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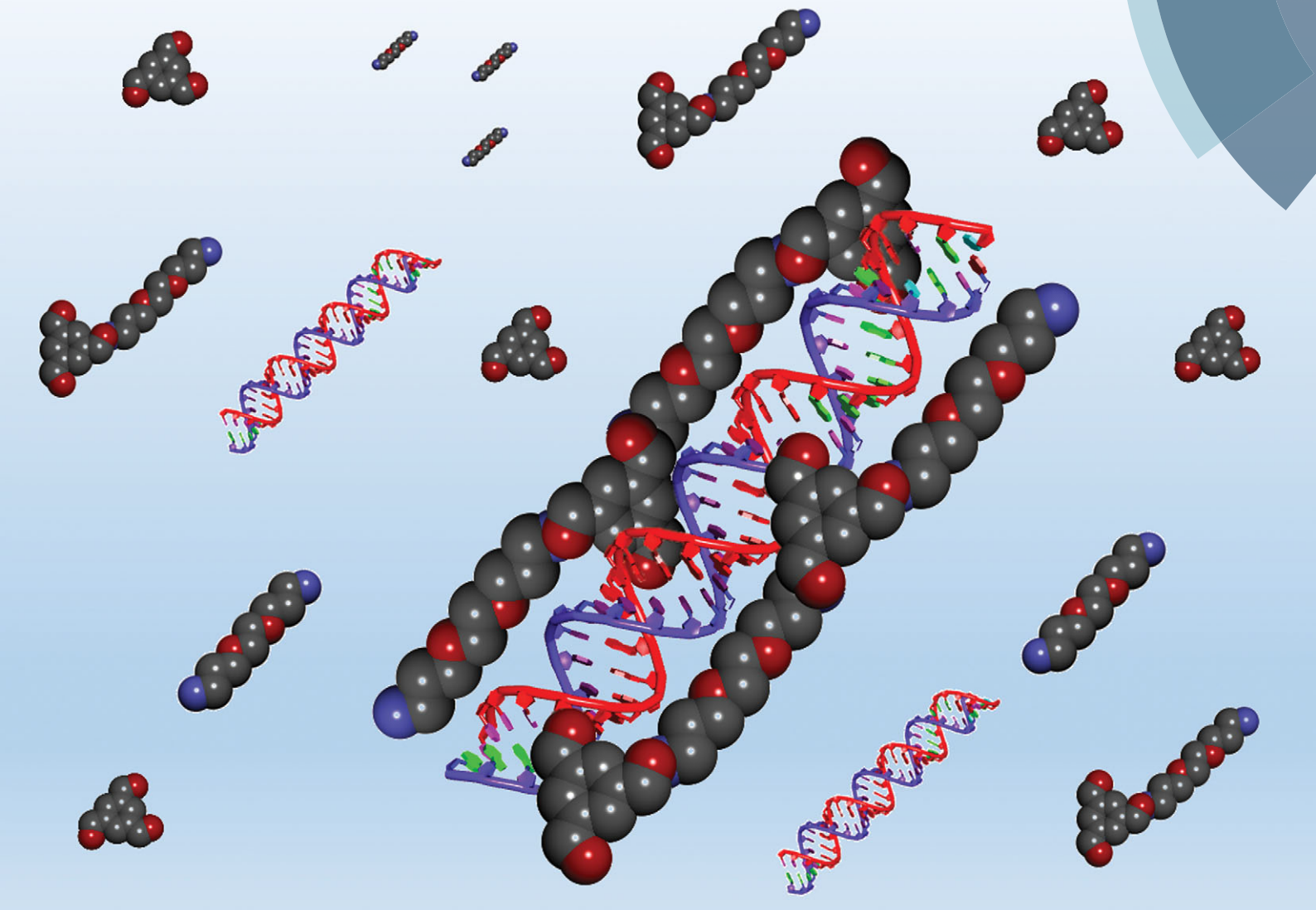

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Dynamic constitutional frameworks for DNA biomimetic recognition

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Dynamic constitutional frameworks for DNA biomimetic recognition

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Linear and cross-linked dynamic constitutional frameworks generated from reversibly interacting linear PEG/core constituents and cationic sites shed light on the dominant coiling *versus* linear DNA binding behaviours, closer to the histone DNA binding wrapping mechanism.

Numerous artificial gene delivery systems utilizing designed molecular or nanocarrier systems have been developed in the last few decades.[1–6] Non-exhaustive cell penetrating examples of cationic lipids,[1] peptides,[2] calixarenes,[3] polymeric structures[4] and fullerenes[5] have all been used in this context by using design approaches (Fig 1a). Concurrently, the design of multivalent systems containing DNA coordination, membrane penetration and anti-opsonisation functions has attracted a great deal of interest.[2] Convergent self-assembly strategies have been used for the synthesis of multivalent supramolecular nanodevices, designed to mimic natural delivery functions (Fig. 1b).[1,6] Despite such impressive progress, important application problems, deriving from the enormous variability of both DNA targets and nature of the transfected cells, the rational design became limited to the introduction of a reduced number of components and should be completed by combinatorial approaches.

Within this context, the dynamic combinatorial strategy[7] appeared to be one of the most attractive screening methods for the rapid access to the active systems from large and complex libraries (Fig. 1c, top).

By virtue of the reversible interchanges between the hydrophilic heads and hydrophobic tails, the fittest dynamic transfector can adapt simultaneously to the DNA biotarget and the cell membrane barrier.[7] As for the design approaches, a future alternative constitutional selection strategy may embody the flow of structural information from the molecular level to dynamic multivalent nanodevices that bind DNA on their nanosurfaces. This concerns the use of Dynamic Constitutional Frameworks–(DCFs) composed of combinations of linear and/or cross-linked arrays of components reversibly interconnected *via* core connectors and containing functional groups synergistically interacting with DNA and bilayer membrane components (Fig. 1c, bottom). As previously observed,[8,9] the DCF may implement adaptive reversible rearrangements of the components toward a high level of correlativity of its hypersurfaces in interaction with the DNA biotargets[10] and the cell membrane barrier. In this study, linear PEG macromonomers, trialdehyde core connectors and positively charged molecular heads have been used to conceive DCFs for DNA recognition (Fig. 2). 1,3,5-Benzenetrialdehyde, **1**, poly-(ethyleneglycol)-bis(3-amino-propyl)-terminated ($M_n \sim 1500$ g mol^{-1}), **2** and Girard's reagent T, **3** monoprotonated *N*,*N*-dimethylethylene amine, **4** or aminoguanidine hydrochloride, **5** are the building blocks subjected to conceive **DCFR 1·2·R**, **R** = **3–5**, by using the amino-carbonyl/imine reversible chemistry. Treatment of **1** with 1 eq. of **2** in acetonitrile (reflux, 48 h) afforded a mixture of linear and cross-linked (Fig. 2) frameworks, whose ^{1}H-NMR spectral properties agree with the formation of a 1 : 1 mixture of **DCF1 : DCF2** (with $M_n \sim 15\,000$–$18\,000$ g mol^{-1}, Fig. 3a). Very interestingly the ^{1}H-NMR spectra of the **DCF1:DCF2** mixture recorded in CD_3CN and D_2O are similar and remain unchanged for months at neutral pH. As previously observed, the PEG chains may have a protecting effect against the hydrolysis of the imine bonds, favoring the imine formation.[9]

Upon progressive addition of cationic molecular heads **3–5** to the **DCF1:DCF2** mixture, the ^{1}H-NMR spectra are reminiscent with the formation of linear frameworks **DCF3** and **DCF4** and a more complex cross-linked framework **DCF5**. The conversion of the aldehyde groups is almost total upon the addition of 1–1.5 eq. of cationic head **3–5**. This is proven to be the analysis of chemical shifts of the imino bonds, showing a very simple pattern of signals for **DCF3** and **DCF4** reminiscent of the presence of the two linear forms presented in Fig. 3a, while the **DCF5** network presents a complicated pattern of imino-proton signals, reminiscent of the formation of a complex, cross-linked network. The strong H-bonding between guanidinium cationic

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