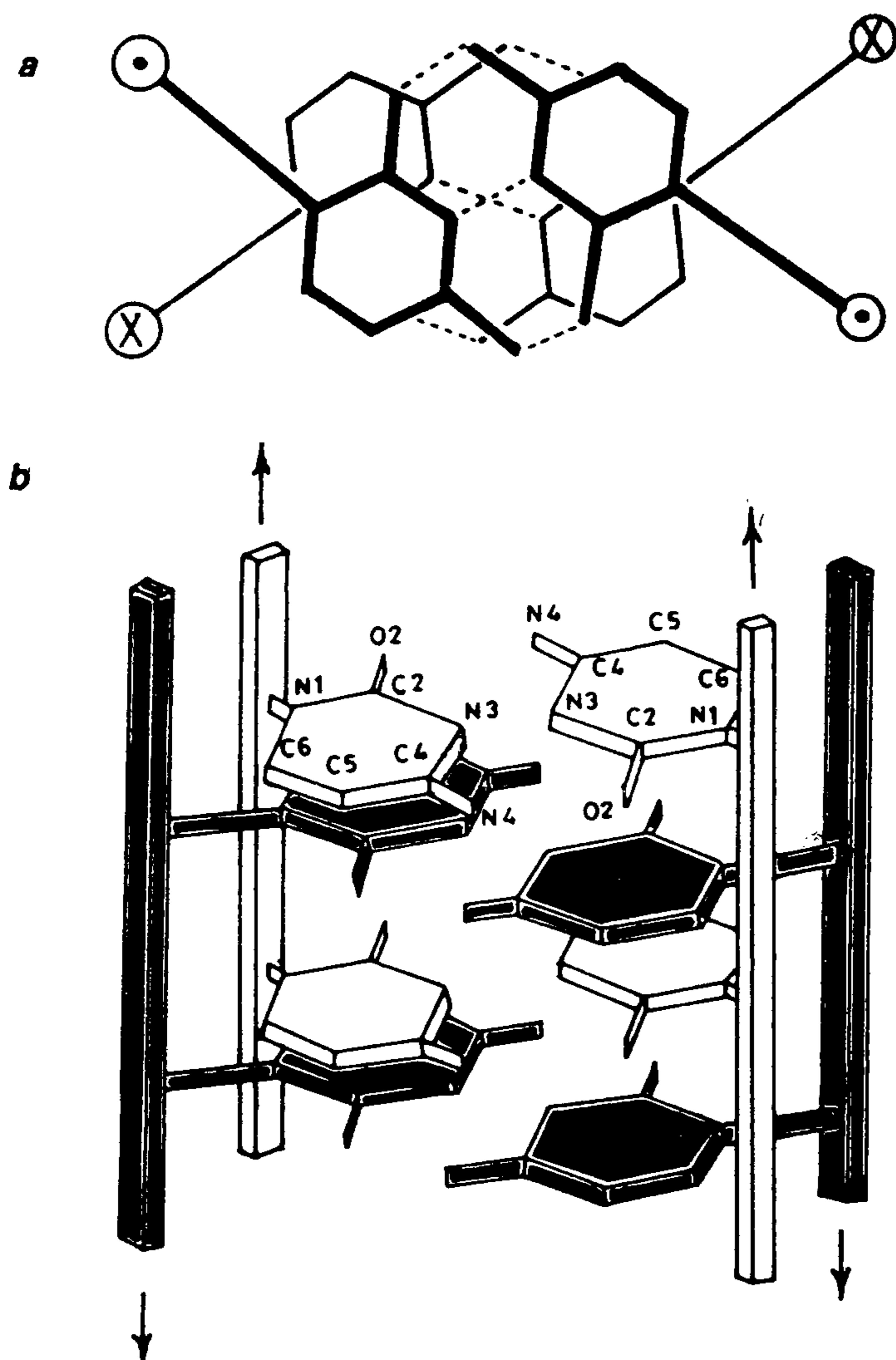


Figure 1.

patterns of poly(dC)⁴ and were observed in single crystals of ribo(CpA)⁵ and deoxyribo(CpG)⁶. An intercalated helical duplex model for poly(dC) had also been extrapolated⁷ from the single-crystal structure of dCMP. The NMR studies of the tetrad brought together both the C.C⁺ base pairing scheme and the intercalated pattern in a single molecular complex.

Subsequent biochemical and spectroscopic studies⁸⁻¹⁰ have identified several sequences with propensities for both intermolecular and intramolecular 'i' structures built up from only one or two or four molecules. In particular, sequences with sets of three cytosine residues repeated

in tandem with A or T interrupts have been shown to adopt such three-dimensional arrangements. Thus, sequences such as (CCCTAA)₃CCCT and (C₃TA₂)₄ have been studied by gel electrophoresis and CD, UV and NMR spectroscopy. At low pH (~5-6.5) migration patterns and the spectra of these sequences strongly indicate an intramolecular 'i' motif.

The two recent crystal structures^{1,2}, one of d(CCCT) at 14 Å and the other of d(CCCC) at 2.3 Å, reveal a four-stranded intercalated complex very similar in most of the details to the NMR results. The overall shape of the tetrad is not, as may be naïvely expected, that of a cylinder.

It is more like a thickish, long book, twisted about the long axis. The twist angle in going from one C.C⁺ base pair to the next in the same duplex varies from structure to structure, from 12° in d(CCCC) to 16° in the NMR study to about 17° in d(CCCT). Thus, the tetraplex as a whole requires about 50 intercalated base pairs and 160 Å to twist around once. The 222 symmetry seen in the NMR study is absent in the crystal structure. Instead, the phosphate groups on the two strands on one face of the tetraplex curve up to form a groove. The other face is flat.

One of the suggested biological roles for the 'i' motif considers the tandemly repeated sequences of cytosines (and guanines on the complementary strand), which have been found at the 5'-end of telomeres of eucaryotic chromosomes. Rich and coworkers suggest that DNA sequences containing C repeats on one strand, and complementary G repeats on the other, may form cruciform structures with the C- and G-rich portions on opposite tips of the cruciform extrusions. Two such cruciforms may then interact and stabilize each other by means of a double-handed handshake. One pair of hands would form the 'i' motif C tetrad and the other a G tetraplex. It is possible that this is the physical basis of interaction of the two DNA sequences during recombination, though the biochemistry would probably require specific proteins to stabilize the structure even under unfavourable conditions of pH, etc. Stretches of cytosines have also been discovered in other non-coding regions of the genome such as introns and satellite DNA. The discovery of C stretches as a necessary component of the promoter region of the *c-k-ras* proto-oncogene suggests the possible structure-based regulation mechanisms. And when we remember that a stretch of C always implies a stretch of G on the complementary strand, exciting structural possibilities arise. Apart from the 'normal' double helix, such sequences can also exist as triplex or 'i' motif/G tetraplex structures.

Forty years after Watson and Crick wrote what was, perhaps, thought to be the concluding chapter of the DNA structure story, the molecule continues to spring surprises.

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