

Oligonucleosides with Integrated Backbone and Base: Foldamers with a Novel Architecture

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Abstract: Dinucleoside and tetranucleoside analogues with integrated backbone and nucleobase represent a novel type of oligonucleotide foldamers. They are characterized by a linker between C(5') of one nucleoside moiety and C(8) of an adjacent adenosine, or C(6) of an adjacent uridine. Solutions in chloroform or chloroform/DMSO of these partially protected di-, or tetranucleoside analogues associate. The strength of the association depends on the nature of the linker, the presence, or absence of a hydroxymethyl group on the terminal nucleobase, other protecting groups, and intramolecular hydrogen bonds. The thiomethylene-linked dimers were studied in detail; one of them associates strongly enough that a melting temperature can be determined, evidencing base stacking in chloroform solution. Some dimers form organogels. Two 2',3'-O-isopropylidene protected self-complementary tetramers were prepared. Their duplexes are conformationally homogeneous. One of the tetramers was characterised in detail; it associates *via* hydrogen bonds of the Watson-Crick type to form a partial A-type helix with all bases in a *syn*-conformation and a rather large twist angle. Also studied were di- and tetranucleotide analogues possessing an all-carbon linker; they were derived from (hydroxy)propynylene linked dimers by deoxygenation, partial reduction to the (*E*)- and (*Z*)-propenylene linked analogues, and further hydrogenation to propanylene-linked analogues. The propargylic hydroxy group forms an intramolecular hydrogen bond to N(3) of the adenine moiety of the same unit; the resulting conformers associate weakly. Deoxygenation leads to foldamers that associate much more strongly. A (*Z*)-propenylene-linked dimer also associates strongly, its (*E*) isomer less so, and the propanylene-linked analogues associate weakly. The results show that backbone-base integration defines a novel structural relation between backbone and nucleobases that favours selective pairing and leads to oligonucleotide foldamers.

Keywords: Hydrogen bonding · Oligonucleoside foldamers · Pairing · Stacking

Introduction

The strongest motives for the design and synthesis of oligonucleotide mimics have been the search for antisense or antigene activities [1–14] and the quest for a rational insight into the prebiotic origin of nucleic acids [15]. They led to the synthesis of numerous analogues, modifying nucleobases, ribose or deoxyribose units, and the phos-

phodiester linkage. Peptide nucleic acids ([16–23] and earlier papers) even do away with the monosaccharide and the phosphate moieties. However, as a consequence of these goals, the essential architecture of nucleic acids – the structural differentiation between a contiguous backbone and nucleobases attached to it – has always been maintained. There are no obvious reasons why the structural differentiation between backbone and nucleobases should be an absolute requirement for a base- and sequence-specific mutual recognition of oligonucleotide mimics by hydrogen bonding and base stacking, *i.e.* for the formation of autonomous pairing systems.

Considering the relevance of information encoding, storage, and transmission, and impressed by the variety of secondary structural elements and functions of RNAs [5] [24–30] and references quoted there) we set out to experimentally test the contention that oligonucleotide foldamers where the nucleobases are integrated into the backbone (Fig. 1) may associate *via* hydrogen bonding, maintain base stacking, show se-

quence specific recognition, and form well-defined secondary elements.

Incorporating the nucleobases into the backbone means linking the nucleobases through C(2) or C(8) of purines, and C(5) or C(6) of pyrimidines (Fig. 1). A choice between these locations was made on the basis of rather straightforward modelling, starting with B-DNA, removing *in silico* all elements, except the bare nucleobases interacting *via* Watson-Crick hydrogen bonds, and introducing possible linkers at the indicated positions of adenosine and uridine [31]. The structure of the resulting oligomers was relaxed by energy minimisation and the characteristics of the resulting helix, stacking, and hydrogen bonding were compared. This led to a number of possible foldamers and to somewhat more promising structures if C(6) of pyrimidines and C(8) of purines were chosen as point of attachment for the various linkers under consideration.

While the question of possible applications of such foldamers has to be asked, it appeared premature to give specific an-

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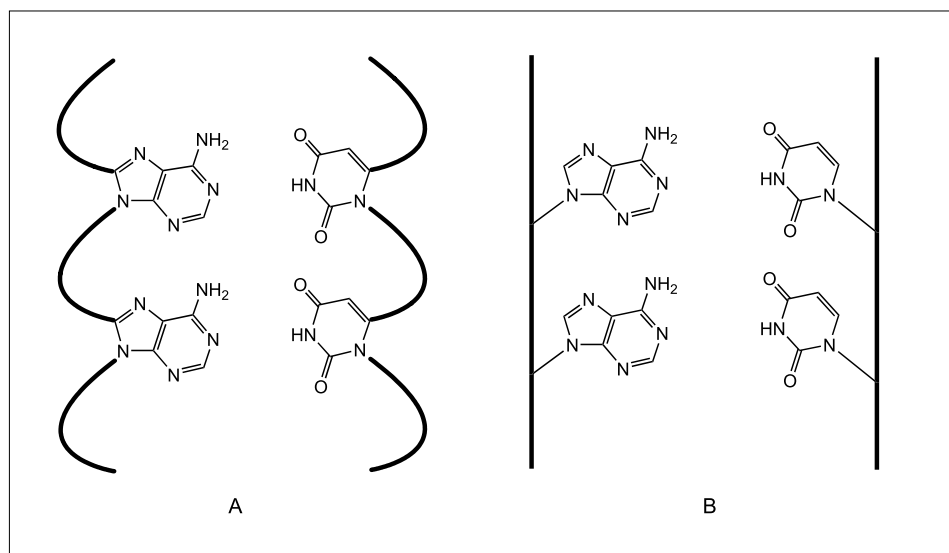


Fig. 1. Base/backbone integrating foldamers **A** and base/backbone differentiated oligonucleotides and analogues **B**

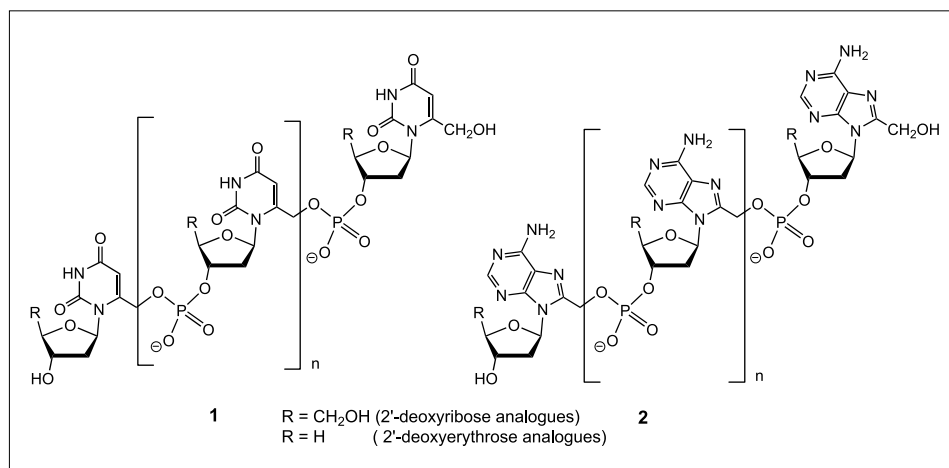


Fig. 2. Phosphodiester analogues **1** and **2**

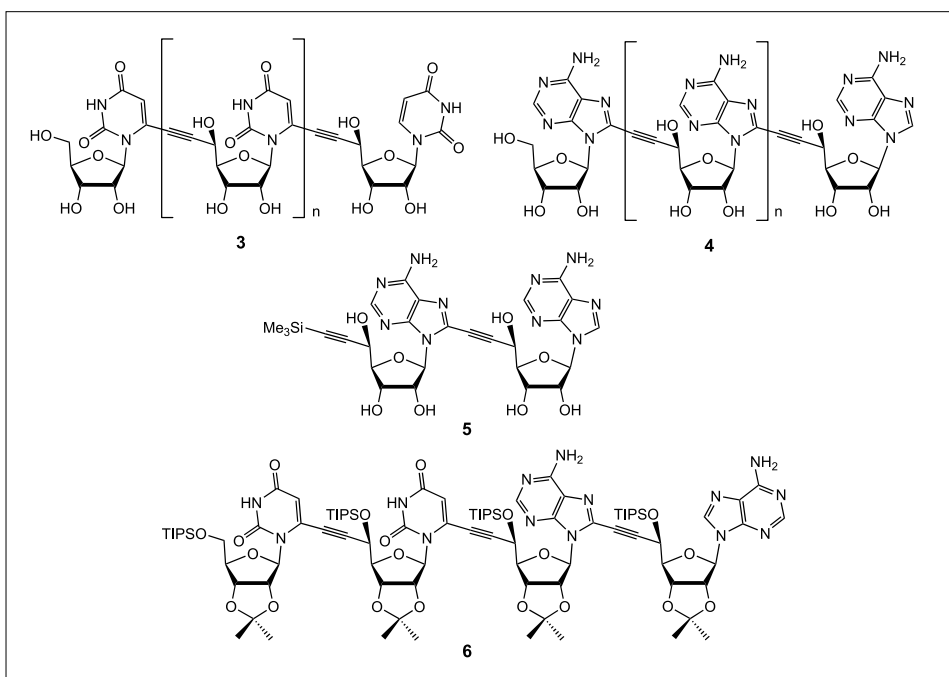


Fig. 3. Ethynylene-bridged oligonucleosides **3** and **4**

swers. The search for novel foldamers and their properties is a discovery programme rather than one based upon invention. While it is necessary to choose a fruitful field for such a programme, it is by definition impossible to predict the nature of discoveries to be made. However, possible applications will be similar to those of other self-associating systems that shape space, and pertain to the domain of material sciences, nanotechnology, catalysis, and biology [22][32–38]. Biological applications (interference with nucleic acids, proteins, or glycoconjugates) will depend upon the interactions of such foldamers with nucleic acids and/or proteins and require a sufficient degree of water solubility.

Before evaluating any applications we have to show that such a fundamentally altered architecture of oligonucleotide foldamers is compatible with the desired properties. To demonstrate that nucleic acids can be modified more extensively than so far explored and yet show specific recognition and form specific secondary elements appeared sufficiently important to embark on the synthesis of backbone/base integrating oligonucleotide analogues.

Results and Discussion

In the following I will summarise the results of our first steps towards such analogues, leading to a proof of principle.

The first foldamers we aimed at are the decamers **1** and **2** ($n = 8$) (Fig. 2), incorporating adenosine (A) and uridine (U) only [39]. As A and U can only associate *via* two hydrogen bonds, pairing of such foldamers would constitute a more stringent proof of concept. A solid-phase synthesis provided the protected 10mers **dU*₁₀** and **dA*₁₀**. While **dU*₁₀** was successfully deprotected, attempted deprotection of **dA*₁₀** under a variety of conditions led to strand break, rationalised by a facile elimination triggered by N-debenzoylation. This persistent problem led us abandon these mimics.

In a parallel effort we synthesised RNA analogues of type **3** and **4** (Fig. 3). An ethynylene-linked uridine-derived hexamer and an adenosine-derived tetramer were obtained by a linear and/or convergent approach, including oxidation of the C(5') hydroxymethyl to a formyl group, a diastereoselective addition of an ethynyl zinc or magnesium reagent, and Sonogashira coupling to a C(8) bromo or iodo nucleoside [40–42]. As a rule, C(8)-substituted purines and C(6)-substituted pyrimidines prefer the *syn* conformation, while the design of the oligomers **3** and **4**, based upon the structure of B DNA, postulated an *anti* conformation of the nucleobases.

We had hoped that the sterically undemanding ethynyl substituent might be compatible with a sufficient population of the *anti* conformation to allow base pairing. However, conformational analysis of the dimer **5** demonstrated a persistent hydrogen bond between the propargylic hydroxy group and N(3) of the same monomeric unit that is only compatible with a *syn* conformation [43]. In keeping with this observation, fully deprotected tetramers did not pair in MeOH, while the protected tetramer **6** associated in CDCl₃ [41][44]. This suggested to either remove the propargylic hydroxy group, or to design new analogues that pair in a *syn* conformation.

In view of the demanding synthesis of higher oligomers of type **3** and **4**, we first explored the second possibility. The simplest representative of such analogues were the oxymethylene-linked U*-[o]-U and A*-[o]-A oligomers **7** and **9** (a star denotes a CH₂X group at C(6) of U or at C(8) of A, and [x] denotes the element in the linking unit; Fig. 4) [45]. Maruzen model studies and MacroModel V. 4.5 Amber* force-field calculations indicated that the corresponding U*-[o]-U* and A*-[o]-A* oligomers adopt the *syn*-conformation and form a parallel right-handed B-helix, characterized by seven residues per turn and Watson-Crick H-bonds at a distance of 2.96 Å.

The synthesis of **7** and **9** was based on a C(5')O alkylation by the electrophiles **8** and **10**. While **8** formed the desired ethers, the adenosine-derived electrophiles **10** did not, presumably due to the facile formation of a cationic intermediate **11** that already explained the facile strand-break of the decameric phosphodiester **2**. Pairing studies were conducted with the accessible dimers in chloroform solution, following the concentration dependent chemical shift of H-N(3) of the uridine moiety.

This ¹H-NMR analysis showed that **12**, the self-complementary dimers **13** and **15**, and their partially deprotected derivatives **14**, **16**, and **17** do pair (Fig. 5 and Table). The association constants and the thermodynamic parameters show a remarkably strong association in chloroform, entropy-enthalpy compensation, and a strong influence of the protecting groups on pairing.

The fully deprotected dimers derived from **12**, **13**, and **15** did not pair in aqueous solution, suggesting that the association might be due mostly or exclusively to hydrogen bonding.

Although these results constitute a proof of concept for the pairing of this type of foldamers, one may argue that the formation of H-bonds in chloroform is neither a surprise nor much of a proof before the H-bond characteristics (Watson-Crick or Hoogsteen), a 1:1 stoichiometry of pairing, stacking of the nucleobases, and sequence

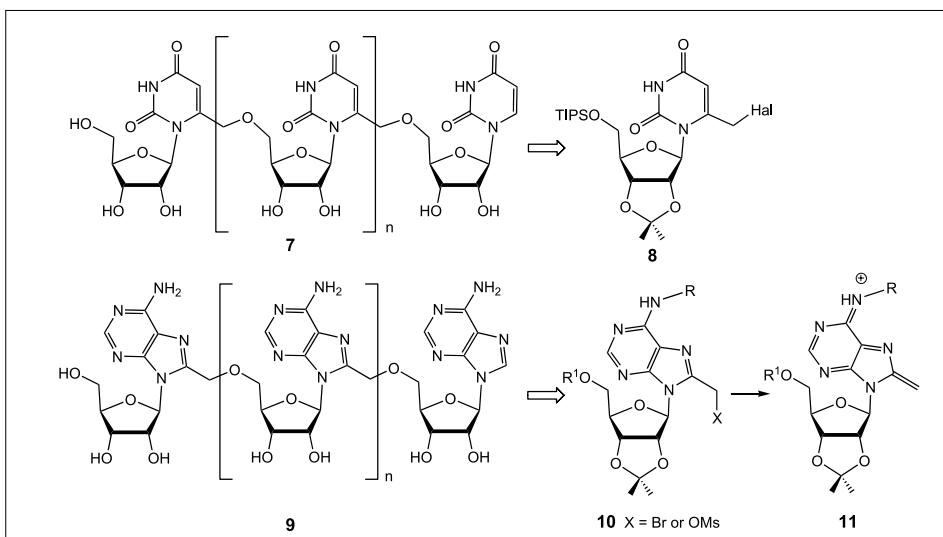


Fig. 4. Oxymethylene-linked foldamers **7** and **9**

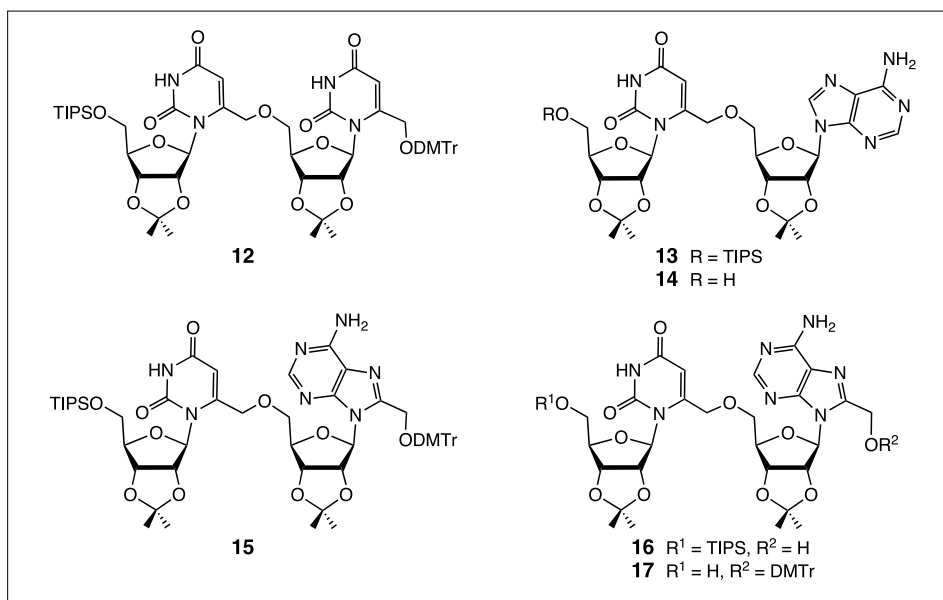
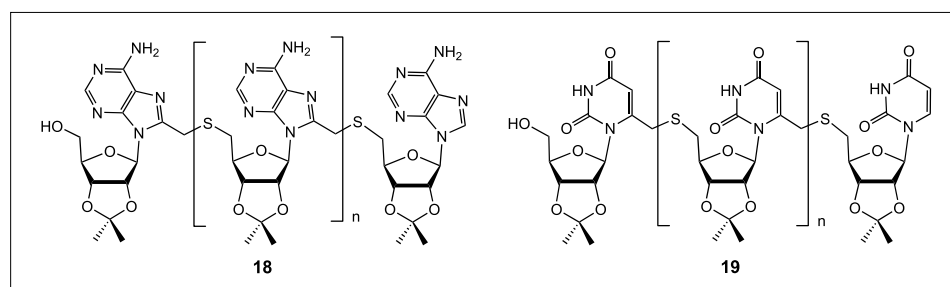
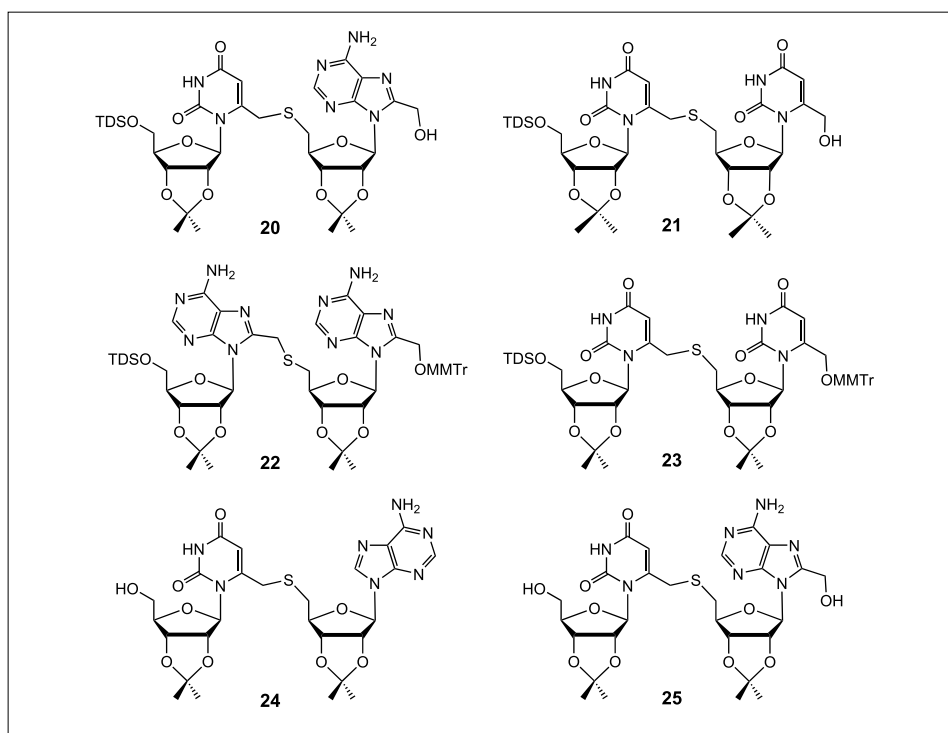
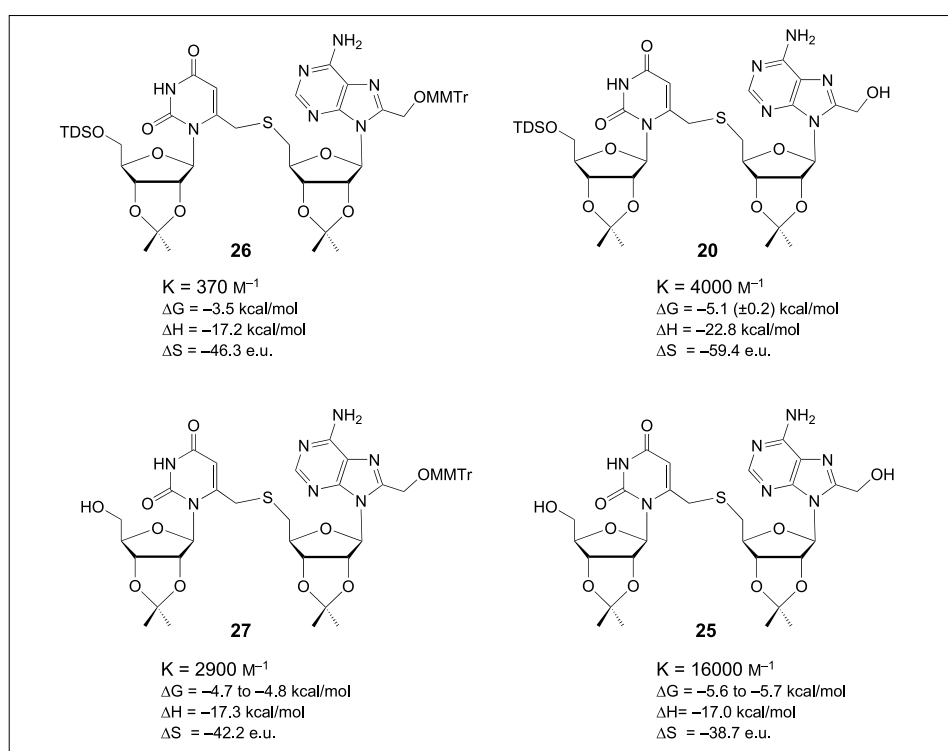


Fig. 5. U*-[o]-U*, U*-[o]-A, and U*-[o]-A* dimers **12**–**17**

Table. Association constants and thermodynamic parameters for the U*-[o]-U dimers **13** and **14**, the U*-[o]-A* dimers **15**–**17**, and association constant and ΔG for the U*-[o]-U* dimer **12**

Dimer	K_a [M ⁻¹]	$-\Delta H$ [kcal/mol]	$-\Delta S$ [e.u.]	$-\Delta G$ [kcal/mol] ^{a)}	
13	1890	22	62	4.0	4.4
14	2500	13	30	4.6	4.2
15	970	16	40	4.0	3.9
16	280	22	64	3.3	3.0
17	3220	24	65	4.7	5.3
12	265	–	–	3.3	

a) The first value is calculated from K_a , the second one from ΔH and ΔS .

Fig. 6. Thiomethylene-linked oligonucleotide analogues **18** and **19**Fig. 7. Selected S-linked dimers **20–25** used for the determination of the association (strength and stoichiometry)Fig. 8. Dependence of the association of **20** and **25–27** upon the protecting groups

dependence are evidenced. To obtain this information, we needed at least all dimers derived from A and U. The rationalisation of the difficulty of obtaining ether-linked dimers derived from **10** suggested the preparation of thioethers. Modelling indicated that the thioether linkage does not significantly change the conformation of the oxymethylene-linked oligomers.

All dimers resulting from S-alkylation of protected 5'-thio-U(*) and 5'-thio-A(*) with the electrophiles **8** (Hal = Br or OMs) and **10** (R = Br; Fig. 4) and their partially or fully deprotected derivatives **18** and **19** were prepared in 62–78% yield (Fig. 6) [46].

The self-pairing O-isopropylidene-protected U*-[s]-A* silyl ether **20** (TDS = thexyldimethylsilyl) associates strongly in CDCl₃ ($K_{\text{ass}} = 4000 \text{ M}^{-1}$), the U*-[s]-U* analogue **21** associates with $K_{\text{ass}} = 1000 \text{ M}^{-1}$, while the corresponding A*-[s]-A* **22** does not associate (Fig. 7). A Job's plot showed a 1:1 stoichiometry for the pairing of **22** and **23**. The concentration dependence of the chemical shift for H-C(2) and H-C(8) of **24** evidenced a Hoogsteen, or reverse-Hoogsteen hydrogen bonding; the crystal-structure analysis of **25** showed a reverse-Hoogsteen association.

The association constants depend strongly on the C(6/I or 8/I) and C(5'/II) substituents, as illustrated by the association constants and thermodynamic parameters for the dimers **20** and **25–27** (Fig. 8). The difference of the ΔH values means (in agreement with the ΔS values) that **20** forms six H-bonds (Hoogsteen type according to modelling) and the other three dimers only four of them. The intramolecular H-bond between C(5')OH and C(2)=O entails a conformation that is incompatible with an intermolecular hydrogen bond of the C(8)-hydroxymethyl group of **25**. The strong association of **25** resulting from the favourable entropy of association suggested to check for stacking of the two bases. As shown in Fig. 9, one indeed finds the dependence of the absorption coefficient on temperature for **25** and **28** that evidences stacking of the nucleobases. This is not a trivial observation for a nucleotide dimer in chloroform solution, and strongly supports stacking and pairing of these analogues in chloroform.

The A*-[s]-U dimer **29** and the A*-[s]-U* dimer **30** gelate chloroform, dichloromethane, and ethyl acetate at a concentration between 0.4% and 1% wt/vol (Fig. 10). These gels are stable below 30 °C, as determined by CD spectroscopy. SEM pictures revealed the formation of porous, lamellar structures. The propensity of these foldamers to form organogels (and perhaps hydrogels) deserves further attention, and is under scrutiny [47].

The strong dependence of the association strength upon the protecting groups of the hydroxymethyl substituents, and the presence of several conformations means that the structure of these dimers is not sufficiently well defined, and not well suited for a detailed study of the way in which they associate. Indeed, temperature-dependent $^1\text{H-NMR}$ studies showed that the $\text{U}^*-[s]-\text{U}^*$ dimer **21** adopts at least two conformations. Longer oligomers appeared necessary, and we have so far synthesised the two self-associating tetramers $\text{U}^*-[s]-\text{A}^*-[s]-\text{U}^*-[s]-\text{A}^*$ (**31**) and $\text{A}^*-[s]-\text{U}^*-[s]-\text{A}^*-[s]-\text{U}^*$ (**32**) (Fig. 11) according to the Scheme.

These tetramers strongly self-associate in $\text{CDCl}_3/5\%$ DMSO (K_{ass} reaches $6 \cdot 10^5 \text{ M}^{-1}$). Vapour pressure osmometry evidenced a 1:1 association, and $^1\text{H-NMR}$ spectroscopy showed that **31** is conformationally homogeneous.

The structure of the duplex of **31** was elucidated using $^1\text{H-NMR}$ spectroscopy (NOESY) and molecular modelling (Fig. 12) [48]. The duplex folds into a stable, unique structure (incipient right-handed A-type helix). The bases adopt a *syn* conformation, are stacked, and associate in a Watson-Crick mode.

The fully deprotected tetramers derived from **31** and **32** are well soluble in DMSO, but 'practically' insoluble in water (no UV absorption of the supernatant). This restricts the interest in these foldamers to applications in material sciences. We have started the synthesis of a cytidine- and guanosine-incorporating octamer, to study a complete helix, and obtain more precise information about its structural parameters; we have also begun with the synthesis of close analogues that promise to be water soluble.

There were several reasons for re-examining the acetyleno-analogues: to show that more than one representative of the novel foldamers may pair and that there must be a family of such analogues, to access analogues with an all-carbon linker so as to determine the conformation of the linker in a duplex, and to test for the relevance of the *syn/anti* conformation of these acetyleno-analogues. Determination of the pairing of dimers and oligomers with a hydrogen bond to N(3) will allow the determination of whether association with the bases in a *syn* conformation is at all possible – there was no proof for the contention that an *anti* conformation is required for association. Reductive removal of the propargylic hydroxy group should allow these analogues to adopt an *anti* conformation, and lead to pairing.

For this reason, we prepared additional self-complementary, acetyleno-linked dimers and tetramers [44]. There is indeed a strong influence of the hydrogen bond to N(3) (Fig. 13). The self-complementary dimer **33** associates *via* only two (rather

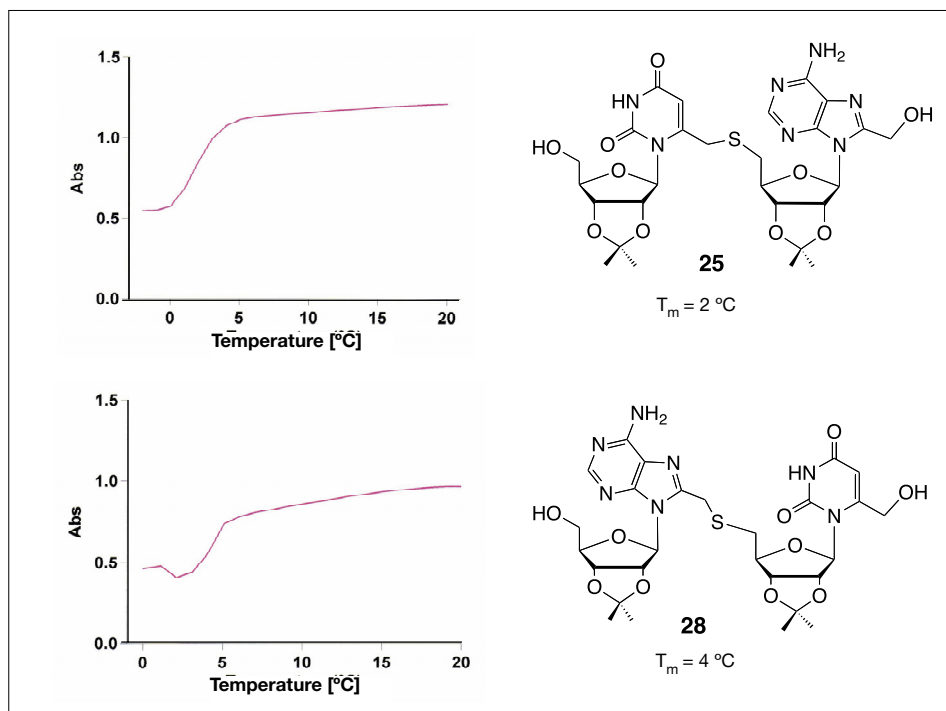


Fig. 9. Melting curve of the $\text{U}^*-[s]-\text{A}^*$ dimer **25** and the $\text{A}^*-[s]-\text{U}^*$ dimer **28** in chloroform ($c = 21 \mu\text{M}$)

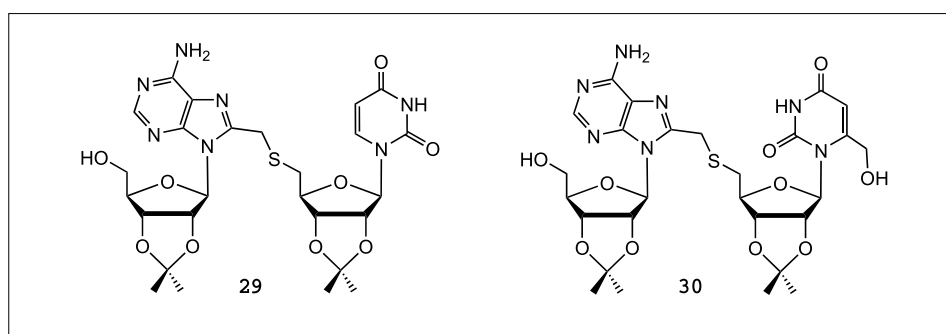


Fig. 10. The gelating $\text{A}^*-[s]-\text{U}$ dimer **29** and $\text{A}^*-[s]-\text{U}^*$ dimer **30**

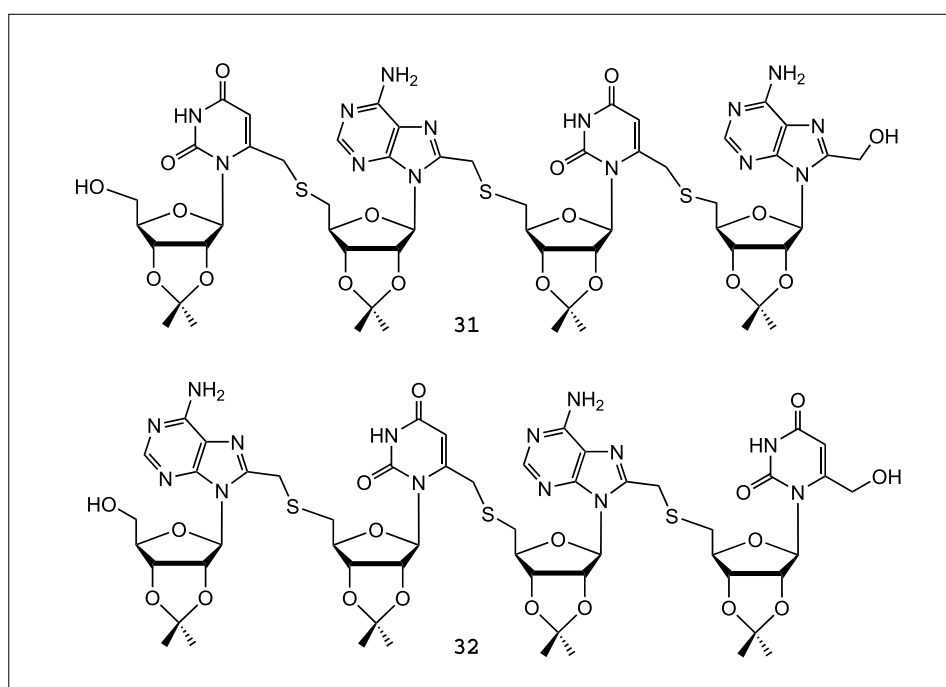
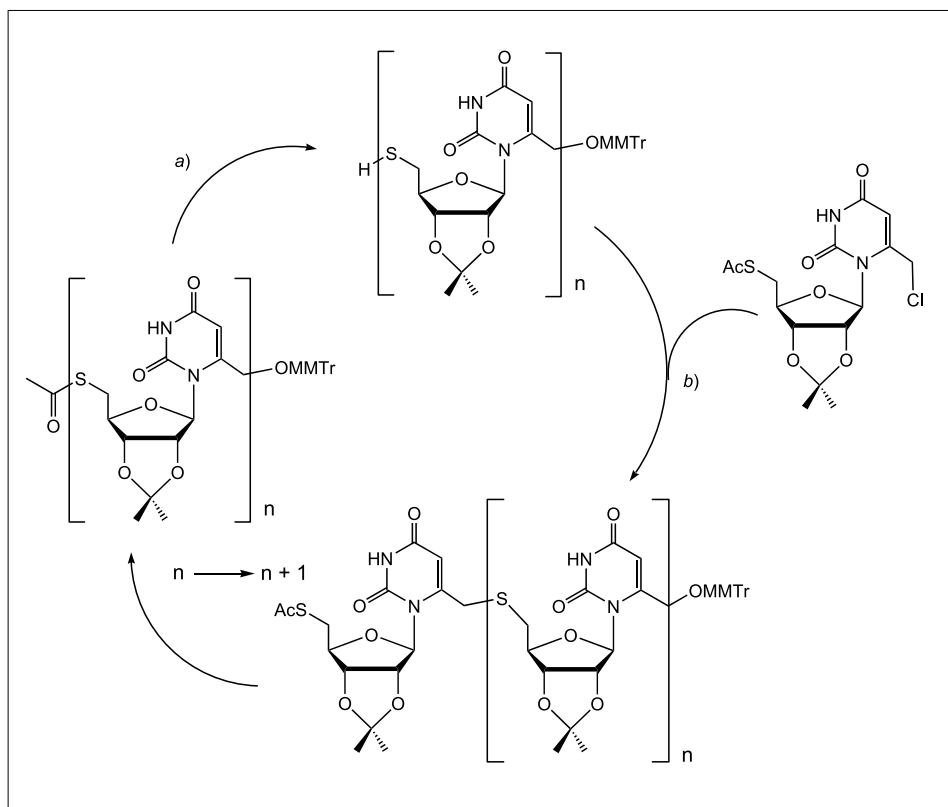
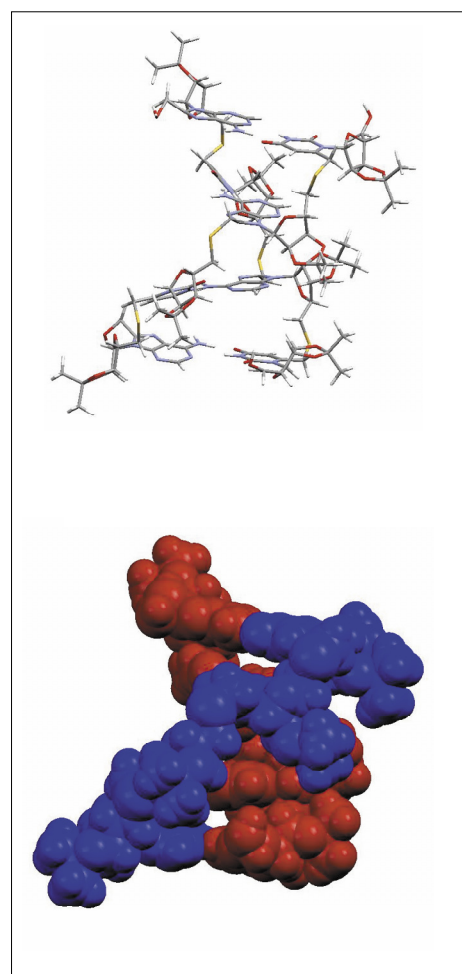
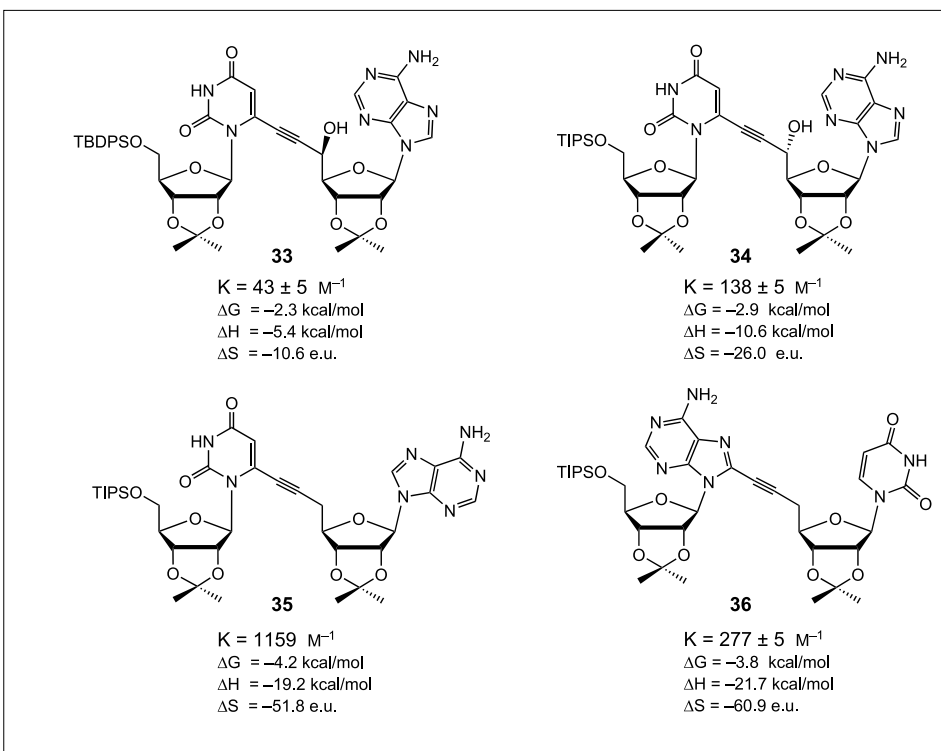


Fig. 11. The self-associating $\text{U}^*-[s]-\text{A}^*-[s]-\text{U}^*-[s]-\text{A}^*$ and $\text{A}^*-[s]-\text{U}^*-[s]-\text{A}^*-[s]-\text{U}^*$ tetramers **31** and **32**

Scheme. a) Deprotonation with K_2CO_3 in MeOH; b) coupling with K_2CO_3 in DMFFig. 12. Wire-frame and space-filling representation of the duplex **31**

weak) hydrogen bonds. The configuration plays a role; enthalpy and entropy of association of **34** are twice as large as for **33**. A slight sequence dependence is evidenced by comparing **35** and **36**; much more important is the effect of deoxygenation, as discussed below.

Fig. 13. Pairing of the partially protected acetyleno analogues **33–36** in chloroform

The A*-[c]-U dimer **37** forms a gel in $CDCl_3$ solution (Fig. 14). The solid-state structure of the closely related **38** is characterised by Watson-Crick and reverse-Hoogsteen hydrogen bonds.

The effect of the hydrogen bond to N(3) depends upon the position of the A* residue, and is not much influenced by the hydrogen bond of the propargylic hydroxy group to U*, as evidenced by comparing the association of **39** vs. **40** and of **41** vs. **42** (Fig. 15).

Although these few comparisons show some regularity, the correlation between structure and association of these and additional self-complementary dimers is not straightforward. The low value of the enthalpy of association for **33** ($\Delta H = -5.4$ kcal/mol) suggests association *via* two weak hydrogen bonds, and no contribution from stacking, while **39** and **41** (ΔH of -12 to -13 kcal/mol) appear to associate *via* four slightly stronger hydrogen bonds, again without any contribution from stacking. The deoxy dimers **35** and **36** (ΔH ca. -20 kcal/mol) must associate *via* four hydrogen bonds (more are not possible), and the high enthalpy value suggests that base stacking contributes to association. A model (**33A**; for modelling TBDPSO was replaced by a Me_3SiO group) of the U*-[c]-A dimer **33** (Fig. 13) is shown in Fig. 16. Only two intermolecular hydrogen bonds can be formed in the presence of the intramolecular hydrogen bond from the propargylic OH to N(3) of the adenine moiety. Four intermolecular hydrogen bonds for **33B** can only be formed at the expense of this intramo-

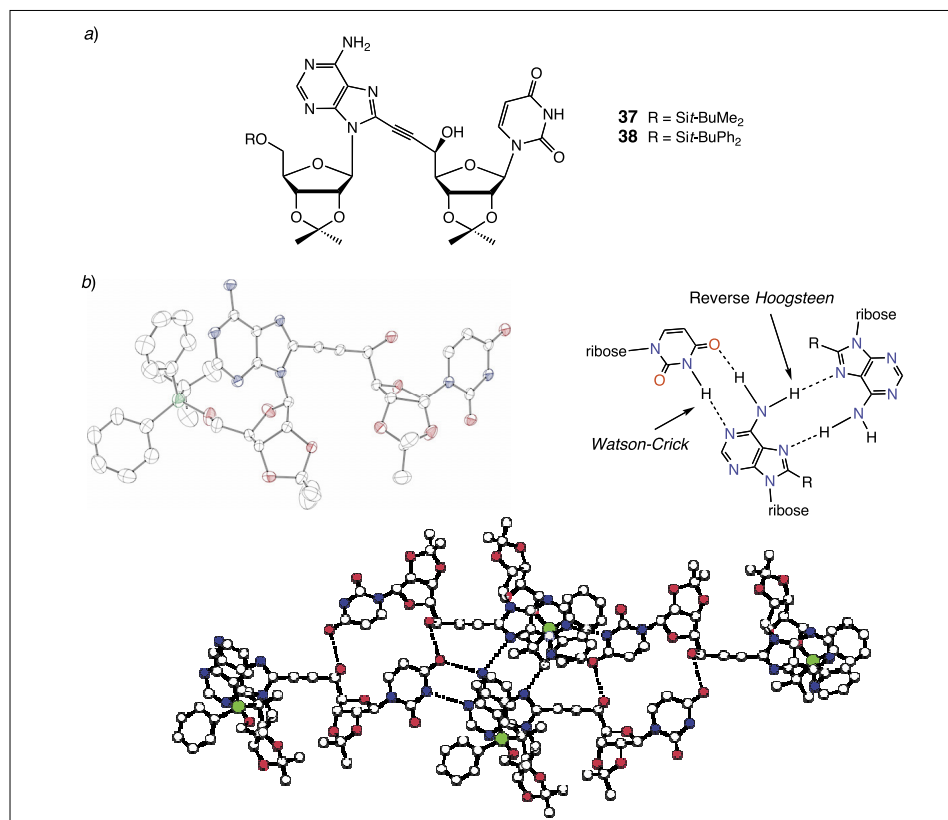


Fig. 14. a) A^{*}-[c]-U-dimers **37** and **38**, and b) crystal structure of **38**

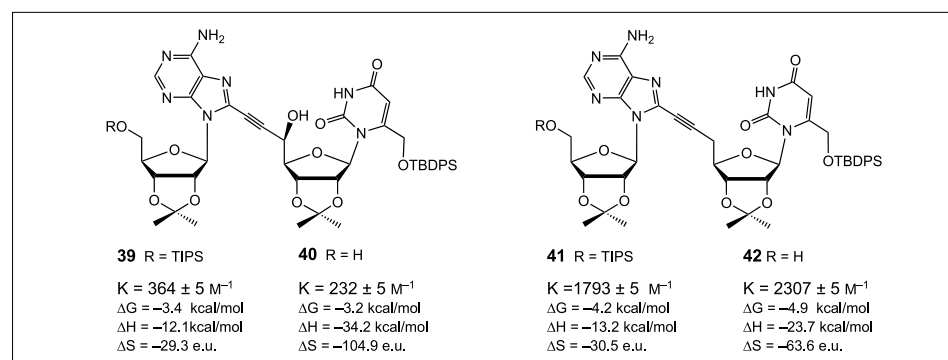


Fig. 15. Influence of the hydrogen bond to N(3) in A^{*}-[c]-U^{*} dimers **39-42**

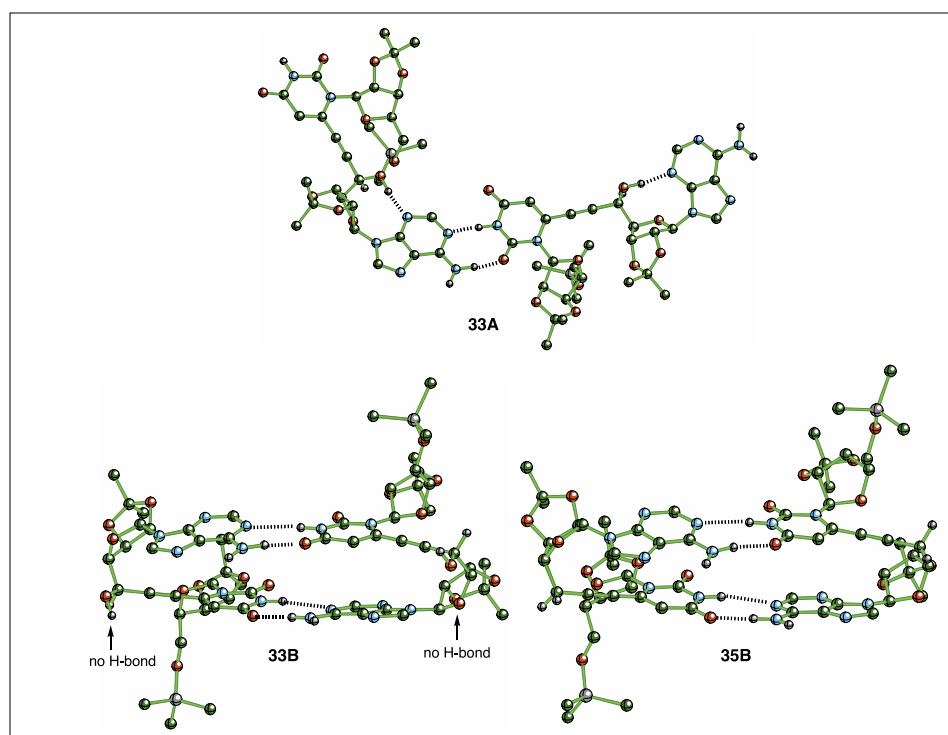


Fig. 16. Models of **33** and **35**: association via two and four hydrogen bonds, and the influence of the intramolecular hydrogen bond to N(3)

lecular hydrogen bond; there is no similar penalty for **35**, as shown by the model of its duplex **35B** featuring four hydrogen bonds and base stacking.

A clear dependence of the association upon the sequence is also evident by comparing the association in $\text{CHCl}_3/\text{DMSO}$ 1:4 of the four tetramers **43–46** (Fig. 17); only two of them associate.

Reduction of the triple bond gave the desired propylene-linked dimers **47** and **48** (Fig. 18); they associate only weakly so that the desired conformational analysis was not feasible. Surprisingly, the (*Z*)-alkene analogues **49** ($\Delta G = -3.5$ kcal/mol) and **50** ($\Delta G = -5.1$ kcal/mol) pair significantly more strongly; the (*E*) isomer of **50** pairs about as strongly as the saturated **48**.

Outlook

These findings evidence that pairing by the thioethers is not a singular case, and that there must be (many) more representatives of this novel type of base-integrating oligonucleotide analogues. It should be possible to tune the structure of duplexes and the strength of the association, and to shape secondary structural elements. It is obvious that we are only at the beginning. The immediate goals pursued by the group are the incorporation of cytidine and guanosine monomers, the synthesis of octamers, and of water-soluble analogues.

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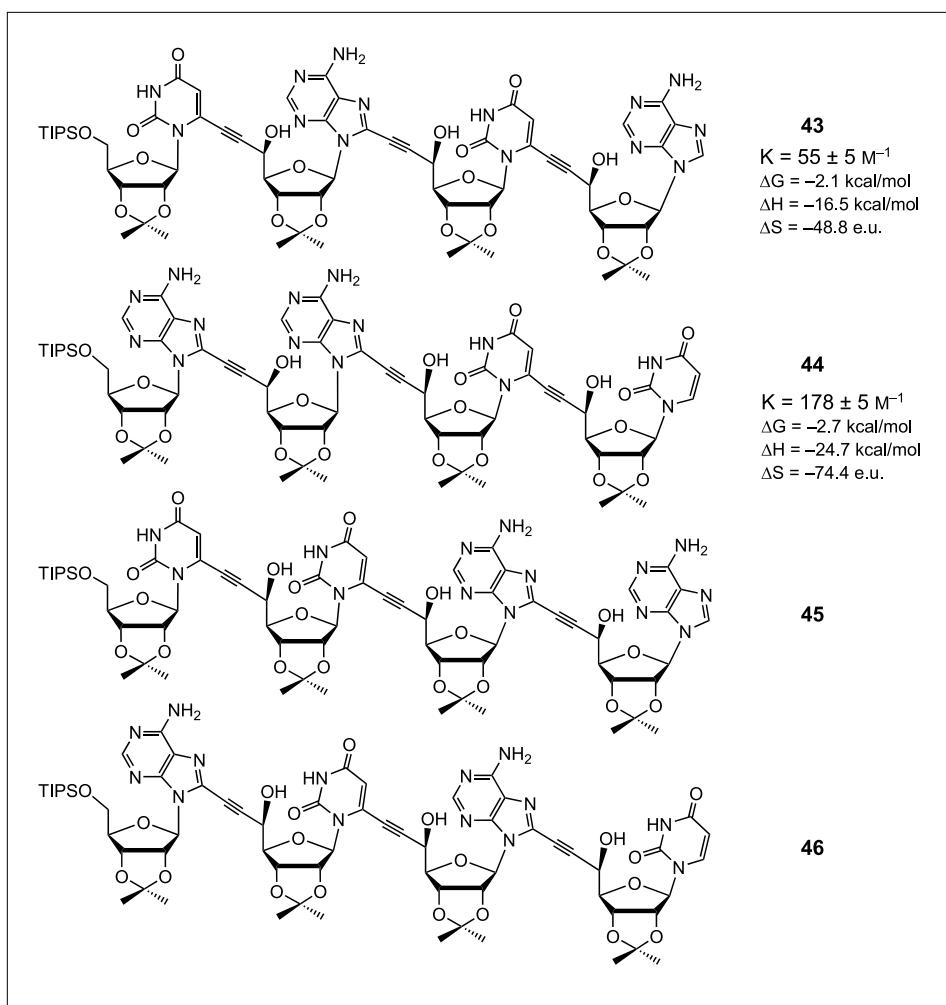


Fig. 17. Association of self-complementary tetramers **43–46**

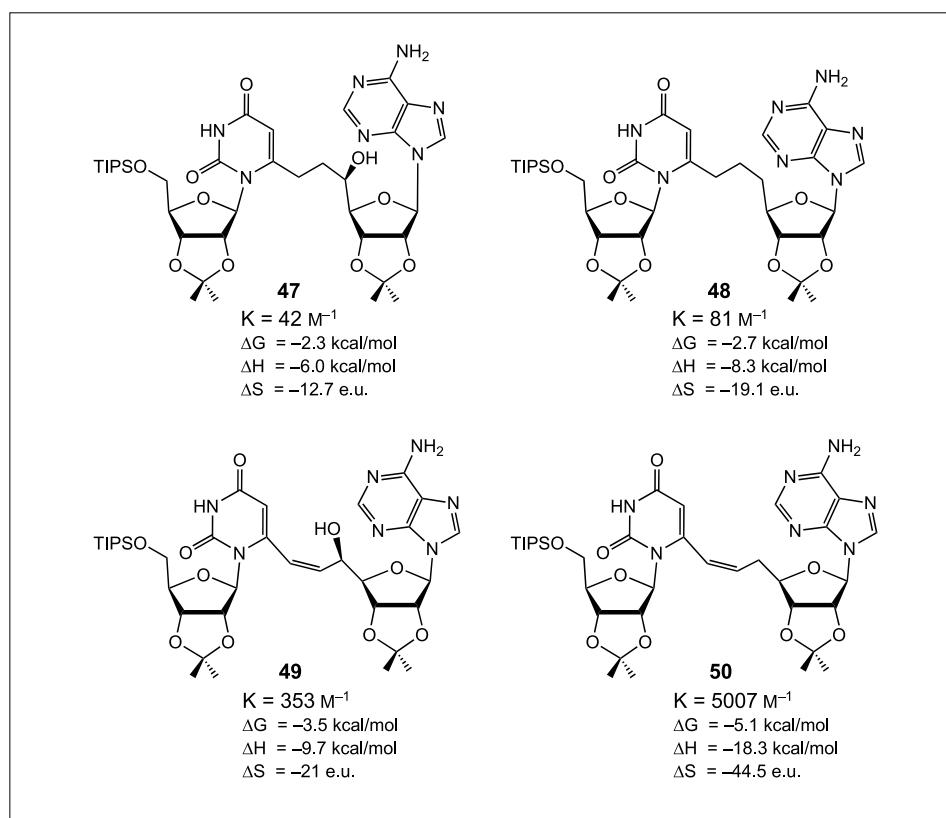


Fig. 18. Propylene- and (*Z*)-propenylene-linked dimers **47–50**

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