

has been removed (this experiment generated the data presented in Figure 5). The micrograph shows a plate surface on which there are several cells and many black spots of the fullerene/DNA complex. These black spots, of irregular outline, are more densely distributed on the cells than on the bare plate surface. Figures 7B and C are the DIC and fluorescence micrographs of the cells taken in the same series of experiments after 2 days incubation with **1**. As seen more clearly in Figure 7D, which is the superimposition of Figure 7B and 7C, the morphology and the distribution of the black objects in the fluorescent cells are different from those of the objects outside the cells. These black globules of 2–10 μm in diameter are located within the cytoplasm of the fluorescent cells, indicating that the fullerene/DNA complexes have been taken into the cells during incubation.

Departing from the conventional lipid-mimicking strategy for designing transfection reagents, we have synthesized an entirely new class of transfection agent (**1**) through tailor-made functionalization of [60]fullerene. The structure/activity relationship of the DNA binding properties indicate that the structural synergy in **1** plays an important role in binding. The efficiency of gene transfer by this first-generation fullerene-based transfection reagent is already comparable to that of commercial reagents. The morphology of large aggregates of the fullerene/DNA complex in the GFP-expressing cells indicates that the complex is taken up by cells through phagocytosis. The fullerene-based transfection reagent is unique among known transfection reagents in its ability to effect sustained protein expression for a prolonged period, suggesting that plasmid DNA in fullerene complex is stable inside phagosomes.

Received: May 26, 2000

Revised: August 24, 2000 [Z15181]

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Ternary Complexes Between DNA, Polyamine, and Cucurbituril: A Modular Approach to DNA-Binding Molecules**

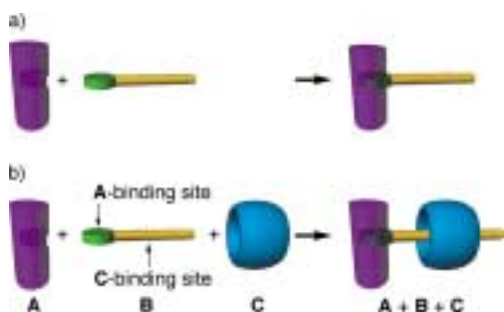
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The design of a rational method for the delivery of a molecule to a target site of a biomolecule is an issue of general interest for chemists. Although a conventional targeting scheme relies on the covalent installation of a binding site on the molecule to be delivered (Scheme 1a), another intriguing approach is a modular strategy relying on a non-covalent many-body assembly of molecules as illustrated in Scheme 1b.^[1] We report herein a chemical prototype of such supramolecular chemistry in the binding of a small molecule (**C**, that can not bind to DNA) to DNA (**A**) with the aid of a

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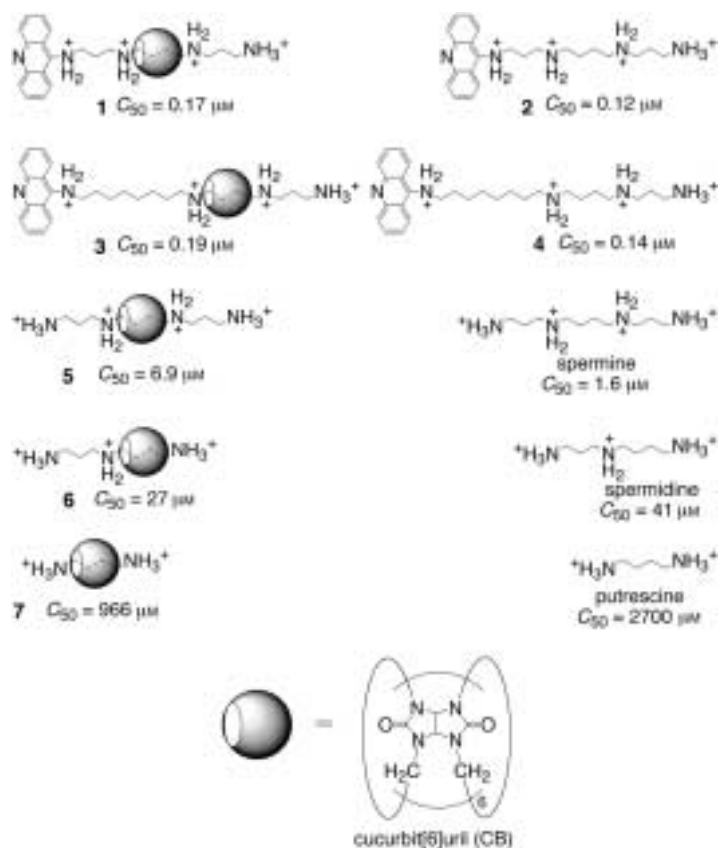
[**] We thank Prof. B. C. Baguley for the detailed information on the ethidium displacement assay. This work was supported by a Grant-in-Aid for Scientific Research from Monbusho and the Creative Research Initiative Program of the Korean Ministry of Science and Technology.



Scheme 1. a) Conventional targeting scheme. b) Modular strategy: Molecule **C**, which cannot bind to the target molecule **A**, can bind with the aid of the linker molecule **B**.

linker molecule (**B**) that has two different types of binding sites. The $A + B + C$ strategy relies on non-covalent assembly between DNA and acridine, and between spermine and cucurbit[6]uril (CB).

CB is a large-cage compound composed of six glycoluril units interconnected with twelve methylene bridges. First prepared nearly 100 years ago,^[2] this cyclic molecule has been attracting much attention because of its unique ability to tightly bind to diamines through the formation of a pseudo-rotaxane structure such as **5**.^[3] To test our targeting scheme we



designed linker molecules **2** and **4**.^[4] These bifunctional linkers are composed of a spermine moiety attached covalently to an acridine unit. Since acridine binds specifically to double stranded DNA between the nucleobases by intercalation, and spermine binds specifically to CB in a thread-in-

hole fashion, we expected that the acridine/spermine hybrids **2** and **4** would chemospecifically link DNA and CB at the respective binding sites. The known CB/polyamine binary complexes **5**–**7**^[3] were employed as reference compounds and were prepared by simply mixing CB with the respective polyamines in an aqueous solution. The acridine/spermine hybrids **1** and **3** were prepared from the linkers **2** and **4** in the same manner.

The binding ability of a DNA intercalator can be assessed through competition with ethidium bromide, and is shown in a value known as C_{50} .^[5] The C_{50} values in the binding with calf thymus DNA for the parent aminoacridine compounds **2** and **4** were determined to be 0.12 and 0.14 μM , respectively. The binary complexes **1** and **3** were found to be slightly less tightly binding with $C_{50} = 0.17$ and 0.19 μM , respectively.^[6, 7]

For comparison, we also examined the binding properties of CB/polyamine binary complexes **5**, **6**, and **7** that lack the acridine moiety.^[8] The C_{50} values were found to be 6.9, 27, and 966 μM , respectively. CB itself was unable to induce 50 % displacement even on the addition of a large excess of the reagent (11 % displacement at 255 μM).^[9] These values for the binary complexes as well as the C_{50} values for the parent polyamines (1.6, 41, and 2700 μM) indicate the following: 1) CB binds DNA extremely weakly if at all. 2) The low binding ability of the diamine complex **7** suggests that the CB/diamine part in **1**, **3**, **5**, and **6** does not contribute very much toward DNA binding. 3) The DNA binding ability increases in the order of $7 > 6 > 5$ suggesting that the presence of the free ammonium group(s) increases DNA binding. 4) In general, CB may attenuate the binding properties of spermine (and its analogues) as suggested from the data for **1**, **3**, and **5**.

The small C_{50} values obtained for **1** and **3** at μM concentration, however, do not necessarily guarantee the high binding power of these complexes, the polyamine moiety could have slipped out of the CB and become bound by itself to DNA and thus give the small C_{50} values. If a free polyamine were indeed a major contributor to the observed ethidium displacement with **1**, **3**, and **5**–**7**, addition of excess free CB to the test mixture would reduce the concentration of the free polyamine and hence increase the observed C_{50} value. However, essentially the same C_{50} data ($\pm 20\%$, for **1**, **3**, and **5**–**7**) were obtained in the presence of a large excess of free CB (20 μM). Thus, the contribution of the free polyamine must be negligible under these conditions.^[10]

Gel electrophoresis experiments (Figures 1 a and b) afforded conclusive evidence that the binary complex **1** binds tightly to the DNA duplex to form the expected **1**/DNA ternary complex (not the **2**/DNA complex). Thus, **1** was incubated with DNA duplex (studied simultaneously for three representative topologies, supercoiled (*S*), circular (*C*), and linear (*L*)) and the mobility of the resulting intercalated DNA was examined. As shown in Figure 1 a (lanes 2 and 3), the DNAs migrated as single bands and the degree of retardation differed between **1** and **2**,^[11, 12] clearly indicating that the **1**/DNA complex is different from the **2**/DNA complex and hence that **1** maintains its integrity upon binding to DNA.

Further evidence of ternary complex formation was obtained in the experiments where the effect of CB–polyamine complexation was gauged by the rate of nuclease-induced

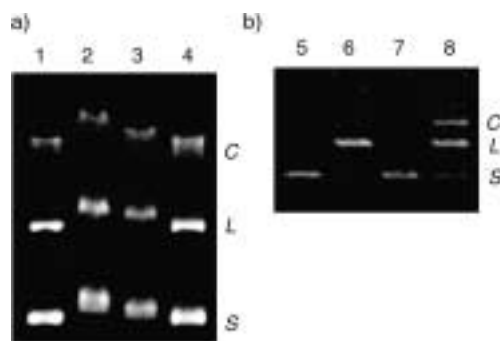


Figure 1. a) Change of gel mobility caused by complexation of DNA duplexes to **1** and **2**. Lanes 1 and 4: DNA, lane 2: DNA + **2**, lane 3: DNA + **1**. b) Retardation of enzymatic DNA hydrolysis by **1** and **2**. Lane 5: intact plasmid DNA pBR322 (S); lane 6: complete cleavage of S to L with *Ban* II restriction enzyme; lane 7: complete inhibition of the DNA cleavage by prior treatment of pBR322 with **2**; lane 8: partial inhibition of the DNA cleavage by prior treatment with **1** leading to production of only 72% of L, 26% of C (because of single strand cleavage) and 2% of S left unchanged. S = supercoiled, C = circular, and L = linear DNA.

hydrolysis of DNA strands. For this purpose, we employed the restriction enzyme *Ban* II that cuts plasmid DNA pBR322 at specific sites,^[13] the results are shown in Figure 1 b). When we allowed excess acridine **2** to intercalate to the supercoiled DNA (reagent/base pair (bp) ratio, $R=2.6$; lane 5), we observed complete inhibition of the nuclease action (lane 7) under the conditions where, without **2**, the DNA was completely hydrolyzed to linear DNA (lane 6). When we performed the same experiment but with **2** replaced by the same amount of **1** ($R=2.6$), we found considerable retardation of the strand cleavage.^[14] Thus, the C_{50} data, the gel mobility shift assay, and the nuclease inhibition experiments have shown that the acridine/spermine linker module can effectively deliver CB to the target DNA through ternary supramolecule as illustrated in Scheme 1 b). Further studies on the sequence preference of ternary complex formation and the effect of CB complexation on the polyamine activities are ongoing.

Experimental Section

Ethidium bromide displacement assay:^[5] The displacement assay was carried out in a buffer containing 2-[4-(2-hydroxyethyl)-1-piperazinyl]-ethanesulfonic acid (HEPES; 2 mM), ethylenediaminetetraacetate (EDTA; 10 μ M), and NaCl (9.4 mM), pH 7.0. Ethidium bromide was dissolved (1.26 μ M) in the buffer and a solution of calf thymus DNA (Sigma) was added to provide a base pair concentration of 0.5 μ M. A reagent solution (0.1–1.0 mM) was added in microliter portions. Fluorescence emission was measured at 595 nm (slit width 0.75 nm) with excitation at 546 nm on a Hitachi 650-40 spectrometer at 25 °C. The final reagent concentration that induced 50% reduction of the original fluorescence intensity (based on more than three runs) was taken as the C_{50} value of the reagent. Experimental error under these conditions is $\pm 26\%$.

Change of gel mobility caused by complexation of DNA duplexes: Gel mobility shift assay was carried out on agarose gel for pBR322 partially digested with *Sph* I (a mixture of S, C, and L DNA, [bp] = 38 μ M). A mixture of S, C, and L was incubated with **1** or **2** at $R=0.5$ in a HEPES–Mg buffer (40 mM HEPES–KOH and 10 mM $MgCl_2$; pH 7.0) for 1 h. Electrophoresis was performed by using 1% agarose gel and the DNA bands are subsequently visualized by ethidium bromide (Figure 1 a).

Retardation of enzymatic DNA hydrolysis: Plasmid pBR322 DNA ([bp] = 38 μ M) was incubated with **1** or **2** (at $R=2.6$) and *Ban* II restriction enzyme

(0.02 U μ L⁻¹; TaKaRa) in an H buffer (50 mM Tris-HCl, 10 mM $MgCl_2$, 1 mM dithiothreitol, 100 mM NaCl; pH 7.5) at 37 °C for 1 h. After purification of DNA through phenol treatment and ethanol precipitation, the reaction mixture was analyzed by agarose gel electrophoresis (Figure 1 b).

Received: May 26, 2000

Revised: September 4, 2000 [Z15182]

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- [6] In DNA/9-aminoacridine intercalation complexes, the amine residue of the 9-aminoacridine is located in the minor groove, and the binding constant value has been reported as $K=4 \times 10^5$ M⁻¹; see ref. [5], and references therein.
- [7] The quenching values (ref. [5]) of intercalative compounds (**1–4**) were found to be small ($Q_{0.1}$ values (percentage quenching of ethidium fluorescence at $R=0$): 1.3% for **1**, 1.6% for **2**, 1.0% for **3**, and 1.0% for **4**), which combined with the small C_{50} values, suggests that the binding constants of these compounds are larger than that of ethidium bromide ($K=3 \times 10^6$ M⁻¹).
- [8] Unlike the acridine/ethidium competition, the competition between spermine (groove binder) and ethidium (intercalator) is not a true competitive experiment because their binding sites are different. Nonetheless, C_{50} values for groove binders (such as spermine, $K=1 \times 10^6$ M⁻¹) have widely been taken as a qualitative measure of DNA binding ability, but their magnitude cannot be directly compared with those for intercalator (such as **1**): K. D. Stewart, T. A. Gray, *J. Phys. Org. Chem.* **1992**, 5, 461–466.
- [9] The experiments with CB were carried out with an aqueous solution of CB (447 μ M) in an aqueous 10 mM Na_2SO_4 .
- [10] The reported dissociation constant for the spermine/CB complex **5** (7.6×10^{-8} M) was measured in a H_2O/HCO_2H (hence acidic) solution under competition between spermine and a weaker amine (ref. [3]). The present results suggest that the dissociation constant under the buffer conditions is much smaller. This point may need further studies. We thank a referee for pointing out the issues concerning the dissociation constants.
- [11] The mobility of the **1**/DNA and the **2**/DNA complexes differ from each other over a wide range of the reagent/base pair ratio ($R=0.1–1.5$). The same degree of difference in the gel mobility shift was also detected for the pair **3** and **4** (data not shown).
- [12] To ascertain that the binding of **1–4** to DNA observed under electrophoretic conditions is caused by acridine intercalation and not to the spermine/DNA interaction, spermine and its CB complex **5** were examined under the same gel electrophoresis conditions. The spermine/DNA or **5**/DNA complexes showed the same mobility as the intact DNA (data not shown), indicating that these positively charged

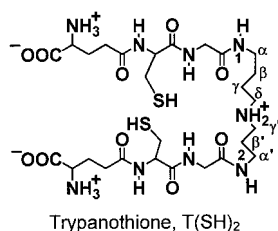
polyamine binders were removed from the negatively charged DNA duplex under the applied electric field used for electrophoresis.

- [13] Restriction enzyme *Ban* II cuts pBR322 at a GA(G)GCT(C)C sequence (locations 471 and 485).
- [14] A referee suggested that the observed retardation of hydrolysis could have been caused by a small amount of free amine **2** liberated from **1** (used in a 100 μ M concentration), such an equilibrium would liberate **2** in a 2.7 μ M or less concentration (ref. [10]). A series of experiments with various concentrations of **2** indicated that no inhibition of the nuclease activity occurs with such a small concentration of **2**, indicating in turn that the free amine is not responsible for the observed retardation with **1**.

Complexation of Antimony(III) by Trypanothione**

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In contrast to almost all other organisms, trypanosomatids can conjugate the sulfur-containing tripeptide glutathione and the polyamine spermidine to form trypanothione (N^1, N^8 -bis(glutathionyl)spermidine).^[1–3] Together with trypanothione reductase (TR), the dithiol form of trypanothione ($T(SH)_2$), which is an analogue of glutathione found in the mammalian host, provides a uniquely intracellular reducing environment in parasites. Besides its protective and regulatory roles, $T(SH)_2$ and its related enzymes are essential for growth and survival of these parasites.^[4–6] The trypanosomatid protozoan



parasite *Leishmania* is the causative of kala azar and severe forms of leishmaniasis that afflict more than ten million people worldwide. Several antimony compounds are currently the agents of choice for the treatment of leishmaniasis and have been used for decades. Analogous to arsenical drugs against African trypanosomes,^[7] one of the major targets for

antimony drugs is probably $T(SH)_2$. Overproduction of $T(SH)_2$ in cells is also related to resistance to antimonials in *Leishmania*.^[8] We show here that Sb^{III} forms a novel complex with $T(SH)_2$ by binding to two sulfur atoms and to the oxygen atom of a water molecule. This appears to be the first chemical characterization of a metal complex of $T(SH)_2$, which may play a role in the mechanism of action of the antimony antileishmanial drugs.

Trypanothione $T(SH)_2$ can be readily obtained by the reduction of trypanothione disulfide (TS_2) by tris(2-carboxyethyl)phosphane.^[8] The electrospray (ESI) mass spectrum of $T(SH)_2$ at around pH 7 exhibits a cluster of ions at m/z 724.9 corresponding to $C_{27}H_{50}N_9O_{10}S_2$ (calcd 724.3). The reaction product of an antimony compound and $T(SH)_2$ at pH 7.4 displayed a prominent cluster of ions related to the isotopic distribution of Sb and C, with an $[M^+]$ peak at m/z 842.6 corresponding to $SbS_2C_{27}H_{50}N_9O_{10}H_{48}$ (calcd for $SbT(S)_2$ complex: 843.2; see Figure S1 in the Supporting Information). This represents a 1:1 antimony(III) trypanothione complex, in contrast to the antimony(III) glutathione complex $Sb(GS)_3$.^[9]

The 1H NMR signals of $T(SH)_2$ in aqueous solution were assigned with the aid of various 2D TOCSY, NOESY, and ROESY spectra. Signals from pairs of like residues overlap, with only minor differences attributable to the actual asymmetry of the spermidine moiety. This indicates an approximate symmetry of the two halves of $T(SH)_2$ that is similar to that of its oxidized form.^[10] Only four relatively sharp NH peaks and one very broad peak were observed at pH 4.6, and the very broad one disappeared above pH 5. The NH peaks of both Cys and Gly are significantly broadened at pH 7.4 (Figure 1). Addition of 0.5 of a molar equivalent of antimony(III) tartrate at pH 4.6 resulted in a peak at $\delta = 3.36$, while the signal of the β protons of the Cys residues of free

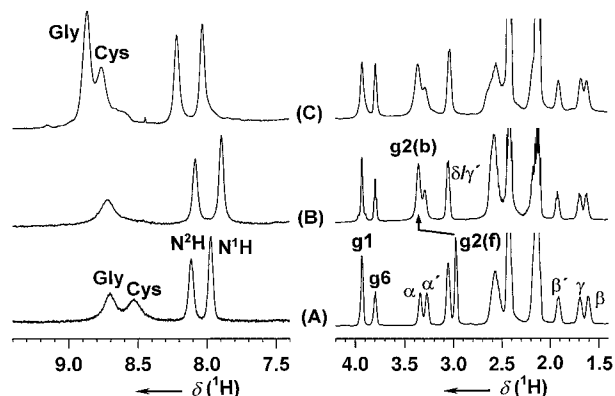


Figure 1. 500 MHz 1H NMR spectra. A) Trypanothione $T(SH)_2$. B) $T(SH)_2$ after addition of antimony(III) tartrate (molar ratio 1:1) at 298 K and pH 7.4; C) as B) but at 278 K. Note the large low-field shifts of the peaks for Cys β -CH₂ (g2) on complexation to Sb^{III} . Labels: g1, α -CH₂ of Gly; g6, α -CH₂ of Glu.

$T(SH)_2$ at $\delta = 2.97$ decreased in intensity. Similarly, the NH signal of the Cys residue of $T(SH)_2$ at $\delta = 8.54$ decreased in intensity, while a new peak appeared at slightly lower field ($\delta = 8.59$). A 2D TOCSY spectrum confirmed that the peaks at $\delta = 4.52$, 2.97, and 8.54 are coupled to each other, as are those at $\delta = 4.68$, 3.36, and 8.59. The former set can therefore

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[**] This work was supported by the University of Hong Kong. We are grateful to Professor Alan H. Fairlamb (University of Dundee) for stimulating discussions and the University of Hong Kong for Research Studentships (for S.Y. and L.Z.).

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