Comparative Studies on the DNA-binding Properties of Linear and Angular Dibenzoquinolizinium Ions

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Experimental Section

Materials and Methods. Dibenzo[*a,f*]quinolizinium (6)¹ and benzo[*b*]quinolizinium (9)² were prepared according to literature procedures. All solvents and reagents were purchased from commercial sources and used without further purification. Only deionised ultrapure water (18.2 MΩcm⁻¹) was used for buffer solutions. Melting points were determined in open capillary tubes and are uncorrected. ¹H and ¹³C spectra were obtained on 200 MHz, 400 MHz and 600 MHz NMR spectrometers. Chemical shifts are given as δ values (internal standard TMS). Mass spectra were obtained by ESI-MS techniques.

Nucleic Acids. Calf thymus DNA (type I, Highly polymerized sodium salt) and micrococcus luteus DNA (type XI, highly polymerized) as well as the polynucleotides poly[dA-dT]-poly[dA-dT], poly[dG-C]-poly[dG-dC] and poly[dA]-poly[dT] and the homopolymer poly[dT] were purchased from commercial sources and used without further purification. Triplex poly[dA]-poly[dT]₂ was prepared by mixing equimolar amounts of poly[dA]-poly[dT] and poly[dT], dissolved each in BPES buffer, heating to 90 °C and slow cooling to 4 °C. The concentrations of nucleic acid samples were determined by UV absorbance measurements using the following extinction coefficients (cm⁻¹ M⁻¹ for nucleic bases, base pairs (bp) or base triplets (bt), respectively): ct DNA and micrococcus luteus DNA, λ₂₆₀ = 12824 cm⁻¹ (bp), λ₂₆₀ = 6600 cm⁻¹ (bases); poly[dA-dT]-poly[dA-dT], λ₂₆₂ = 13200 cm⁻¹ (bp), λ₂₆₀ = 6600 cm⁻¹ (bases), poly[dG-dC]-poly[dG-dC] λ₂₅₄ = 16800 cm⁻¹ (bp), λ₂₅₄ = 8400 cm⁻¹ (bases); poly[dA]-poly[dT] λ₂₆₀ = 12000 cm⁻¹ (bp); poly[dT] λ₂₆₄ = 8520 cm⁻¹ (bases); poly[dA]-poly[dT]₂, λ₂₆₀ = 17200 cm⁻¹ (bt).

Figure S1. ¹H-NMR spectrum of **ahh-(5a)₂** in *d*₆-DMSO (additional peaks: 0 = TMS; 2.1 = CH₃CN; 2.5 = DMSO, 3.3 = H₂O).

D. Otto, do23a, 600.13 MHz 1H

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Current Data Parameters
NAME      dmX23633
EXPNO     1
PROCNO    1

F2 - Acquisition Parameters
Date_     20030602
Time      18.42
INSTRUM   spect
PROBHD    5 mm Triple
PULPROG   zg30
TD         65536
SOLVENT   DMSO
NS         32
DS         2
SWH        7309.941 Hz
FIDRES     0.111541 Hz
AQ         4.4827123 sec
RG         64
DW         68.400 usec
DE         4.50 usec
TE         300.0 K
D1         1.00000000 sec

===== CHANNEL f1 =====
NUC1       1H
P1         7.55 usec
PL1        0.00 dB
SF01       600.1331904 MHz

F2 - Processing parameters
SI         65536
SF         600.1300019 MHz
WDW        no
SSB        0
LB         0.00 Hz
GB         0
PC         1.00

1D NMR plot parameters
CX         20.00 cm
F1P        8.777 ppm
F1         5267.36 Hz
F2P        6.905 ppm
F2         4144.14 Hz
PPMCM      0.09358 ppm/cm
HZCM       56.16064 Hz/cm
  
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Figure S2. ¹H-NMR spectrum of **aHh-(5a)₂** in *d*₆-DMSO.

Figure S3. ROESY-NMR spectrum of **ahh-(5a)₂** in *d*₆-DMSO; crosspeaks due to NOE between 11-H and 13'-H are indicated in the spectrum.

Figure S4. ROESY-NMR spectrum of **ahh-(5a)₂** in *d*₆-DMSO; crosspeaks due to NOE between 5-H and 8'-H are indicated in the spectrum

Figure S5. Spectrophotometric titration of poly[dG-dC]-poly[dG-dC] to dibenzoquinolizinium derivatives [**5a**(BF₄)] (A) and **6** (B) ($c = 10^{-4} \text{ M}$) in phosphate buffer (10 mM, pH 7.0, $T = 25^\circ \text{C}$).

Figure S6. Spectrophotometric titration of poly[dA-dT]-poly[dA-dT] to dibenzo-quinolizinium ions [**5a**(BF₄)] (A) and **6** (B) ($c = 10^{-4} \text{ M}$) in phosphate buffer (10 mM, pH 7.0, $T = 25 \text{ }^\circ\text{C}$).

Figure S7. Scatchard plots derived from the spectrophotometric titration of ct DNA to dibenzoquinolizinium ions **[5a(BF₄)]** (A) and **6** (B) in phosphate buffer [10 mM, pH 7.0, $T = 25^\circ\text{C}$; $c(\text{quinolizinium}) = 10^{-4} \text{ M}$].

Figure S8. A: Melting profiles of poly[dA-dT]-poly[dA-dT] in the presence of dibenzo[*b,g*]quinolizinium tetrafluoroborate **[5a(BF₄)]** at different Na^+ concentrations [from right to left: 16 mM, 20 mM, 40 mM, 60 mM, 100 mM and 194 mM; $c(\text{DNA}) = 40 \mu\text{M}$ (bt) in BPES buffer]. B: Dependence of Na^+ concentration on the DNA melting temperature of **[5a(BF₄)]** (filled squares) in comparison to DNA melting profiles in the absence of ligands (open squares).

Figure S9. Melting profiles of poly[dA-dT]-poly[dA-dT] (●) and calf thymus DNA (■) in the presence of **9** at ligand-to-DNA ratios of 0 (half filled circles and squares), 0.2 (filled circles and squares), and 0.5 (open circles and squares); $c(\text{DNA}) = 40 \mu\text{M}$ (bp) in BPE buffer.

Figure S10. Melting profiles of poly[dA]-poly[dT]₂ in the presence of **9** at ligand-to-DNA ratios (r) of 0, 0.1, 0.2, 0.3, 0.4 and 0.5; $c(\text{DNA}) = 40 \mu\text{M}$ (bt) in BPES buffer. Inset shows the dependence of T_m shifts ($\Delta T_m^{3 \rightarrow 2}$: filled circles; $\Delta T_m^{2 \rightarrow 1}$: open circles) on the ligand-to-DNA ratio.

Figure S11. Competition-dialysis data for **9**. Data are presented as bar graph in which the amount of ligand bound to each nucleic acid structure is plotted.

Figure S12. Thermal decomposition of **5a(BF₄)** ($c = 10^{-4}$ mol/) in BPES buffer as monitored by absorption spectroscopy at increasing temperature; $T = 20 - 100$ °C.

Figure S13. Decomposition of **5a(Br)** (black line) in H₂O; the photometric detection was performed directly after irradiation of the dimer **ahh-(5a)₂** ($c = 1 \times 10^{-4}$ M) and removal of 1-methoxynaphthalene; the arrow indicates the decrease of the monomer absorption; detection intervals: 4 h for 24 h, then additional 12 h, the sample was stored in the dark during the experiment.

Figure S14. A: Absorption spectra of 1-methoxynaphthalene (dotted line, $c = 2 \times 10^{-3}$ M), **ahh-(5a)₂** (dashed line; $c = 1 \times 10^{-4}$ M), and **5a(Br)** (solid line, $c = 2 \times 10^{-4}$ M); **5a(Br)** was obtained by irradiation (55 sec, $\lambda = 350$ nm) of **ahh-(5a)₂** in the presence of 1-methoxynaphthalene in H₂O. B: Absorption spectra of **5a(Br)** (solid line) that was obtained by irradiation of **ahh-(5a)₂** (dashed line; $c = 1 \times 10^{-4}$ M) in the presence of 1-methoxynaphthalene ($c = 2 \times 10^{-3}$ M) in H₂O through a cut-off-filter ($\lambda \geq 335$ nm).

Figure S15. Optimized geometries of the intercalation complexes of dibenzoquinolizinium ions **5a** and **6** with ds DNA as obtained by molecular docking simulations (see Experimental Section for details); ds DNA is represented by its Connolly's surface.

References

- ¹ Fozard, A.; Bradsher, C.K. *J. Org. Chem.* **1966**, *31*, 3683.
- ² Bradsher, C. K.; Beavers, L. E. *J. Am. Chem. Soc.* **1955**, *77*, 4812