Enantioselectivity in the Interaction of Calf Thymus DNA with Acridine Derivatives Having an Amino Ester or Amino Alcohol Substituent

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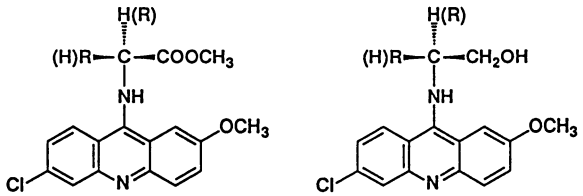
Unless a bulky aromatic side chain is involved, acridine derivatives **1** and **2** having an amino ester or amino alcohol substituent bind to calf thymus DNA via intercalation. The binding constants evaluated by the Scatchard analysis of the hypochromicity data indicate that (1) the substituents introduced are rather inhibitory of the binding and (2) L-enantiomers are preferred than the D-enantiomers by a factor of K_L/K_D=1.1—1.4, except for the case of aspartic and glutamic esters where the optical selectivity is very low or even reversed. The present enantioselectivity is discussed in terms of a local C_2 chirality of the intercalation site, steric effects of the amino ester or amino alcohol substituents, and a possible conformation-controlling effect of the CO_2CH_3 or CH_2OH group.

The basic structural elements of double helical DNA are vertically π–π stacked heteroaromatic bases, in-plane hydrogen-bonded Watson–Crick base pairs having peripheral polar groups, and polyanionic phosphodiester backbones.[1] These moieties provide the sites of intercalation,[2,3] hydrogen bonding,[4] and electrostatic interaction, respectively, for DNA-binding proteins,[5] antibiotics,[4,6,7] and synthetic molecules.[2,4,8] Another essential aspect is chirality that gives rise to a handedness or screw sense to the so-called groove, where elaborate molecular recognition of DNA should take place.

In the present work, we have studied the DNA-intercalation behaviors of acridine derivatives having an enantiomeric amino ester or amino alcohol substituent. It was hoped that interaction of the chiral substituents having both apolar alkyl and polar CO_2CH_3 or CH_2OH groups in the groove would be reflected on the overall binding properties.[9] So far, only scattered information is available as to chiral discrimination of DNA for small DNA-binding molecules.[10,11] We report here that calf thymus DNA shows a slight but notable preference for the L-enantiomers of *simple* amino ester and amino alcohol derivatives.

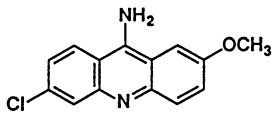
Results and Discussion

Acridine Derivatives Having an Amino Ester or Amino Alcohol Substituent. A series of 6-chloro-2-methoxy-9-acridinyl derivatives **1** having an L-or D-α-amino acid methyl ester substituent were prepared as hydrochlorides from the reactions of 6-chloro-2-methoxy-9-phenoxyacridine with a corresponding amino ester hydrochloride in phenol at 120 °C. The amino esters investigated include those of glycine (**1a**), alanine (**1b**), valine (**1c**), leucine (**1d**), serine (**1e**), phenylalanine (**1f**), tyrosine (**1g**), aspartic acid (**1h**), glutamic acid (**1i**), norvaline (**1j**), and norleucine (**1k**). Analogous L- and D-amino alcohol derivatives **2** were also obtained as free bases from the corresponding reactions with alaninol (**2b**), valinol (**2b**), leucinol (**2c**), and phenylalaninol (**2f**) in phenol at 90 °C. The products were identified on the basis of elemental analyses (Table 1) and ^{1}H NMR spectra (Table 2).



L-1 (D-1)

L-2 (D-2)



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Interaction with Calf Thymus DNA. Acridine is a typical DNA intercalator.[9] Upon intercalation, an acridine derivative undergoes a characteristic red shift of the absorption band with concomitant reduction in the intensity (hypochromicity); it also undergoes fluorescence quenching. Intercalation of a drug into nucleic acid also results in enhancement of the melting or helix-to-coil transition temperature of the latter.[12] The present acridine derivatives **1** and **2**, except for those having an aromatic side chain (**1f**, **1g**, and **2f**), were found to similarly intercalate into calf thymus DNA. In Figs. 1 and 2 are shown, as typical examples, the absorption and fluorescence spectra, respectively, for L-alanine ester derivative L-**1b** in the presence of increasing amounts of DNA in water–DMSO (96:4 v/v) at pH 6.50 (4-morpholinylethanesulfonate) and at 25 °C.

Saturation in the absorption spectral change (cf. Fig. 1) could be reached at higher DNA concentrations in every case, so as to allow evaluation of the concentrations of bound and free acridine derivative. The results of titration of L-**1b** are shown in Fig. 3 in the

Table 1. Mp's and Analytical Data for Acridine Derivatives **1** and **2**

Compound	R	Mp	Analysis (%) Found (Calcd)		
		°C	C	H	N
1a·HCl	H	207	55.38 (55.60)	4.32 (4.39)	7.45 (7.63)
L-**1b**·HCl	CH_3	190	55.52 (56.71)	4.73 (4.76)	7.25 (7.35)
D-**1b**·HCl	CH_3	190	55.70 (56.71)	4.80 (4.76)	7.21 (7.35)
L-**1c**·HCl	$CH(CH_3)_2$	173	57.35 (58.69)	5.47 (5.42)	6.84 (6.84)
D-**1c**·HCl	$CH(CH_3)_2$	173	56.83 (58.69)	5.30 (5.42)	6.60 (6.84)
L-**1d**·HCl	$CH_2CH(CH_3)_2$	205	58.62 (59.58)	5.66 (5.71)	6.55 (6.62)
D-**1d**·HCl	$CH_2CH(CH_3)_2$	205	58.79 (59.58)	5.78 (5.71)	6.51 (6.62)
L-**1e**·HCl	CH_2OH	200	54.29 (54.41)	4.77 (4.57)	7.03 (7.05)
D-**1e**·HCl	CH_2OH	200	54.23 (54.41)	4.63 (4.57)	6.83 (7.05)
L-**1f**·HCl	$CH_2C_6H_5$	155	62.19 (63.03)	4.84 (4.85)	6.10 (6.13)
D-**1f**·HCl	$CH_2C_6H_5$	165	62.76 (63.03)	4.83 (4.85)	6.05 (6.13)
L-**1g**·HCl	$CH_2C_6H_4OH$-*p*	193	60.03 (60.90)	4.70 (4.68)	5.75 (5.82)
D-**1g**·HCl	$CH_2C_6H_4OH$-*p*	212	60.78 (60.90)	4.75 (4.68)	6.04 (5.82)
L-**1h**·HCl	$CH_2CO_2CH_3$	115	49.10 (54.68)	4.88 (4.59)	5.23 (6.38)
D-**1h**·HCl	$CH_2CO_2CH_3$	105	52.58 (54.68)	5.09 (4.59)	6.25 (6.38)
L-**1i**·HCl	$CH_2CH_2CO_2CH_3$	98	55.35 (55.64)	4.81 (4.89)	5.95 (6.18)
D-**1i**·HCl	$CH_2CH_2CO_2CH_3$	98	54.56 (55.64)	4.87 (4.89)	6.12 (6.18)
L-**1j**·HCl	$CH_2CH_2CH_3$	138	57.03 (58.69)	5.46 (5.42)	6.70 (6.84)
L-**1k**·HCl	$CH_2CH_2CH_2CH_3$	115	57.35 (59.58)	5.80 (5.71)	6.28 (6.62)
L-**2b**	CH_3	251	64.63 (64.46)	5.37 (5.41)	8.82 (8.84)
D-**2b**	CH_3	249	64.18 (64.46)	5.30 (5.41)	8.82 (8.84)
L-**2c**	$CH(CH_3)_2$	233	65.93 (66.18)	6.08 (6.14)	8.04 (8.12)
D-**2c**	$CH(CH_3)_2$	233	66.01 (66.18)	6.05 (6.14)	8.03 (8.12)
L-**2d**	$CH_2CH(CH_3)_2$	224	66.87 (66.94)	6.39 (6.46)	7.85 (7.81)
D-**2d**	$CH_2CH(CH_3)_2$	224	66.95 (66.94)	6.40 (6.46)	7.66 (7.81)
L-**2f**	$CH_2C_6H_5$	235	70.13 (70.31)	5.38 (5.39)	7.11 (7.13)
D-**2f**	$CH_2C_6H_5$	235	70.28 (70.31)	5.39 (5.39)	7.20 (7.13)

Table 2. ^{1}H NMR Data for the Amino Ester or Amino Alcohol Moieties of Acridine Derivatives **1** and **2** in DMSO-d_6

Compounds	δ/ppm				
	NH[a]	N-CH[b]	OCH_3[c]	OH[d]	Other H
1a·HCl	9.90	5.05	3.74		
L-**1b**·HCl	9.33	5.41	3.70		1.77 (d, 3H, CH_3)
L-**1c**·HCl[e]	9.00	4.83	3.82		0.92, 0.94 (each d, each 3H, CH_3)
L-**1d**·HCl	9.30	5.19	3.79		0.59, 0.89 (each d, each 3H, CH_3), 1.50 (m, 1H, CH), 1.89, 2.19 (each m, each 1H, CH_2)
L-**1e**·HCl	9.23	5.49	3.77	5.60	4.12 (m, 2H, CH_2)
L-**1f**·HCl[e]	9.18	5.51	3.80		6.91—7.11 (m, 5H, phenyl-H)
L-**1g**·HCl	9.20	5.40	3.79		6.29, 6.89 (each d, each 2H, phenyl-H), 9.10 (s, 1H, OH)
L-**1h**·HCl[e]	9.02	5.58	3.49, 3.69		
L-**1i**·HCl[e]	9.25	5.36	3.35, 3.70		
L-**1j**·HCl	9.17	5.23	3.80		0.80 (t, 3H, CH_3), 1.30 (m, 2H, CH_2CH_3), 2.15 (m, 2H, $CH_2CH_2CH_3$)
L-**1k**·HCl	9.08	5.19	3.76		0.78 (t, 3H, CH_3), 1.26 (m, 4H, $CH_2CH_2CH_3$), 2.12 (m, 2H, $CH_2CH_2CH_2CH_3$)
L-**2b**	6.20	3.95		4.89	1.24 (d, 3H, CH_3), 3.51, 3.59 (each m, each 1H, CH_2)
L-**2c**	6.28	3.85		4.93	0.78, 0.93 (each d, each 3H, CH_3), 1.99 (m, 1H, CH), 3.66, 3.72 (each m, each 1H, CH_2)
L-**2d**	6.28	4.06		5.00	0.59, 0.77 (each d, each 3H, CH_3), 1.52 (m, 2H, CH_2), 1.61 (m, 1H, CH), 3.58, 3.69 (each m, each 1H, CH_2OH)
L-**2f**	6.30	4.13		4.98	2.99 (m, 2H, CH_2OH), 3.50 (m, 2H, CH_2-phenyl), 7.12—7.24 (m, 5H, phenyl)

a) Broad doublet. b) Multiplet. c) Singlet. d) Broad singlet. e) Resonance for $(CH_3)_2CH$-(**1c**·HCl), CH_2-phenyl (**1f**·HCl), CH_2-(**1h**·HCl), or CH_2CH_2-(**1i**·HCl) could not be observed because of overlap with the solvent signal.

form of a Scatchard plot.[13] The data in the range of 20—80% binding were satisfactorily fit by nonlinear least-squares analysis to the McGhee-Hippel equation (Eq. 1),[14] where r is the ratio of the concentration of bound **1b** to the concentration of DNA phosphate, C is the concentration of free **1b**, K is the binding constant,

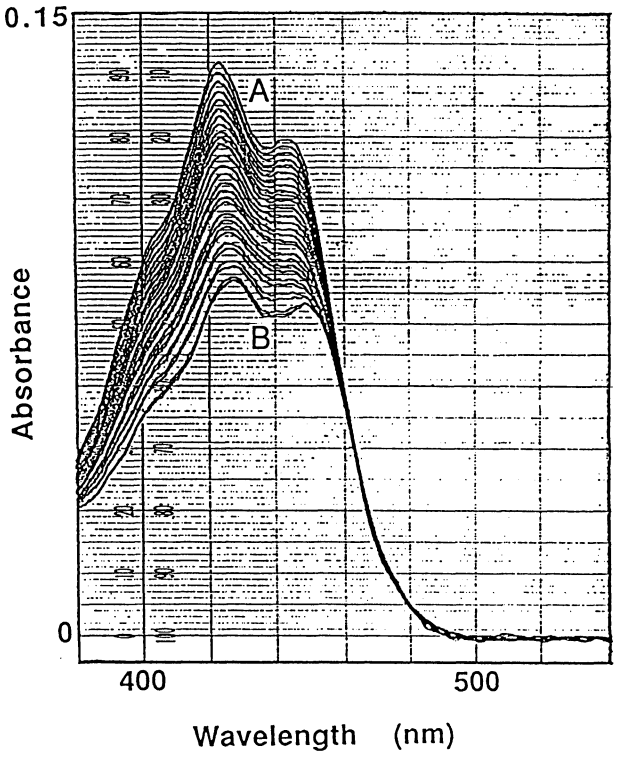


Fig. 1. Electronic spectra of compound L-**1b** (0.016 mmol dm^{-3} in the absence and presence of calf thymus DNA in water–DMSO (96 : 4 v/v) with NaCl (50 mmol dm^{-3} at pH 6.50 and at 25 °C; [DNA phosphate]=0, 0.00529, 0.0106, 0.0158, 0.0210, 0.0261, 0.0313, 0.0363, 0.0414, 0.0464, 0.0514, 0.0613, 0.0710, 0.0807, 0.0902, 0.0996, 0.109, 0.118, 0.136, 0.154, 0.171, 0.188, 0.228, 0.266, 0.336, 0.399, 0.638, 0.797, 0.911, and 1.59 mmol dm^{-3}, read from A to B.

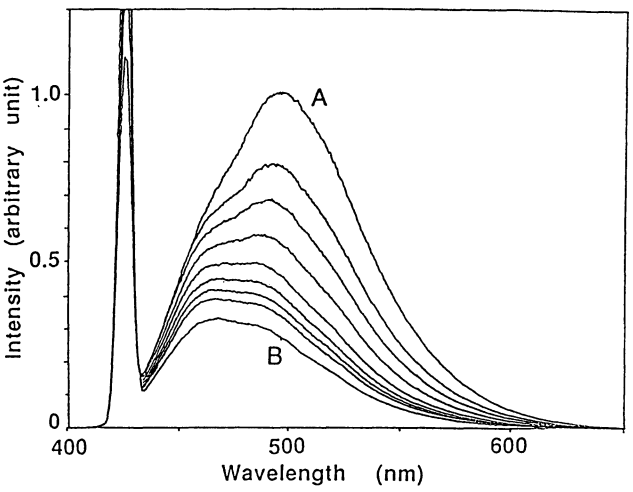


Fig. 2. Fluorescence spectra of compound L-**1b** (0.0080 mmol dm^{-3}) in the absence and presence of calf thymus DNA in water–DMSO (96 : 4 v/v) with NaCl (50 mmol dm^{-3}) at pH 6.50 and at 25 °C; excitation wavelength, 424 nm: [DNA phosphate]=0, 0.0394, 0.0788, 0.158, 0.315, 0.473, 0.630, 0.788, and 1.58 mmol dm^{-3}, read from A to B.

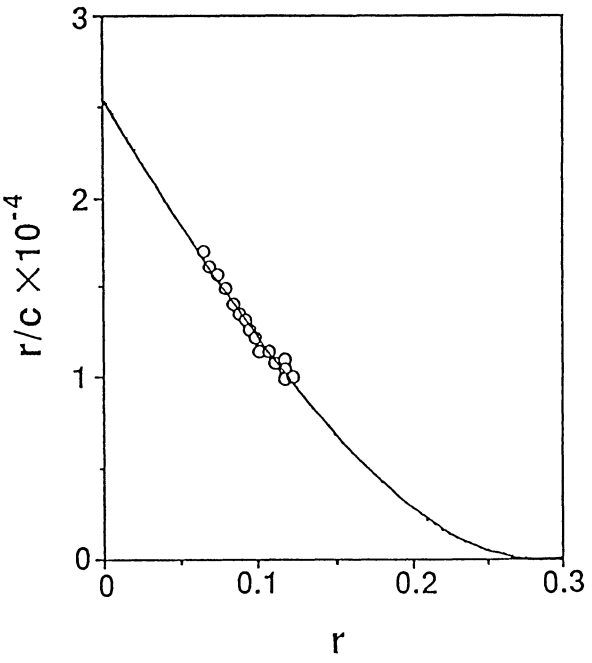


Fig. 3. Scatchard plot for the binding of compound L-**1b** (0.016 mmol dm^{-3}) to calf thymus DNA in water–DMSO (96 : 4 v/v) with NaCl (50 mmol dm^{-3}) at pH 6.50 and at 25 °C. The solid line is the best-fit line on the basis of Eq. 1 and K=2.6×10^4 dm^{3}mol^{-1} and n=3.7.

and n is the size of a binding site in base pairs. The best fit, shown as the solid line in Fig. 3, gives the binding constant $K_{\text{L-1b}}$=2.6×10^4 l mol^{-1} and an exclusion site size n=3.7. Similarly were analyzed the binding behaviors of other derivatives. In Table 3 are summarized the values of K and n, enantioselectivities (K_L/K_D), hypochromicities at saturation binding, and the percent binding covered for satisfactory fit to Eq. 1 for derivatives **1** and **2**, together with those for the parent aminoacridine reference **3**. Most derivatives have exclusion site sizes n=3—5, which are slightly larger than that for the parent compound **3** (n=2.2), in a similar manner as in other cases.[15] The serine (**1e**) and phenylalaninol systems (**2f**) show larger valus (n=7—8) for reasons which are not clear at present.

$$\frac{r}{C} = K(1-nr)\left(\frac{1-nr}{1-(n-1)r}\right)^{n-1} \quad (1)$$

In the case of aromatic amino ester and amino alcohol systems **1f**, **1g**, and **2f**, only small hypochromicities were observed. In addition, the titration data could not satisfactorily be fit to Eq. 1, except for the case of L-**2f**.

Enantioselectivity. Inspection of Table 3 allows a couple of general trends to be uncovered. First, the present DNA shows a preference for the L- over the D-enantiomers of both amino ester and amino alcohol substituted acridines, except for aspartic and glutamic ester systems where the enantioselectivity is very low or even reversed. The selectivity of K_L/K_D=1.1—1.4 is

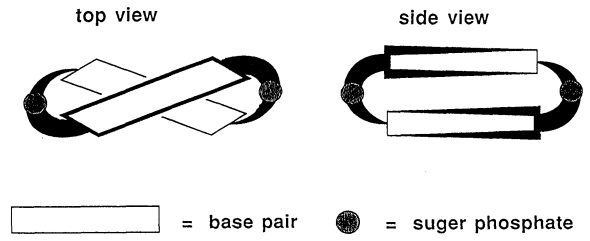
Table 3. Binding Constants (K), Sizes of Binding Sites in Base Pairs (n), Enantioselectivities (K_L/K_D), Hypochromicities and Percent Binding Covered for the Interaction of Acridine Derivatives **1** and **2** with Calf Thymus DNA[a)]

Compound	K / $dm^3 mol^{-1}$	n	K_L/K_D	Hypochromicity / %	% Binding covered
1a	6.4×10^4	3.4		35	20—80
L-**1b**	2.6×10^4	3.7		40	20—80
			1.2		
D-**1b**	2.2×10^4	3.6		38	20—80
L-**1c**	3.3×10^4	4.4		31	20—80
			1.4		
D-**1c**	2.3×10^4	2.7		23	30—80
L-**1d**	2.3×10^4	4.3		25	30—80
			1.4		
D-**1d**	1.7×10^4	3.9		22	20—80
L-**1e**	5.7×10^4	7.6		35	20—80
			1.3		
D-**1e**	4.5×10^4	8.2		28	20—80
L-**1f**	—	—		16	—
			—		
D-**1f**	—	—		14	—
L-**1g**	—	—		15	—
			—		
D-**1g**	—	—		19	—
L-**1h**	1.1×10^4	4.9		30	20—80
			0.96		
D-**1h**	1.1×10^4	3.3		28	28—80
L-**1i**	1.9×10^4	3.2		36	25—80
			0.87		
D-**1i**	2.8×10^4	3.1		30	20—80
L-**1j**	1.2×10^4	3.2		44	20—80
L-**1k**	1.4×10^4	4.6		43	35—80
L-**2b**	2.6×10^4	3.9		40	20—80
			1.3		
D-**2b**	2.0×10^4	3.3		42	20—80
L-**2c**	9.4×10^3	4.2		35	30—80
			1.2		
D-**2c**	8.0×10^3	4.0		34	30—80
L-**2d**	1.4×10^4	4.5		31	35—80
			1.1		
D-**2d**	1.2×10^4	2.1		29	38—80
L-**2f**	1.3×10^4	7.2		17	30—80
			—		
D-**2f**	—	—		12	—
3	6.6×10^4	2.2		59	25—85

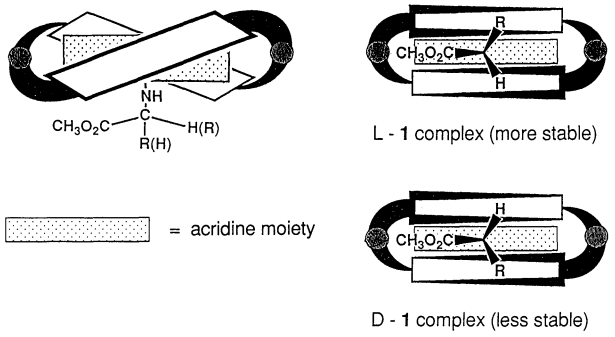
a) In water–DMSO (96:4 v/v) containing NaCl (50 mmol dm^{-3}) at pH 6.50 (2-(*N*-morpholino)ethanesulfonate) and at 25 °C. [**1**, **2** or **3**]=0.016 mmol dm^{-3}.

similar to that observed for the binding of enantiomeric tris(phenanthroline)ruthenium(II) to calf thymus DNA.[11)] Second, the effect of amino ester or amino alcohol substituents on the acridine intercalation is rather inhibitory, probably for steric reasons. In fact, no member of modified acridines **1** and **2** shows a higher affinity to DNA than the parent amino derivative **3**. The enantioselectivity observed is independent on the relative bulkiness of alkyl and CO_2CH_3 or CH_2OH groups. In the alanine system (**1b**), for example, CO_2CH_3 is bulkier than CH_3, while in the case of valinol (**2c**) or leucinol (**2d**) the alkyl group is bulkier than CH_2OH; nevertheless, both of them exhibit L-enantiomer selectivity. Thus, the present optical selectivity could not be explained by a simple steric consideration alone. In another word, apolar alkyl and polar CO_2CH_3 or CH_2OH groups, even of a similar bulkiness, are not exchangeable; they must have their own characteristic interactions with DNA.

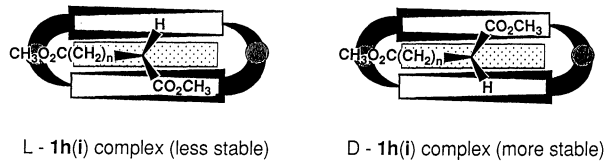
Calf thymus DNA in water takes the B-form with a right-handed double helix.[1)] The base pairs undergo a clockwise twisting on going down along the helix axis. Thus, two adjacent base pairs generate a local C_2 chirality, as schematically shown in Scheme 1, in a similar manner as in chiral biaryls. Intercalation of the acridine moiety of compounds **1** and **2** leaves the amino ester or amino alcohol substituent in a chiral environment. Preferred conformation is not known at present. If it is assumed, however, that the bulky and polar CO_2CH_3 or CH_2OH group takes the least hindered *in-*



Scheme 1.



Scheme 2.



Scheme 3.

plane position pointing to a sugar-phosphate moiety to allow some kind of polar interaction between these, then the alkyl group (R) and hydrogen in an L-enantiomer would occupy the less and more crowded positions, respectively. The reverse is true when a D-enantiomer is involved (Scheme 2, in the case of binding of **1**). L-enantiomers may thus lead to more stable complexes than the D-enantiomers, in accord with the observed enantioselectivity. In the case of the binding of **1c**, **1d**, **2c**, and **2d**, the bulky alkyl side chains (R) would tend to occupy the least crowed in-plane position. This may be why the enantioselectivity K_L/K_D is rather insensitive to the bulkiness of R.

The suggested mechanism is consistent with a number of other observations. First, the steric hindrance effect of the alkyl groups in compounds **1** is reflected on their binding constants (K), which decrease in the order **1a**>**1b**≈**1c**>**1d** as far as D-enantiomers of the lower affinities are concerned. In the case of aromatic amino esters **1f** and **1g**, the side chain seems to be too bulky to allow a well-defined intercalation of the acridine moiety. Second, there seems to be some attractive interaction, as suggested above, between DNA and the CO_2CH_3 group,[16] which compensates its otherwise inhibitory steric effects. Thus, the glycine system **1a** and parent aminoacridine (**3**) show practically the same binding constants (Table 3). Furthermore, amino esters **1b**—**d** are somewhat more strongly bound than the corresponding amino alcohols **2b**—**d**, even though CO_2CH_3 is definitely bulkier than CH_2OH. Third, the lack or even reversion of enantioselectivity observed for aspartic and glutamic diester compounds **1h** and **1i** could be readily understood on the basis of competition between the α-CO_2CH_3 and $(CH_2)_nCO_2CH_3$ groups (n=1 or 2). If the latter occupies the conformation-controlling position pointing to a sugar-phosphate moiety, then the D-enantiomer would form a more stable complex than the L-enantiomer (Scheme 3).

To summarize, the present work demonstrates that calf thymus DNA shows a slight but notable preference for the L-enentiomers of acridine derivatives having a *simple* amino ester or amino alcohol substituent. The enantioselectivity most likely arises from a combination of steric and conformation effects; the *polar* CO_2CH_3 and CH_2OH groups play an important role in the conformation-controlling, but details of the interaction is not clear at present. Further work is now under way to get deeper insight into DNA-substituent interactions as well as to further characterize the DNA grooves by use of intercalators having a more potential *probe* as substituent.

Experimental

Instruments and Materials. ^{1}H NMR, electronic absorption, and fluorescence spectra were obtained with a JEOL-GX 270 spectrometer, a Hitachi 320 spectrophotometer, and a Hitachi F-4000 fluorescence spectrophotometer, respectively. 9-Amino-6-chloro-2-methoxyacridine (**3**) was commercially available. Calf thymus DNA (Pharmacia) dissolved in water was sonicated with a cell disruptor W-220F (Heat Systems-Untrasonics Inc.) at 0 °C for 1 min and allowed to stand for 1 min at the same temperature.[17] This cycle was repeated 180 times, i.e., for 6 h. The DNA was precipitated upon addition of ethanol and was recovered by centrifugation. The binding constants were obtained by computor assisted nonlinear least-squares analysis of the Scatchard plots.

***N*-[6-Chloro-2-methoxy-9-acridinyl]-L-amino Acid Methyl Esters (1).** The preparation of the L-leucine ester derivative L-**1d** is described as a typical example.[18] A solution of 6-chloro-2-methoxy-9-phenoxyacridine (1.0 g, 3.0 mmol) and L-leucine methyl ester hydrochloride (540 mg, 3.0 mmol) in phenol (4.0 g) was stirred at 120 °C for 2.5 h. When the reaction mixture was cooled down, ether (100 ml) was added. Yellow precipitates which separated were recovered by filtration and recrystallized from ethanol–ether to give compound L-**1d** as hydrochloride (1.1 g, 98%).

***N*-(6-Chloro-2-methoxy-9-acridinyl)-L-amino Alcohols (2).** The preparation of the L-leucinol derivative (L-**2d**) is described as a typical example.[18] A solution of 6-chloro-2-methoxy-9-phenoxyacridine (0.50 g, 1.5 mmol) and L-leucinol (0.35 g, 3.0 mmol) in phenol (10 g) was stirred at 90 °C for 6 h. The solvent was removed in vacuo. Chromatography of the residue on a column of silica gel (Wakogel C-200) with $CHCl_3$–CH_3OH (97 : 3 v/v) as eluant, followed by recrystallization from methanol gave compound L-**2d** (0.092 g, 17%).

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