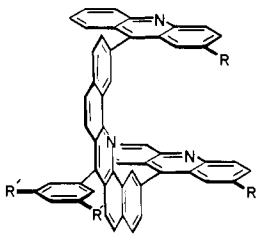
Rigid Molecular Tweezers: Preorganized Hosts for Electron Donor–Acceptor Complexation in Organic Solvents

Steven C. Zimmerman,* Craig M. VanZyl, and Gregory S. Hamilton

Contribution from the Department of Chemistry, University of Illinois, Urbana, Illinois 61801.
Received July 13, 1988

Abstract: Novel nonmacrocyclic receptor molecules **1** and **7** have been synthesized which are capable of acting as molecular tweezers. These molecules are 7-aryl-2,12-bis(9-acridinyl)dibenz[*c,h*]acridines, which when unsymmetrically substituted exhibit atropisomerism. In addition to being rigid and providing a ca. 7 Å interchromophore distance, the dibenz[*c,h*]acridine spacer is the first to enforce a syn cofacial orientation of the complexing chromophores. ^{1}H NMR studies indicate that **1** and **7** have open clefts. These preorganized clefts form highly oriented inclusion complexes with 2,4,7-trinitrofluorenone (TNF) in $CDCl_3$ as monitored by ^{1}H NMR. The complexation has a strong electron donor–acceptor component. As such, the association constants for TNF are dependent on the π-basicity of the host and range from 149 M^{-1} for *tert*-butyl-substituted **7b** to 697 M^{-1} for dimethylamino-substituted **7f** ($CDCl_3$). Monoacridines and a flexible diacridine, under identical conditions, bind TNF very weakly ($K_{assoc} < 5$ M^{-1}).

Molecules containing two aromatic chromophores linked by a single spacer unit have found use in studies of important processes such as electron donor–acceptor interactions,[1] electron (energy) transfer reactions,[2] drug–DNA interactions,[3,4] and host–guest complexation.[5] We recently described the synthesis and complexation chemistry of a rigid "molecular tweezer" (**1b**) which



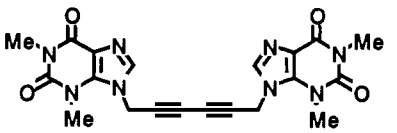
1b: R,R' = t-Bu

consists of two acridine chromophores attached to a rigid dibenz[*c,h*]acridine spacer.[6] This is the first spacer to rigidly enforce a syn cofacial orientation of the attached chromophores, with a ca. 7-Å interchromophore separation.[7]

The rigidity was shown to be essential for effective complexation of 2,4,7-trinitrofluorenone (TNF) in chloroform-*d* solution. In this paper we present evidence that the complexation of TNF by molecular tweezers (e.g. **1b**) is largely driven by electron donor–acceptor (EDA) interactions. We report results from the first complexation study involving systematic changes in the π-basicity of the host.[8] This has allowed elucidation of the cooperative role played by the two acridine chromophores in complexation. Additionally, we describe atropisomerism in unsymmetrically substituted molecular tweezers.

Results and Discussion

Design of Molecular Tweezers. Earlier investigations of rigid molecular tweezers by Chen and Whitlock involved caffeine chromophores linked by a 2,4-hexadiyne unit (i.e. **2**).[5] This



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important study demonstrated that the rigid spacer could prevent self-association of the attached chromophores, in water, thereby increasing the complexation efficiency ca. 100-fold over a flexible (aliphatic) analogue. However, as noted by these authors, this diyne spacer does not fix the caffeine moieties in a syn arrangement, nor does it orient them in parallel planes.

We were attracted to dibenz[*c,h*]acridine as a possible spacer because it is a U-shaped molecule with a C-2 to C-12 distance of 7.24 Å[9] (Figure 1). This is slightly larger than the 6.8-Å interchromophore separation which is optimum for "sandwiching" an aromatic guest. It appeared likely that chromophores attached at these positions would lie in parallel planes. Additionally, the spacer unit would fix the chromophores in a syn orientation, thereby creating a cleft which is *preorganized* for complexation.

Cram has defined preorganized host and guest molecules as those which are structurally arranged for binding and low solvation prior to complexation.[10] Preorganization has been argued to be the central determinant of complex stability. Strong support for this assertion comes from the observation that large classes of synthetic ionophores exhibit binding affinities which are well correlated with their degree of structural organization and solvation. Much less is known about the importance of preorganization in the complexation of neutral guests, but the large increase in binding affinity of water-soluble cyclophanes for aromatic guests relative to that of acyclic analogues probably results from their greater degree of organization.[11]

Synthesis of Molecular Tweezers. The synthesis began with 7-bromo-1-tetralone,[12] which was converted into ethylene ketal

(1) Cf.: Foster, R. *Organic Charge-Transfer Complexes*; Academic: New York, 1969. Foster, R. *J. Phys. Chem.* **1980**, *84*, 2135–2141.
(2) Cf.: Schanze, K. S.; Sauer, K. *J. Am. Chem. Soc.* **1988**, *110*, 1180–1186 and references therein.
(3) Gale, E. F.; Cundliffe, E.; Reynolds, P. E.; Richmond, M. H.; Waring, M. J. *The Molecular Basis of Antibiotic Action*; Wiley: New York, 1981; Chapter 5.
(4) DNA bis-intercalators: Wakelin, L. P. G. *Med. Res. Rev.* **1986**, *6*, 275–340.
(5) Chen, C.-W.; Whitlock, H. W., Jr. *J. Am. Chem. Soc.* **1978**, *100*, 4921–4922.
(6) Zimmerman, S. C.; VanZyl, C. M. *J. Am. Chem. Soc.* **1987**, *109*, 7894–7896.
(7) Porphyrins have been linked in a syn cofacial orientation by shorter aromatic spacers: Fillers, J. P.; Ravichandran, K. G.; Abdalmuhdi, I.; Tulinksy, A.; Chang, C. K. *J. Am. Chem. Soc.* **1986**, *108*, 417–424 and references therein.
(8) Recently, important studies have appeared in which the π-basicity of the guest molecule has been changed: (a) Ferguson, S. B.; Diederich, F. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1127–1129. (b) Shepodd, T. J.; Petti, M. A.; Dougherty, D. A. *J. Am. Chem. Soc.* **1988**, *110*, 1983–1985. (c) In a footnote to ref 8a the authors described a host with increased donor potential which shows altered guest affinities.
(9) Mason, R. *Proc. R. Soc. London, A* **1960**, *258*, 302–318.
(10) Cram, D. J. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1039–1055.
(11) (a) Tabushi, I.; Sasaki, H.; Kuroda, Y. *J. Am. Chem. Soc.* **1976**, *98*, 5727–5728. (b) Odashima, K.; Itai, A.; Iitaka, Y.; Koga, K. *Ibid.* **1980**, *102*, 2504–2505. (c) Jarvi, E. T.; Whitlock, H. W., Jr. *J. Am. Chem. Soc.* **1982**, *104*, 7196–7204. (d) Diederich, F.; Dick, K. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 715–716. (e) Shepodd, T. J.; Petti, M. A.; Dougherty, D. A. *J. Am. Chem. Soc.* **1986**, *108*, 6085–6087. (f) Wilcox, C. S.; Cowart, M. D. *Tetrahedron Lett.* **1986**, 5563–5566.

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Scheme I

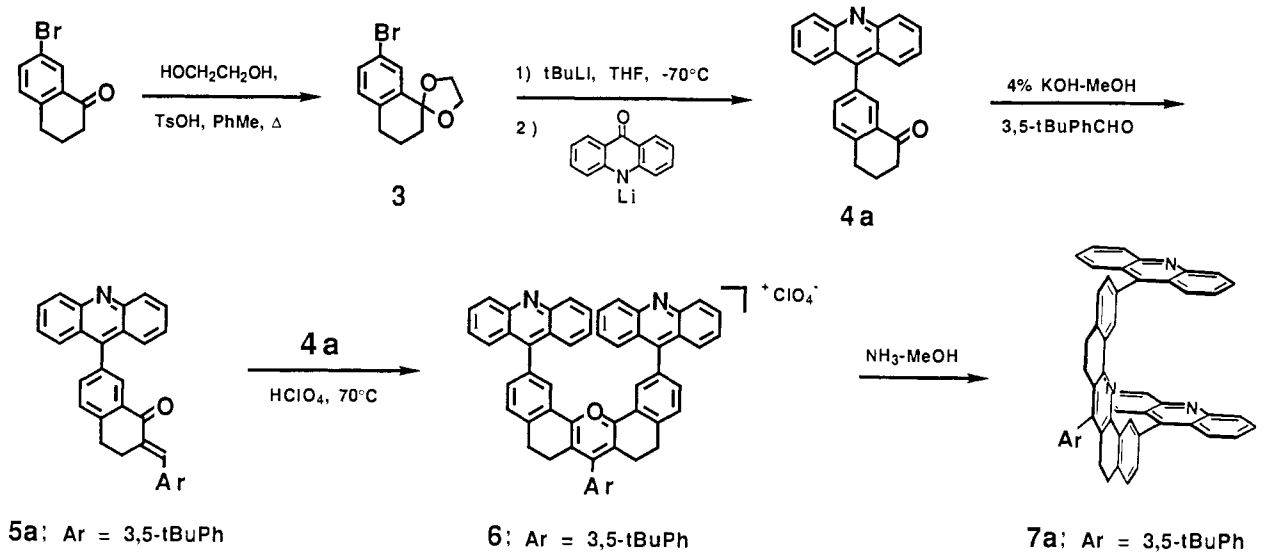

Table I. Synthesis of Molecular Tweezers

	substituent position[a]				acridinyl tetralone		benzylidene			molecular tweezer	
entry	C-2	C-4	C-6	C-7	prodt	% yield	Ar-CHO[b]	prodt	% yield	prodt	% yield
1	H	H	H	H	**4a**	50	A	**5a**	66	**7a**	50
2	tBu	H	H	H	**4b**	67	A	**5b**	81	**7b**	56
3	tBu	H	tBu	H	**4c**	51	B	**5c**	55	**7c**	50
4	H	OMe	H	H	**4d**	55	A	**5d**	62	**7d**	24
5	H	OMe	H	OMe	**4e**	50	A	**5e**	60	**7e**	43
6	NMe_2	H	H	H	**4f**	30	A	**5f**	50	**7f**	32
7	Cl	H	H	tBu	**4g**	15	A	**5g**	33	**7g**	36

[a] See Figure 2 for numbering scheme. [b] A: 3,5-di-*tert*-butylbenzaldehyde. B: 3,5-dimethylbenzaldehyde.

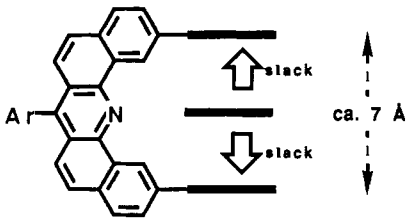

Figure 1. Schematic representation of complexation by a rigid molecular tweezer.

3 in 92% yield by treatment with ethylene glycol and *p*-toluenesulfonic acid in toluene, with azeotropic distillation of water (Scheme I). Treatment of **3** with 2 equiv of *tert*-butyllithium in THF (−70 °C) readily effected metal–halogen exchange. The THF solution of this lithium reagent was added at −70 °C to a THF solution of the lithium salt of acridone, generated by deprotonation with *n*-butyllithium in THF. Warming the solution to room temperature resulted in smooth addition of the aryllithium to the 9-position of the acridone anion. Quenching the reaction with 2 N HCl effected aromatization and deketalization, affording **4a** in 50% yield. This reaction, which is a modification of a procedure reported by Lehmstedt in 1938 for the synthesis of 9-phenylacridine,[13] has been found to be useful with a number of substituted acridones (Table I).

Construction of the spacer unit was accomplished by initial synthesis of pyrylium salt **6**, using a protocol reported by Katritzky for the preparation of phenyldibenzoxanthylium perchlorate.[14] Thus, tetralone **4a** was converted into benzylidene **5a** in 49% yield by reaction with 3,5-di-*tert*-butylbenzaldehyde and 4% KOH in methanol. As the 3,5-di-*tert*-butylphenyl group afforded high solubility of the molecular tweezer in organic solvents, this benzylidene was used in most cases (Table I).

Benzylidene **5a** was coupled with tetralone **4a** in perchloric acid to produce a pyrylium salt **6**, which was not isolated but treated directly with ammonia to form reduced molecular tweezer **7a** (57% yield from tetralone **4a**). In general, the coupling reactions gave only moderate yields. Higher yields have been reported with boron trifluoride etherate,[14] but in our early work with unsubstituted components[5] lower yields were obtained (however, see below). In the perchloric acid catalyzed reactions, it is not known what species serves as the oxidant to produce the pyrylium salt. Balaban has suggested that the enone may serve to accept a hydride from the 4*H*-pyran. This proposal is based on the finding that the yield of 1,3,5-triphenylpyrylium perchlorate, formed from the condensation of acetophenone with benzaldehyde, is improved if the intermediate condensation product chalcone is added to the reaction mixture.[15] Additionally, reduced chalcone is an isolated byproduct. In our system no effort was made to optimize the yields since gram quatities of the molecular tweezers could easily be prepared. In those cases where the fully unsaturated spacer was desired, dehydrogenation was effected with DDQ in refluxing chlorobenzene to produce molecular tweezer **1** (eq 1).

Molecular tweezers **7** are symmetrical but in principle need not be, since the tetralone and benzylidene can carry different substituents. Thus it was possible to vary the π-basicity of the two acridine moieties independently. However, unsymmetrical couplings of tetralones and benzylidenes in perchloric acid proved not to be a viable synthetic approach since retroaldol chemistry prevailed and mixtures of symmetrical and unsymmetrical molecular tweezers were obtained. To circumvent this problem, the boron trifluoride etherate protocol was utilized to couple tetralone **4e** and benzylidene **5b** (eq 2). Unexpectedly, the yield of **8** was

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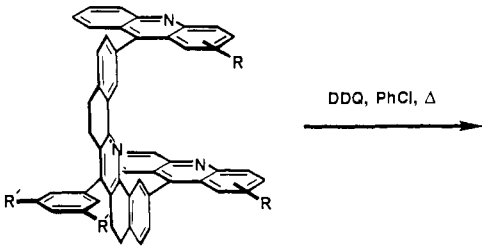
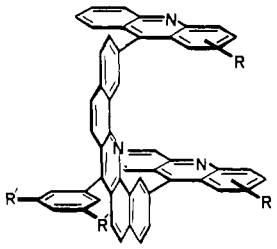
(13) Lehmstedt, K.; Dostal, F. *Chem. Ber.* **1939**, *72*, 804–807.
(14) Katritzky, A. R.; Thind, S. S. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1895–1900. See also: Balaban, A. T.; Dinculescu, A.; Dorofeenko, G. N.; Fischer, G. W.; Koblik, A. V.; Mezheritskii, V. V.; Schroth, W. In *Pyrylium Salts*; Katritzky, A. R., Ed.; Advances in Heterocyclic Chemistry, Academic: New York, 1982; Chapter 2.
(15) Balaban, A. T. *C. R. Hebd. Seances Acad. Sci.* **1963**, *256*, 4239–4242.

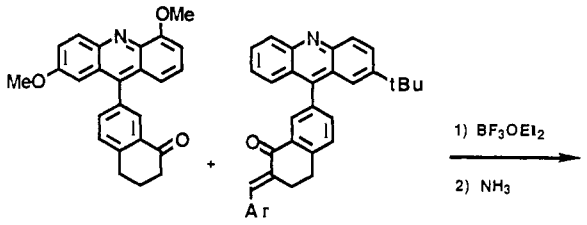


7b: R' = tBu, R = 2-tBu
7c: R' = tBu, R = 2,6-tBu
7g: R' = tBu, R = 2-Cl, 7-tBu

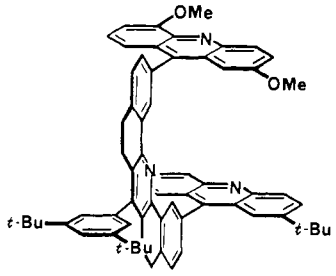


(1)

1b: R' = tBu, R = 2-tBu
1c: R' = tBu, R = 2,6-tBu
1g: R' = tBu, R = 2-Cl, 7-tBu



4e **5b**



(2)

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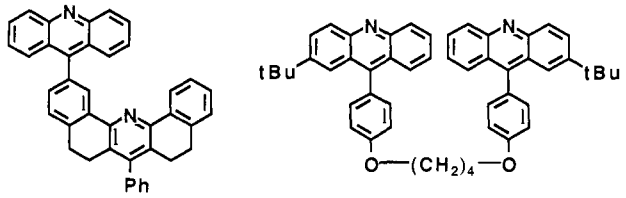
55%, higher than most of the yields in the symmetrical couplings with perchloric acid. This can be attributed to the greater solubility of the substituted tetralone **4e** and benzylidene **5b** in boron trifluoride etherate. No effort was made to see if higher yields could be obtained in the symmetrical couplings using this protocol.

Conformation of Molecular Tweezers. In molecular tweezer **7** the dimensions of the binding cleft are determined by the dihedral angle between the spacer and the acridine rings and by the conformation of the spacer. The latter most likely plays a minor role since CPK models suggest that a number of conformations for the ethano bridges lead to very similar C-2 to C-12 distances (ca. 7 Å) with very little skewing of the acridine rings. This is consistent with experimental findings which suggest only slight differences between molecular tweezers **1** and **7** in their "cyclization shifts" and in complexation (vide infra).

Thus, the acridine-spacer dihedral angle determines the cleft dimensions. No structural data are available for 9-arylacridine; however, the phenyl rings in 9,10-diphenylanthracene are twisted out of planarity by 67°.[16] The role of crystal-packing forces in determining the exact phenyl–anthracene dihedral angle is uncertain, but it is reasonable that the lack of planarity arises from nonbonded interactions between the peri hydrogens and the ortho protons of the phenyl substituent. These same nonbonded interactions in **1** and **7**, between H-1'(H-8') and H-1(H-3), make an edge to face conformation between the two acridines likely to be very unfavorable energetically and probably close in structure to the transition state for interconversion of atropisomers (Figure 2). Torsion in the inter-ring bond of the binaphthyl system results in very similar hydrogen–hydrogen contacts, and it is a reasonable analogy. In this case, potential functions derived from molecular mechanics calculations[17] and crystal structures[18] indicate a very flat minimum centered at 90° and extending ±30°. This suggests that **1** and **7** will have an open cleft with an easily adjustable interchromophore distance. Thus, small rotations will "clamp" the acridine rings down on the guest molecule, a motion which is operationally similar to that of a tweezer.

Support for these arguments was obtained by comparing the ^{1}H NMR spectra of molecular tweezers **1** and **7** to those of their respective tetralone precursors. As seen in Table II, the acridine resonances of **1** and **7** are shifted upfield slightly. These upfield shifts could be induced either by the neighboring acridine ring or the spacer unit. The latter possibility was examined by synthesis of monoacridine **9**. Relative to acridinyl tetralone **4b**, the chemical



9 **10**

shift of H-2', H-3', and H-4' of **9** show only very small downfield shifts (<0.05 ppm). The downfield shift of H-1' is somewhat larger (0.22 ppm), which is not unexpected since it passes through the deshielding bay region of the spacer during rotation of the acridine chromophore. Thus, the upfield shifts seen in the molecular tweezer spectra (Table II) must result from the proximity of the acridine chromophores.

As with Whitlock's "cyclization shift" analysis, the magnitude of the upfield shifts observed in the molecular tweezers indicates the degree to which the cavity is collapsed.[11c,19] In order to have a flexible diacridine for comparison, **10** was synthesized from 1,4-bis(4-bromophenoxy)butane and 2-*tert*-butylacridone by using the modified Lehmstedt procedure (vide supra). Remarkably, the flexible diacridine **10** shows negligible shift changes compared with tetralone **4b**, suggesting that either there is no driving force for association of the acridine chromophores of **10** in $CDCl_3$ or that it is sterically or entropically disfavored. The former possibility is unlikely given that Whitlock has observed sizeable upfield shifts in flexible cyclophanes in $CDCl_3$. The shifts seen in molecular tweezers **1** and **7** reflect the enforced proximity of the acridine rings.

The magnitude of the shifts appears to be largely independent of the type and position of substitution, suggesting that **7a–7e** adopt similar conformations. The signals of the protons and substituents on the long axis of the acridine rings in **7a–7e** are shifted upfield by only 0.12–0.34 ppm relative to those of their tetralone precursors, **4**. The upfield shifts of the protons on the short axis are all less than 0.16 ppm. The magnitude of these upfield shifts is slightly larger than those seen in rigid naphthalenophanes, but remarkably less than those seen in the corresponding "floppy" naphthalenophanes.[11c,19] These data support the idea that the dibenz[*c,h*]acridine spacer effectively isolates the attached acridine

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(17) Carter, R. E.; Liljefors, T. *Tetrahedron* **1976**, *32*, 2915–2922.

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(19) Whitlock, B. J.; Jarvi, E. T.; Whitlock, H. W., Jr. *J. Org. Chem.* **1981**, *46*, 1832–1835. Adams, S. P.; Whitlock, H. W., Jr. *Ibid.* **1981**, *46*, 3474–3478. Adams, S. P.; Whitlock, H. W., Jr. *J. Am. Chem. Soc.* **1982**, *104*, 1602–1611.

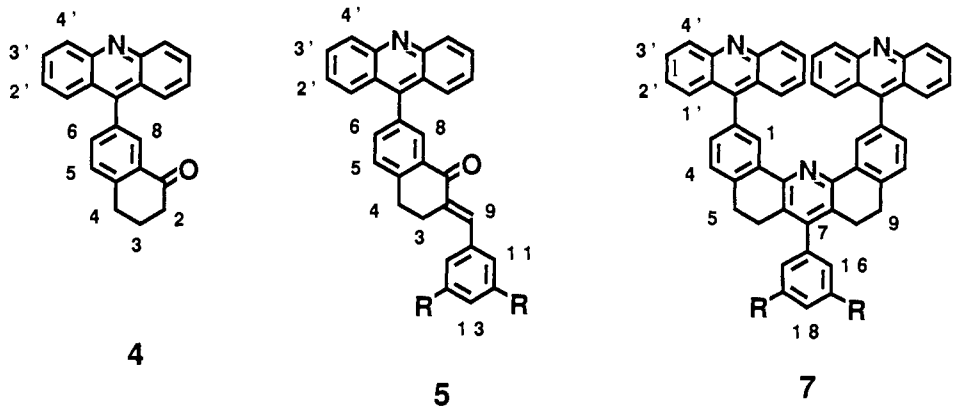


Figure 2. Numbering scheme for tetralone **4**, benzylidene **5**, and molecular tweezer **7** (**1**).

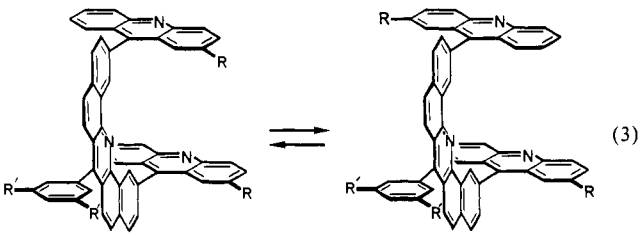
Table II. ^{1}H NMR Shifts of Acridine Moieties in Molecular Tweezers Relative to That of Model Acridines[a]

compd	model	H-1'	H-2'	H-3'	H-4'	H-5'	H-6'	H-7'	H-8'	substituent
9	**4b**	−0.22	−0.02	−0.01	−0.04					
10	**4b**	−0.13		0.00	0.00	−0.01	−0.01	0.00	0.22	−0.02 (2-*t*Bu)
7a	**4a**	−0.10	−0.28	0.16	0.10					
7b	**4b**				0.10	0.10		0.29	−0.11	0.34 (2-*t*Bu)
7c	**4c**			0.17	0.15	0.13				0.26 (2-*t*Bu)
										0.09 (6-*t*Bu)
7d	**4d**	−0.12	0.12	0.14	0.08		0.21	0.34	0.03	0.03 (5-OMe)
7e	**4e**	−0.12		0.14	0.08		0.16	0.29	−0.09	0.03 (5-OMe)
										0.26 (2-OMe)
1b	**4b**			0.14	0.09	0.09		0.13		0.27 (2-*t*Bu)

[a] $\Delta\delta$, ppm in $CDCl_3$. Positive values represent upfield shifts. Upfield shifts for the atropisomers of **1** and **7** were averaged. T = 293 K.

chromophores and that molecular tweezers **1** and **7** possess open clefts.

Atropisomerism of Molecular Tweezers. The ^{1}H NMR spectra of unsymmetrically substituted molecular tweezers exhibited doubling of some of the resonances, indicating a ca. 1:1 mixture of atropisomers (eq 3). It was of interest to determine the barrier



(3)

to interconversion of the atropisomers as a function of the size and position of the substituent. It has been shown that the energetics of a related process with cyclophanes can be used to provide information about the size and rigidity of the cavity.[20]

The *tert*-butyl-substituted molecular tweezers were particularly well-suited for variable-temperature ^{1}H NMR studies since the resonances due to the *tert*-butyl substituent in the two atropisomers were well resolved, and their coalescence could be easily monitored as a function of temperature. In the case of **1c** and **7c**, coalescence of both *tert*-butyl substituents could be observed, providing an internal check. Variable-temperature ^{1}H NMR studies were carried out in the normal fashion, and free energies of activation were determined with $\Delta G^{\ddagger}_c = 4.57T_c[9.97 + \log (T_c/\Delta\nu)]$. The data are tabulated in Table III.

The rotational barriers may result from contact between the acridine chromophores and the spacer unit [H-1'(H-8') and H-1(H-3)], contact between acridine rings, or a combination of both. If contact between the acridine rings is a factor then one would expect the barrier to increase as the spacer is rigidified (i.e., **7** → **1**) since the time-averaged distance between the acridine rings is decreased. Space-filling models suggest that an unsubstituted acridine chromophore, coplanar with the spacer, will come close

Table III. Atropisomerism of Molecular Tweezers[a]

compd	group	$\Delta\nu$, Hz	temp, °C[b]	T_c, K	$\Delta G^{\ddagger}_c$, kcal mol^{-1}
7b	2-tBu	22.3	21	366	18.7
1b	2-tBu	16.4	24	363	18.8
7c	2-tBu	25.5	24	413	21.1
	6-tBu	6.6	24	393	21.1
1c	2-tBu	4.7	21	404	22.0
	6-tBu	22.4	21	425	22.4
7g	7-tBu	7.3	21	387	20.7
1g	7-tBu	3.3	21	398	21.9

[a] Duplicate runs gave results within 10%. [b] Temperature at which $\Delta\nu$ was measured.

to but not quite contact the second acridine ring. This is consistent with the experimental findings as $\Delta G^{\ddagger}_c$ is nearly the same for **1b** and **7b** (Table III). With the knowledge that the "length" of an acridine ring is ca. 11 Å (CPK models) and the "width" is 3.4 Å, a minimum interchromophore distance of 7.2 Å can be calculated.

It is remarkable how close the $\Delta G^{\ddagger}_c$ values are for all the molecular tweezers in Table III. While interconversion of the atropisomers in **1b** can be achieved by rotation of the unsubstituted side of the acridine chromophore through the cleft, a bulky *tert*-butyl or chlorine substituent must pass through the cavity in **1c** and **1g**. CPK models suggest that, with minor deformations of the spacer, the 6-*tert*-butyl group in **1c** can skirt the outside edge of the second acridine ring to readily interconvert atropisomers. However, in **1g** it appears that either the *tert*-butyl or the chlorine substituent will experience large steric interactions during the rotation of the acridine ring, and our prediction was that interconversion of meso and *d,l* isomers would be slowed substantially. Contrary to this expectation, $\Delta G^{\ddagger}_c$ is only 21.9 kcal mol^{-1}.

The results suggest that CPK models are too rigid to accurately reflect the steric constraints to atropisomer interconversion. Deformations in the spacer allow passage of large substituents through the cavity with little cost in energy and the barrier to rotation results almost exclusively from nonbonded interactions between H-1'(H-8') and H-1(H-3). As such, simple substitution on the acridines is unlikely to allow for separation of atropisomers.

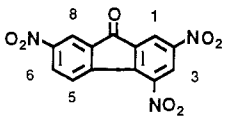
(20) Cf.: Whitlock, B. J.; Whitlock, H. W., Jr. *J. Am. Chem. Soc.* **1985**, *107*, 1325–1329.

Table IV. Association Constants and $\Delta\delta_{max}$ Values Obtained from the ^{1}H NMR Complexation Data of 2,4,7-Trinitrofluorenone by Molecular Tweezers and Related Acridines[a]

entry	compd	solvent	guest	$\Delta\delta_{max}$,[b] ppm H-1	H-3	H-5	H-6	H-8	K_{assoc},[c] M^{-1}
1	**9**	$CDCl_3$	TNF						<5
2	**11**								<5
3	**7b**			1.58	0.75	*d*	0.48	*d*	149
4	**1b**			*d*	0.69	0.40	0.43	1.56	197
5	**10**								<5
6	**4e**	$CDCl_3$							<5
7	**7b**			1.58	0.75	*d*	0.48	*d*	149
8	**7d**			1.79	0.59	0.41	0.53	1.76	320
9	**7e**			1.70	0.52	0.36	0.47	1.53	475
10	**7f**			*d*	0.70	0.41	0.49	*d*	697
11	**7b**	$CDCl_3$		1.58	0.75	*d*	0.48	*d*	149
12	**7b**	THF-d_8		1.30	0.63	*d*	*d*	*d*	28
13	**7b**	$C_4D_8O_2$		1.29	0.53	*d*	0.35	1.24	47
14	**7b**	$CDCl_3$	TNF	1.58	0.75	*d*	0.48	*d*	149
15	**7b**		DNF[e]	1.46	0.87	*d*			52
16	**7b**		TNF	1.58	0.75	*d*	0.48	*d*	149
17	**8**			1.44	0.59	0.38	0.46	1.38	358
18	**7e**			1.70	0.52	0.36	0.47	1.53	475

[a] [TNF] ≈ 5 × 10^{-4} M, [host] ≈ (5–30) × 10^{-3} M. Data between 10% and 80% of saturation were used. T = 293 K. [b] For protons of TNF. All duplicate runs agreed within 6% (most within 4%) and were averaged. [c] Duplicate runs agreed within 15% and were averaged as were binding constants obtained from analysis of the individual resonances. [d] Peaks became obscured during the titration. [e] DNF: 2,7-dinitrofluorenone.

Complexation of Neutral Organic Guests in Organic Solvents. Molecular tweezer **7b** is highly soluble in aprotic solvents (e.g. CH_2Cl_2, $CHCl_3$, THF, dioxane, EtOAc) and it was used for several series of experiments. The remaining molecular tweezers possessed high solubility in halogenated solvents and only slightly lower solubility in other solvents. The complexation studies were best monitored by ^{1}H NMR, and the results of several studies using 2,4,7-trinitrofluorenone (TNF) are compiled in Table IV.



TNF

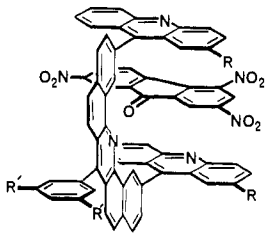
In our earlier work association constants were determined by the Hildebrand–Benesi analysis.[6] In order to avoid the approximations inherent in this method,[21] we have reanalyzed the titration data for **7b** and **1b** and analyzed the present data by using a nonlinear least-squares curve-fitting procedure similar to that described by Wilcox and Cowart.[22]

Comparison of the first four entries in Table IV reveals that the dibenz[*c*,*h*]acridine spacer unit is an essential, but not a sufficient criterion, for obtaining a high affinity for TNF. Thus, monoacridine **9** and 9-phenylacridine (**11**) induce very small upfield shifts (<0.10 ppm) in TNF, even at very high concentrations (>0.05 M), and similar shifts are seen in all the protons of TNF. A plot of $\Delta\delta$ vs [host] in these cases shows little or no curvature, suggesting that only a small degree of saturation has been achieved. As such, a binding constant is difficult to measure, but K_{assoc} = 5 M^{-1} could be readily seen under these conditions, and therefore it serves as a conservative upper limit. The more electron rich π-system of carbazole is known to complex TNF with an association constant of 6.5 M^{-1}.[23]

In contrast to these results, molecular tweezer **7b** induces very large upfield shifts in TNF which level off, indicating saturation (Table IV). This is reflected in the association constants, where **7b** binds TNF (K_{assoc} = 149 M^{-1}) at least 30 times more tightly than 9-phenylacridine (**11**) or **9** (K_{assoc} < 5 M^{-1}). This large increase in binding affinity argues for an inclusion complex, with TNF "sandwiched" between the acridine rings of **7b**. The dibenz[*c*,*h*]acridine spacer is responsible for the increase in binding affinity in so far as it maintains a relative orientation of the *two* acridine moieties which is well disposed for "sandwiching" the guest. In this respect the more rigid, fully unsaturated dibenz[*c*,*h*]acridine spacer appears to be most effective since **1b** binds TNF 1.3 times more strongly than does **7b**.

In order to address the question of preorganization, flexible diacridine **10** was studied and found to complex TNF with an association constant K_{assoc} < 5 M^{-1} (Table IV, entry 5). Diacridine **10**, like molecular tweezer **7b**, is capable of presenting two acridine surfaces to the guest molecule. The low association constant does not result from self-association of the acridine rings since the ^{1}H NMR reveals an unstacked conformation. Thus, the increase in complexation efficiency seen with the molecular tweezers arises primarily from preorganization.

The upfield shifts of TNF bound to molecular tweezers **7b–f** ($\Delta\delta_{max}$ values for entries 7–10, Table IV) indicate the degree to which the complex is oriented. The trends in $\Delta\delta_{max}$ values (H-1 > H-8 > H-3 > H-6 > H-5) are the same for each molecular tweezer, with the $\Delta\delta_{max}$ values of H-1 and H-8 of TNF consistently 2–3 times larger than those seen for H-3, H-5, and H-6. This is independent of the type and position of substitution. These data argue for a tightly oriented inclusion complex, with the carbonyl of TNF directed inward but toward one side of the spacer, as shown in **12**.



12

More precise structural features are less certain. With the proviso that some protons may be more susceptible to anisotropic shielding than others, the observation that $\Delta\delta_{max}$ for H-3 is greater than $\Delta\delta_{max}$ for H-5 and H-6 suggests that the fused ring of TNF bearing two nitro groups is bound further into the cleft than the ring carrying one nitro group. This is perhaps somewhat surprising since the 4-nitro substituent is known to be twisted 32.7° from planarity and might be thought to sterically resist inclusion.[24] J'

(21) Bergeron, R. J.; Roberts, W. P. *Anal. Biochem.* **1978**, *90*, 844–848. We thank a referee for pointing out our failure to meet the Hildebrand–Benesi boundary conditions.

(22) Reference 11f. We thank Professor Craig S. Wilcox for his encouragement and assistance in our use of this method.

(23) Tazuke, S.; Nagahara, H.; Matsuyama, Y. *Makromol. Chem.* **1980**, *181*, 2199–2206.

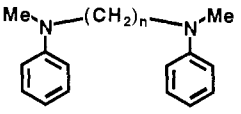
(24) Dorset, D. L.; Hyby, A.; Ammon, H. L. *Acta Crystallogr., Sect. B: Struct. Sci.* **1972**, 3122–3127.

is apparent that the 2,7-dinitrofluorenone (DNF) chromophore is bound further into the cleft (Table IV).

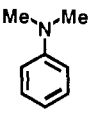
It is clear from entries 7–10 (Table IV) that EDA interactions[1] contribute substantially to the strength of complexation. As the π-basicity of the acridine chromophore is increased (**7b** → **7f**) the association constant increases by nearly 5-fold. The solvent effect (entries 11–13) is consistent with this picture. Good donor solvents like THF-d_8 and dioxane-d_8 solvate TNF better than $CDCl_3$ does, and therefore they compete more effectively with molecular tweezer **7b**. These solvents may also fit into the molecular tweezer cleft better than $CDCl_3$. This improved solvation of host and guest results in a 3–5-fold decrease in the association constants. Further support for the importance of EDA interactions comes from the observation that the poorer electron acceptor, DNF, binds to **7b** with an association constant, 52 M^{-1}, one third of that seen with TNF (entries 14–15). The dimethoxyacridine **4e**, in spite of its increased donor potential, still bound TNF too weakly to obtain an association constant. Therefore, molecular tweezer **7e** binds TNF (K_{assoc} = 475 M^{-1}) a minimum of 95 times tighter than does **4e** (K_{assoc} < 5 M^{-1}).

One remaining question concerns the cooperativity of the two acridine chromophores in the EDA complexation. Clearly, the two good donors in **7e** (K_{assoc} = 475 M^{-1}) are superior to the two poor donors in **7b** (K_{assoc} = 149 M^{-1}), but it is not certain whether the contribution of the two chromophores is additive or multiplicative or whether one dimethoxyacridine ring is solely responsible for the increase in the association constant. Unsymmetrical molecular tweezer **8** was synthesized to answer this question.

As seen in entries 16–18, the affinity of **8** for TNF, K_{assoc} = 358 M^{-1}, is between that of **7b** and **7e**. The ratio K_{assoc}(**7e**)/K_{assoc}(**7b**) = 3.2 is less than twice the ratio K_{assoc}(**8**)/K_{assoc}(**7b**) = 2.4, suggesting that the effect of simultaneous donors is close to but somewhat less than additive. Although this is only one data point, the result is consistent with work in the literature. Foster has shown that bis-donors such as **13** complex 1,3,5-trinitrobenzene with association constants twice that of the corresponding mono-donors (e.g. **14**), indicating a statistical dependence on the number of donors.[25]



13: n = 2-6



14

Conclusions

A new class of nonmacrocyclic receptors has been synthesized and shown to efficiently complex TNF in organic solvents. The dibenz[*c*,*h*]acridine spacer has been shown to be a particularly useful component as a result of its ability to (1) prevent self-association of the acridine rings, (2) maintain a ca. 7-Å interchromophore distance, and (3) effectively enforce a syn cofacial arrangement of the two attached acridine chromophores. The binding cleft of these molecular tweezers has a dramatically increased affinity for TNF relative to that of monoacridines and a flexible diacridine (**10**). This is the case even when the former (e.g. **4e**) is much more π-basic than the molecular tweezer (e.g. **7b**). These results are consistent with the principle of preorganization.[10] Molecular tweezer **1** (**7**) and TNF solvate each other effectively and are structurally well organized to do so. In contrast, diacridine **10** is not well organized for complexation and monoacridines can solvate the TNF with only a single aromatic surface.

Electron donor–acceptor interactions are an important driving force for the complexation by molecular tweezers **1** and **7**. This is evidenced by a 5-fold increase in the association constant for TNF shown by good donor hosts relative to weak donor hosts. Comparison of entry 10 and 15 in Table IV shows that varying the electronic properties of both the host and guest can easily result in a 1 order of magnitude change in the association constant. Ferguson and Diederich, and Dougherty et al. have seen similar trends in association constants by using guests of differing π-basicities.[8a–c] Other investigators have also invoked EDA interactions as contributors to host–guest complex stability.[26]

We have reported the first example where the donor potential of two components of the host have been changed independently. It was found that increasing the donor potential of both acridines (**7b** → **7e**) raises the K_{assoc} slightly less than twice the increase in K_{assoc} observed when the π-basicity of a single acridine is increased (**7b** → **8**). Although this is a single data point, the result suggests that in designing new synthetic receptors efforts to increase the number of donor groups will result in only modest increases in complexation efficiency. Our current efforts are directed toward electron deficient molecular tweezers and molecular tweezers which contain one good *donor* chromophore and one good *acceptor* chromophore. These will give new host–guest complexes with structures ADA and AAD (ADD), respectively, with the latter arrangement expected to be less favorable in the ground state.

Experimental Section

General Procedures. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl prior to use. Ethylene glycol was dried over magnesium sulfate, refluxed with sodium, and then distilled. Methanol was distilled from magnesium methoxide under nitrogen and stored over 3-Å molecular sieves. 9-Acridone was purchased from Fluka and 4-methoxyacridone from Aldrich Chemical Co. Other acridones were prepared from their diphenylamine carboxylic acids (prepared by Ullmann reaction) by cyclization with polyphosphoric acid (for tetralones **4d** and **4e**) or cyclization with phosphorus oxychloride followed by hydrolysis with hydrochloric acid.[27] Chloroform-*d* used in binding studies was distilled from CaH_2. All other solvents and reagents were of reagent-grade quality and used without further purification. Analytical TLC was performed on 0.2-mm silica 60 coated plastic sheets (EM Science) with F-254 indicator. Flash chromatography was performed on Merck 40–63 μm silica gel as described by Still.[28] Melting points were measured on a Thomas-Hoover melting point apparatus and are uncorrected.

^{1}H NMR and ^{13}C NMR spectra were recorded on a General Electric QE-300 spectrometer. ^{1}H NMR spectra for binding studies were recorded on a General Electric GN-500 spectrometer with a high-sensitivity probe. All spectra were run in chloroform-*d* unless stated otherwise. Chemical shifts are reported in parts per million (ppm) with TMS as an internal reference, and coupling constants are reported in hertz (Hz). Those resonances which are doubled in the spectra of molecular tweezers due to atropisomerism are denoted by an asterisk (*). Chemical shifts in ^{1}H NMR spectra obtained in the binding studies were referenced to the residual protio-solvent peak. Mass spectra were obtained on a Varian MAT CH-5 and 731 spectrometers. Elemental analyses were performed at the University of Illinois School of Chemical Sciences.

Attempted crystallizations of the molecular tweezers from a wide range of solvents produced only amorphous powders and glasses, which appeared (^{1}H NMR) to retain solvent. Molecular tweezers obtained from solutions of methylene chloride consistently analyzed ca. 1–2% low in C, which we attribute to trapped methylene chloride. Thus, after heating at ca. 90 °C in vacuo for 12 h, elemental analysis shows the molecular tweezers to contain between 1–5% Cl. The molecular tweezers were chromatographically homogeneous and judged to be >95% pure by ^{1}H NMR.

7-Bromo-1,2,3,4-tetrahydronaphthalene-1-spiro-2'-(1',3'-dioxacyclopentane) (3). To a stirred solution of 4 g (17.8 mmol) of 7-bromo-1-tetralone[12] in 360 mL of toluene was added 64 mL of ethylene glycol and 400 mg of *p*-toluenesulfonic acid. The two-phase system was heated to a vigorous reflux under a drying tube with azeotropic distillation of water (Dean–Stark). After 12 h the mixture was cooled and partitioned between 600 mL of ether and 500 mL of saturated aqueous sodium bicarbonate solution. The organic layer was washed with 500 mL of

(25) Emslie, P. H.; Foster, R.; Horman, J. W. M.; Twiselton, D. R. *J. Chem. Soc. B* **1969**, 1161. Foster, R.; Payne, H. A. S. *Recl. Trav. Chim. Pays-Bas* **1971**, *90*, 630–632. See also: Foster, R.; Fyfe, C. A. *Ibid.* **1971**, *90*, 674–679.

(26) Representative examples: Colquhoun, H. M.; Goodings, E. P.; Maud, J. N.; Stoddart, J. F.; Wolstenholme, J. B.; Williams, D. J. *J. Chem. Soc., Perkin Trans. 2* **1985**, 607–624. Rebek, J., Jr. *J. Am. Chem. Soc.* **1985**, *107*, 6738–6739. Pirkle, W. H.; Pochapsky, T. C. *J. Am. Chem. Soc.* **1986**, *108*, 5627–5628.

(27) Albert, A. *The Acridines*; Arnold: London, 1966; Chapters 2 and 3. *The Acridines*, 2nd ed.; Acheson, R. M., Ed.; The Chemistry of Heterocyclic Compounds, Wiley: New York, 1973; Chapter 3.

(28) Still, W. C.; Kahn, M.; Mitra, A. J. *J. Org. Chem.* **1978**, *43*, 2923–2925.

saturated aqueous sodium bicarbonate solution, dried over magnesium sulfate, and filtered, and the solvent was removed at reduced pressure. The residue was flash chromatographed (5% EtOAc–petroleum ether) on a 60 mm o.d. column to afford 4.38 g (92%) of **3** as a waxy solid: mp 58–60 °C; ^{1}H NMR δ 7.60 (d, $J_{6,8}$ = 2.1, 1 H, H-8), 7.33 (dd, $J_{5,6}$ = 8.3, $J_{6,8}$ = 2.1, 1 H, H-6), 6.97 (d, $J_{5,6}$ = 8.3, 1 H, H-5), 4.24–4.08 (m, 4 H, OCH_2CH_2O), 2.73 (m, 2 H, H-4), 1.94 (m, 4 H, H-2, H-3); ^{13}C NMR δ 139.34, 137.32, 131.43, 130.27, 129.16, 119.61, 106.58, 65.13, 33.28, 28.48, 20.46. Anal. Calcd for $C_{12}H_{13}O_2Br$: C, 53.55; H, 4.87. Found: C, 53.75; H, 5.00.

7-(9-Acridinyl)-1-oxo-1,2,3,4-tetrahydronaphthalene (4a). Representative Procedure for Preparation of Acridinyl Tetralones. To a solution of 907 mg (3.37 mmol) of bromide **3** in 50 mL of THF under a dry nitrogen atmosphere and cooled to ca. −70 °C in an acetone–dry ice bath was added dropwise 4.4 mL (7.41 mmol) of *tert*-butyllithium in hexane solution. The homogeneous, yellow solution was stirred at −70 °C for 1 h. In a second flask, 2.56 mL (3.71 mmol) of *n*-butyllithium was added dropwise to a slurry of 658 mg (3.37 mmol) of 9-acridone in 50 mL of THF under a dry nitrogen atmosphere and cooled to ca. −70 °C in an acetone–dry ice bath. After 30 min the flask was warmed to room temperature. After stirring of the red-orange solution for 30 min, it was cooled to ca. −70 °C and the aryllithium solution was added dropwise with a cannula. After 15 min the cooling bath was removed, and the dark red solution was stirred for 7 h. The reaction mixture was quenched with 10 mL of 2 N HCl solution and 10 mL of acetone was added. After stirring of the mixture for 1 h, the majority of the THF was removed under reduced pressure, and the remaining material was partitioned between 150 mL of water and 150 mL of CH_2Cl_2. The aqueous layer was basicified with 2 N KOH. The aqueous layer was washed with 100 mL of CH_2Cl_2, and the combined organic layers were dried over magnesium sulfate and filtered, and the solvent was removed under reduced pressure. The pale yellow solid was purified by flash chromatography (30% ethyl acetate–petroleum ether) to afford 545 mg (50%) of **4a** as a pale yellow solid: mp 196–198 °C; ^{1}H NMR δ 8.28 (d, $J_{3',4'}$ = 8.8, 2 H, H-4'), 8.16 (d, $J_{6,8}$ = 1.0, 1 H, H-8), 7.78 (m, 2 H, H-3'), 7.66 (d, $J_{1',2'}$ = 8.7, 2 H, H-1'), 7.53 (m, 2 H, H-5, H-6), 7.43 (m, 2 H, H-2'), 3.16 (t, $J_{3,4}$ = 6.0, 2 H, H-4), 2.78 (t, $J_{2,3}$ = 6.0, 2 H, H-2), 2.29 (m, 2 H, H-3); MS, *m/e* (FD) 323 (M$^+$, 100); *m/e* calcd for $C_{23}H_{17}NO$ 323.13101, measured 323.13135.

7-(2-*tert*-Butylacridin-9-yl)-1-oxo-1,2,3,4-tetrahydronaphthalene (4b). Flash chromatography (30% ethyl acetate–petroleum ether) of the crude residue afforded 1.01 gm (67%) of **4b** as a pale yellow solid: mp 188–189 °C; ^{1}H NMR δ 8.26 (d, $J_{5',6'}$ = 8.9, 1 H, H-5'), 8.22 (d, $J_{3',4'}$ = 9.3, 1 H, H-4'), 8.16 (d, $J_{6,8}$ = 1.2, 1 H, H-8), 7.89 (dd, $J_{3',4'}$ = 9.3, $J_{1',3'}$ = 1.7, 1 H, H-3'), 7.74 (m, 1 H, H-6'), 7.62 (d, $J_{7',8'}$ = 8.6, 1 H, H-8'), 7.55 (d, $J_{1',3'}$ = 1.7, 1 H, H-1'), 7.52 (m, 2 H, H-5, H-6), 7.40 (m, 1 H, H-7'), 3.18 (m, 2 H, H-4), 2.79 (t, $J_{2,3}$ = 6.8, 2 H, H-2), 2.30 (m, 2 H, H-3), 1.31 (s, 9 H, tBu); MS, *m/e* (70 eV, EI) 379 (M$^+$, 100), 364 (85). Anal. Calcd for $C_{27}H_{25}NO$: C, 85.50; H, 6.66; N, 3.69. Found: C, 85.20; H, 6.72; N, 3.65.

7-(2,6-Di-*tert*-butylacridin-9-yl)-1-oxo-1,2,3,4-tetrahydronaphthalene (4c). Flash chromatography (10% EtOAc–petroleum ether) of the crude residue afforded 720 mg (51%) of product **4c** as a yellow solid: mp 193–195 °C; ^{1}H NMR δ 8.22 (d, $J_{3',4'}$ = 9.3, 1 H, H-4'), 8.20 (s, 1 H, H-5'), 8.17 (d, $J_{6,8}$ = 1.3, H-8), 7.88 (dd, $J_{3',4'}$ = 9.3, $J_{1',3'}$ = 2.0, 1 H, H-3'), 7.59–7.48 (m, 5 H, H-1', H-5, H-6, H-7', H-8'), 3.17 (m, 2 H, H-4), 2.78 (m, 2 H, H-2), 2.29 (m, 2 H, H-3), 1.45 (s, 9 H, 6'-tBu), 1.31 (s, 9 H, 2'-tBu); MS, *m/e* (70 eV, EI) 435 (M$^+$, 100), 420 (78); *m/e* calcd for $C_{31}H_{33}NO$ 435.25620, measured 435.25663.

7-(4-Methoxyacridin-9-yl)-1-oxo-1,2,3,4-tetrahydronaphthalene (4d). Flash chromatography (30% EtOAc–petroleum ether) of the crude residue afforded 290 mg (55%) of **4d** as an orange solid: mp 109–112 °C dec; ^{1}H NMR δ 8.44 (d, $J_{5',6'}$ = 8.8, 1 H, H-5'), 8.14 (s, 1 H, H-8), 7.76 (dd, $J_{5',6'}$ = 8.8, $J_{6',7'}$ = 7.7, 1 H, H-6'), 7.62 (d, $J_{7',8'}$ = 8.6, 1 H, H-8'), 7.56 (dd, $J_{5,6}$ = 8.0, $J_{6,8}$ = 1.0, 1 H, H-6), 7.50 (d, $J_{5,6}$ = 8.0, 1 H, H-5), 7.43 (dd, $J_{6',7'}$ = 7.7, $J_{7',8'}$ = 8.6, 1 H, H-7'), 7.32 (m, 1 H, H-2'), 7.20 (d, $J_{1',2'}$ = 8.7, 1 H, H-1'), 7.04 (d, $J_{2',3'}$ = 7.3, 1 H, H-3'), 4.19 (s, 3 H, OMe), 3.15 (t, $J_{3,4}$ = 6.0, 2 H, H-4), 2.78 (t, $J_{2,3}$ = 6.5, 2 H, H-2), 2.29 (m, 2 H, H-3); MS, *m/e* (70 eV, EI) 353 (M$^+$, 100), 324 (57); *m/e* calcd for $C_{24}H_{19}NO_2$ 353.14156, measured 353.14055.

7-(2,5-Dimethoxyacridin-9-yl)-1-oxo-1,2,3,4-tetrahydronaphthalene (4e). Flash chromatography (10% acetone–petroleum ether) of the crude residue afforded a mixture **4e** and *n*-butyl adduct. Rechromatography (15% EtOAc–CH_2Cl_2) afforded 713 mg (50%) of **4e** as an amber, glassy foam: mp 105–107 °C dec; ^{1}H NMR δ 8.33 (d, $J_{3',4'}$ = 9.5, 1 H, H-4'), 8.14 (d, $J_{6,8}$ = 1.6, 1 H, H-8), 7.55 (dd, $J_{5,6}$ = 7.8, $J_{6,8}$ = 1.6, 1 H, H-6), 7.49 (d, $J_{5,6}$ = 7.8, 1 H, H-5), 7.44 (dd, $J_{3',4'}$ = 9.5, $J_{1',3'}$ = 2.7, 1 H, H-3'), 7.29 (dd, $J_{7',8'}$ = 8.6, $J_{6',7'}$ = 7.6, 1 H, H-7'), 7.11 (d, $J_{7',8'}$ = 8.6, 1 H, H-8'), 6.97 (d, $J_{6',7'}$ = 7.6, 1 H, H-6'), 6.74 (d, $J_{1',3'}$ = 2.7, 1 H, H-1), 4.17 (s, 3 H, 5-OMe), 3.73 (s, 3 H, 2-OMe), 3.15 (t, $J_{3,4}$ = 6.0, 2 H, H-4), 2.77 (t, $J_{2,3}$ = 7.0, 2 H, H-2), 2.29 (m, 2 H, H-3); MS, *m/e* (70 eV, EI) 383 (M$^+$, 100), 354 (53); *m/e* calcd for $C_{25}H_{21}NO_3$ 383.15213, measured 383.15148.

7-[2-(Dimethylamino)acridin-9-yl]-1-oxo-1,2,3,4-tetrahydronaphthalene (4f). Flash chromatography of the crude residue (gradient from CH_2Cl_2 to 2% MeOH–CH_2Cl_2) afforded 828 mg (30%) of **4f** as a red brown foam, which was >95% pure as judged by its ^{1}H NMR spectrum: ^{1}H NMR δ 8.22–8.15 (m, 3 H, H-4', H-5', H-8), 7.65–7.48 (m, 5 H, H-5, H-6, H-6', H-7', H-8'), 7.34 (m, 1 H, H-3'), 6.47 (d, $J_{1',3'}$ = 2.6, 1 H, H-1'), 3.16 (m, 2 H, H-4), 2.96 (s, 6 H, NMe_2), 2.78 (m, 2 H, H-2), 2.30 (m, 2 H, H-3); MS, *m/e* (70 eV, EI) 366 (M$^+$, 100), 278 (71), 235 (86); *m/e* calcd for $C_{25}H_{22}N_2O$ 366.17320, measured 366.17354.

7-(4-Chloro-7-*tert*-butylacridin-9-yl)-1-oxo-1,2,3,4-tetrahydronaphthalene (4g). Flash chromatography (30% ethyl acetate–petroleum ether) of the crude residue afforded 168 mg (11%) of **4g** as a light yellow crystalline solid: mp 205–207 °C; ^{1}H NMR δ 8.20 (d, $J_{5',6'}$ = 9.3, 1 H, H-5'), 8.18 (d, $J_{3',4'}$ = 9.3, 1 H, H-4'), 8.12 (s, 1 H, H-8), 7.89 (dd, $J_{3',4'}$ = 9.3, $J_{1',3'}$ = 2.0, 1 H, H-3'), 7.66 (dd, $J_{5',6'}$ = 9.3, $J_{6',8'}$ = 2.3, 1 H, H-6'), 7.55 (d, $J_{6',8'}$ = 2.3, 1 H, H-8'), 7.53 (m, 2 H, H-5, H-6), 7.48 (d, $J_{1',3'}$ = 2.0, 1 H, H-1'), 3.18 (t, $J_{3,4}$ = 6.2, 2 H, H-4), 2.80 (t, $J_{2,3}$ = 7.0, 2 H, H-2), 2.32 (m, 2 H, H-3), 1.30 (s, 9 H, tBu); MS, *m/e* (70 eV, EI) 413 (M$^+$, 90), 398 (100); *m/e* calcd for $C_{27}H_{24}NOCl$ 413.15463, measured 413.15378.

2-(9-Acridinyl)-7-phenyl-5,6,8,9-tetrahydrodibenz[*c*,*h*]acridine (9). By the general procedure described for **4a** but starting with 2,12-dibromo-7-phenyl-5,6,8,9-tetrahydrodibenz[*c*,*h*]acridine and with 4 equiv of *tert*-butyllithium, a crude residue was obtained and purified by flash chromatography (50% Et_2O–petroleum ether) to afford 14.1 mg (25%) of **9** as an orange powder: mp 240 °C softened, 250–260 °C dec; ^{1}H NMR δ 8.67 (d, $J_{1,3}$ = 1.5, 1 H, H-1), 8.32 (d, $J_{3',4'}$ = 6.0, 2 H, H-4'), 8.31 (d, $J_{12,13}$ = 6.0, 1 H, H-13), 7.88 (d, $J_{1',2'}$ = 8.7, 2 H, H-1'), 7.79 (m, 2 H, H-3'), 7.6–7.1 (m, 10 H, H-19, H-18, H-17, H-12, H-11, H-10, H-4, H-3), 7.45 (m, 2 H, H-4'), 3.02 (m, 2 H, H-6), 2.80 (m, 4 H, H-8, H-5), 2.65 (m, 2 H, H-9); MS, *m/e* (70 eV, EI) 536 (M$^+$, 100); *m/e* calcd for $C_{40}H_{28}N_2$ 536.22524, measured 536.22328.

4,4'-(Butylenedioxy)-4,4'-bis(2-*tert*-butylacridin-9-yl)dibenzene (10). By the procedure described for **4a** but starting with 4,4'-(butylenedioxy)-4-dibromobenzene afforded 0.6 g (17%) of **10** as a white solid: mp 265–269 °C; ^{1}H NMR δ 8.25 (d, $J_{4',5'}$ = 9.0, 2 H, H-4'), 8.22 (d, $J_{2',3'}$ = 9.3, 2 H, H-3'), 7.89 (dd, $J_{2',3'}$ = 9.3, $J_{1',2'}$ = 2.0, 2 H, H-2'), 7.77 (d, $J_{6',7'}$ = 8.3, 2 H, H-7'), 7.73 (m, 2 H, H-5'), 7.68 (d, $J_{1',2'}$ = 2.0, 2 H, H-1'), 7.40 (m, 2 H, H-6'), 7.40 (d, $J_{2',3'}$ = 8.5, 4 H, H-3'), 7.18 (d, $J_{2',3'}$ = 8.5, 4 H, H-2'), 4.27 (m, 4 H, OCH_2), 2.20 (m, 4 H, CH_2CH_2), 1.33 (s, 9 H, 2-tBu); MS, *m/e* (FD) 708 (M$^+$, 100), (70 eV, EI) 708 (M$^+$, 2), 309 (25); *m/e* calcd for $C_{50}H_{48}N_2O_2$ 708.37156, measured 708.37096.

2-(3,5-Di-*tert*-butylbenzylidene)-7-(9-acridinyl)-1-oxo-1,2,3,4-tetrahydronaphthalene (5a). 3,5-Di-*tert*-butylbenzaldehyde (259 mg, 1.18 mmol) and 283 mg (0.88 mmol) of tetralone **4a** were combined in a 100-mL round-bottom flask, and 20 mL of 4% KOH–MeOH was added. The mixture was heated to 70 °C and stirred under a drying tube for 20 h. After cooling of the mixture to room temperature, it was poured into 50 mL of water and extracted into methylene chloride. The organic extract was dried over magnesium sulfate and filtered, and the solvent was removed at reduced pressure. The residue was flash chromatographed (30% EtOAc–petroleum ether) to afford 305 mg (66%) of **5a** as a yellow, crystalline solid: mp 248–250 °C dec; ^{1}H NMR δ 8.30 (d, $J_{3',4'}$ = 8.8, 2 H, H-4'), 8.25 (d, $J_{6,8}$ = 1.0, 1 H, H-8), 7.98 (s, 1 H, H-9), 7.78 (m, 2 H, H-3'), 7.70 (d, $J_{1',2'}$ = 8.6, 2 H, H-1'), 7.58 (dd, $J_{5,6}$ = 7.8, $J_{6,8}$ = 1.0, 1 H, H-6), 7.51 (d, $J_{5,6}$ = 7.8, 1 H, H-5), 7.47 (s, 1 H, H-13), 7.45 (m, 2 H, H-2'), 7.35 (s, 2 H, H-11), 3.33 (t, $J_{3,4}$ = 5.9, 2 H, H-3), 3.15 (t, $J_{3,4}$ = 5.9, 2 H, H-4), 1.38 (s, 18 H, tBu); MS, *m/e* (70 eV, EI) 523 (M$^+$, 21), 466 (100); *m/e* calcd for $C_{38}H_{37}NO$ 523.28750, measured 523.28856.

2-(3,5-Di-*tert*-butylbenzylidene)-7-(2-*tert*-butylacridin-9-yl)-1-oxo-1,2,3,4-tetrahydronaphthalene (5b). To a solution of sodium methoxide in methanol (300 mg of sodium–25 mL of methanol) were added 8.28 mg (3.8 mmol) of 3,5-di-*tert*-butylbenzaldehyde and 1.2 g (3.17 mmol) of tetralone **4b**. The reaction mixture was stirred for 2.5 h at 70–80 °C, cooled to room temperature, and poured into 200 mL of $CHCl_3$. The solution was washed with 150 mL of 1 N HCl and then with 150 mL of saturated aqueous sodium bicarbonate solution. The organic layer was dried over magnesium sulfate and filtered, and the solvent was removed in vacuo. The residue was flash chromatographed (20% EtOAc–petroleum ether) to afford 1.49 g (81%) of benzylidene **5b** as a yellow, glassy foam: mp 121–125 °C dec; ^{1}H NMR δ 8.28 (m, 2 H, H-4', H-5'), 8.23 (s, 1 H, H-8), 7.98 (s, 1 H, H-9), 7.90 (dd, $J_{3',4'}$ = 9.3, $J_{1',3'}$ = 1.9, 1 H, H-3'), 7.76 (m, 1 H, H-6'), 7.67 (d, $J_{7',8'}$ = 8.7, 1 H, H-8'), 7.58 (d, $J_{1',3'}$ = 1.2, 1 H, H-1'), 7.57 (d, $J_{5,6}$ = 8.0, 1 H, H-6), 7.52 (d, $J_{5,6}$ = 8.0, 1 H, H-5), 7.47 (d, $J_{11,13}$ = 1.0, 1 H, H-13), 7.42 (m, 1 H, H-7'), 7.35 (d, $J_{11,13}$ = 1.0, 2 H, H-11), 3.34 (m, 2 H, H-3), 3.16 (m, 2 H, H-4), 1.38

(s, 18 H, 12-tBu), 1.33 (s, 9 H, 2'-tBu); MS, *m/e* (70 eV, EI) 579 (M^+, 100), 520 (58); *m/e* calcd for $C_{42}H_{45}NO$ 579.35009, measured 579.34970.

2-(3,5-Dimethylbenzylidene)-7-(2,6-di-*tert*-butylacridin-9-yl)-1-oxo-1,2,3,4-tetrahydronaphthalene (5c). Using the procedure described for **5a** with a reaction time of 12 h afforded a crude residue which was flash chromatographed twice (10% acetone–CH_2Cl_2) to produce 240 mg (57%) of **5c** as a yellow solid: mp 145 °C dec; ^1H NMR δ 8.26 (d, $J_{6,8}$ = 1.0, 1 H, H-8), 8.22 (d, $J_{3',4'}$ = 9.0, 1 H, H-4'), 8.20 (s, 1 H, H-5'), 7.89 (s, 1 H, H-9), 7.89 (dd, $J_{3',4'}$ = 9.0, $J_{1',3'}$ = 2.0, 1 H, H-3'), 7.63–7.49 (m, 5 H, H-1', H-5, H-6, H-7', H-8'), 7.11 (s, 2 H, H-11), 7.04 (s, 1 H, H-13), 3.29 (m, 2 H, H-3), 3.14 (m, 2 H, H-4), 2.39 (s, 6 H, Me), 1.46 (s, 9 H, 6'-tBu), 1.32 (s, 9 H, 2'-tBu); MS, *m/e* (70 eV, EI) 551 (M^+, 100), 536 (58); *m/e* calcd for $C_{40}H_{41}NO$ 551.31881, measured 551.31889.

2-(3,5-Di-*tert*-butylbenzylidene)-7-(4-methoxyacridin-9-yl)-1-oxo-1,2,3,4-tetrahydronaphthalene (5d). 3,5-Di-*tert*-butylbenzaldehyde (400 mg, 1.84 mmol) and 500 mg (1.41 mmol) of tetralone **4d** were combined in a 25-mL round-bottom flask, and 7.5 mL of 4% KOH–MeOH was added. The mixture was heated to 75 °C and stirred under a drying tube for 45 min. An additional 5 mL of 4% KOH–MeOH was added and the mixture was stirred 2 h. The thick slurry was cooled to room temperature and a pale yellow powder was filtered off and washed with a minimum amount of methanol. Drying in vacuo afforded 481 mg (62%) of **5d** as a yellow powder: mp 210–214 °C dec; ^1H NMR δ 8.45 (d, $J_{5',6'}$ = 8.7, 1 H, H-5'), 8.23 (d, $J_{6,8}$ = 1.5, 1 H, H-8), 7.97 (s, 1 H, H-9), 7.76 (m, 1 H, H-6'), 7.67 (d, $J_{7',8'}$ = 8.6, 1 H, H-8'), 7.57 (dd, $J_{5,6}$ = 7.8, 1.5, $J_{6,8}$ = 1 H, H-6), 7.50 (d, $J_{5,6}$ = 7.8, 1 H, H-5), 7.47 (s, 1 H, H-13), 7.45 (m, 2 H, H-7', H-2'), 7.35 (s, 2 H, H-11), 7.25 (d, $J_{1',2'}$ = 9.0, 1 H, H-1'), 7.05 (d, $J_{2',3'}$ = 7.3, 1 H, H-3'), 4.20 (s, 3 H, OMe), 3.32 (m, 2 H, H-3), 3.14 (m, 2 H, H-4), 1.38 (s, 18 H, tBu); MS, *m/e* (70 eV, EI) 553 (M^+, 100), 353 (80), 324 (57); *m/e* calcd for $C_{39}H_{39}NO_2$ 553.29806, measured 553.29855.

2-(3,5-Di-*tert*-butylbenzylidene)-7-(2,5-dimethoxyacridin-9-yl)-1-oxo-1,2,3,4-tetrahydronaphthalene (5e). According to the same procedure as described for **5d**, 365 mg (60%) of **5e** was obtained as a tan solid: mp 165–175 °C dec; ^1H NMR δ 8.34 (d, $J_{3',4'}$ = 9.4, 1 H, H-4'), 8.25 (d, $J_{6,8}$ = 1.2, 1 H, H-8), 7.98 (s, 1 H, H-9), 7.57 (dd, $J_{5,6}$ = 7.8, $J_{6,8}$ = 1.4, 1 H, H-6), 7.50 (d, $J_{5,6}$ = 7.8, 1 H, H-5), 7.46 (s, 1 H, H-13), 7.45 (dd, $J_{3',4'}$ = 9.4, $J_{1',3'}$ = 2.6, 1 H, H-3'), 7.35 (s, 2 H, H-11), 7.29 (m, 1 H, H-7'), 7.16 (d, $J_{7',8'}$ = 8.7, 1 H, H-8'), 6.99 (d, $J_{6',7'}$ = 7.4, 1 H, H-6'), 6.80 (d, $J_{1',3'}$ = 2.6, 1 H, H-1'), 4.18 (s, 3 H, 5-OMe), 3.75 (s, 3 H, 2-OMe), 3.31 (m, 2 H, H-3), 3.14 (m, 2 H, H-4), 1.38 (s, 18 H, tBu); MS, *m/e* (70 eV, EI) 583 (M^+, 100), 554 (26); *m/e* calcd for $C_{40}H_{41}NO_3$ 583.30862, measured 583.30868.

2,12-Bis(9-acridinyl)-7-(3,5-di-*tert*-butylphenyl)-5,6,8,9-tetrahydrodibenz[*c*,*h*]acridine (7a). To a thoroughly pulverized mixture of 135 mg (0.42 mmol) of tetralone **4a** and 312 mg (0.60 mmol) of benzylidene **5b** was added 2 mL of 70% perchloric acid. The mixture was heated to 100 °C for 4 h. Absolute ethanol (5 mL) was cautiously added and the mixture was refluxed for 30 min. After cooling of the mixture to room temperature, the solvent was removed at reduced pressure, and the residue was treated with ammonia-saturated methanol until strongly basic. The brown solution was stirred overnight, and then the solution was concentrated by ca. 50% and filtered. The solid was purified by flash chromatography (10% MeOH–CH_2Cl_2) to afford 177 mg (50%) of **7a** as a tan powder: mp >280 °C; ^1H NMR δ 8.46 (d, $J_{1,3}$ = 1.3, 2 H, H-1), 8.18 (d, $J_{3',4'}$ = 8.7, 4 H, H-4'), 7.76 (d, $J_{1',2'}$ = 8.6, 4 H, H-1'), 7.62 (m, 4 H, H-3'), 7.52 (d, $J_{16,18}$ = 1.2, 1 H, H-18), 7.40 (d, $J_{3,4}$ = 7.6, 2 H, H-4), 7.30 (dd, $J_{3,4}$ = 7.6, $J_{1,3}$ = 1.3, 2 H, H-3), 7.15 (m, 4 H, H-2'), 7.12 (d, $J_{16,18}$ = 1.2, 2 H, H-16), 2.99 (m, 4 H, H-6), 2.86 (m, 4 H, H-5), 1.42 (s, 18 H, 17-tBu); MS, *m/e* (70 eV, EI) 825 (M^+, 100); *m/e* calcd for $C_{61}H_{51}N_3$ 825.40653, measured 825.40653.

7-(3,5-Di-*tert*-butylphenyl)-2,12-bis(2-*tert*-butylacridin-9-yl)-5,6,8,9-tetrahydrodibenz[*c*,*h*]acridine (7b). To a thoroughly pulverized mixture of 161 mg (0.42 mmol) of tetralone **4b** and 350 mg (0.60 mmol) of benzylidene **5b** was added 0.57 mL of 70% perchloric acid. The mixture was heated to 100 °C for 15 min and then to 135 °C for 3 h. Absolute ethanol (3 mL) was cautiously added and the mixture was refluxed for 5 min. After cooling of the mixture to room temperature, the solvent was removed at reduced pressure, and the residue was dissolved in 10 mL of CH_2Cl_2 to form a maroon, homogeneous solution. Ammonia-saturated methanol (20 mL) was added and the brown solution was stirred overnight. The solvent was removed at reduced pressure, and the residue was partitioned between 100 mL of water and 100 mL of $CHCl_3$. The aqueous layer was washed once with 30 mL of $CHCl_3$, and the combined organic layers were washed with saturated aqueous sodium bicarbonate solution, dried over magnesium sulfate, and filtered, and the solvent was removed at reduced pressure. The residue was flash chromatographed (50% EtOAc–CH_2Cl_2) to afford 224 mg (56%) of **7b** as a tan powder: mp 239–244 °C dec; ^1H NMR δ 8.48 (d, $J_{1,3}$ = 1.3, 2 H, H-1), 8.16 (m, 2 H, H-5'), 8.12 (m, 2 H, H-4'), 7.73 (d, $J_{7',8'}$ = 8.9, 2 H, H-8'), 7.70–7.55 (m, 6 H, H-1', H-3', H-6'), 7.52 (s, 1 H, H-18), 7.39 (d, $J_{3,4}$ = 7.5, 2 H, H-4), 7.31 (dd, $J_{3,4}$ = 7.5, $J_{1,3}$ = 1.3, 2 H, H-3), 7.18* (t, $J_{6',7'}$ = 8.2, $J_{7',8'}$ = 8.2, 2 H, H-7'), 7.14 (s, 2 H, H-16), 7.03* (t, $J_{6',7'}$ = 7.7, $J_{7',8'}$ = 7.7, 2 H, H-7'), 3.01 (m, 4 H, H-6), 2.89 (m, 4 H, H-5), 1.42 (s, 18 H, 17-tBu), 1.10* (s, 9 H, 2-tBu), 0.94* (s, 9 H, 2-tBu); MS, *m/e* (70 eV, EI) 937 (M^+, weak); *m/e* calcd for $C_{69}H_{67}N_3$ 937.53347, measured 937.53350.

7-(3,5-Dimethylphenyl)-2,12-bis(2,6-di-*tert*-butylacridin-9-yl)-5,6,8,9-tetrahydrodibenz[*c*,*h*]acridine (7c). Tetralone **4c** (63.8 mg, 0.15 mmol) and 113 mg (0.21 mmol) of benzylidene **5c** were combined in a 10-mL flask, and 360 μL of 70% perchloric acid was added. The mixture was heated at 90 °C under nitrogen for 2 h with occasional stirring. After cooling of the mixture slightly, 5 mL of ethanol was added and the resultant slurry was refluxed for 20 min. The mixture was cooled and the ethanol was removed at reduced pressure. The residue was stirred with 20 mL of CH_2Cl_2 and 20 mL of ammonia-saturated methanol overnight. The volume of solvent was reduced by ca. 50% and the solid was filtered off to afford 70 mg of a tan solid. Flash chromatography of this solid (10% EtOAc–petroleum ether) afforded 70 mg (50%) of **7c** as a cream-colored powder: mp >280 °C; ^1H NMR δ 8.43* (d, $J_{1,3}$ = 1.2, 1 H, H-1), 8.42* (d, $J_{1,3}$ = 1.4, 1 H, H-1), 8.07 (m, 2 H, H-4'), 8.07 (m, 2 H, H-5'), 7.7–7.2 (m, 10 H, H-1', H-3, H-4, H-7', H-8'), 7.71 (dd, $J_{3',4'}$ = 9.4, $J_{1',3'}$ = 1.6, 2 H, H-3'), 7.12 (s, 1 H, H-18), 6.90 (s, 2 H, H-16), 2.97 (m, 4 H, H-6), 2.81 (m, 4 H, H-5), 2.44 (s, 6 H, 17-Me), 1.38* (s, 9 H, 6-tBu), 1.34* (s, 9 H, 6-tBu), 1.11* (s, 9 H, 2-tBu), 0.98* (s, 9 H, 2-tBu); MS, *m/e* (70 eV, EI) 966 (M^+, weak); *m/e* calcd for $C_{71}H_{71}N_3$ 965.56476, measured 965.56720.

7-(3,5-Di-*tert*-butyldiphenyl)-2,12-bis(4-methoxyacridin-9-yl)-5,6,8,9-tetrahydrodibenz[*c*,*h*]acridine (7d). Tetralone **4d** (273 mg, 0.77 mmol) and 475 mg (0.86 mmol) of benzylidene **5d** were combined in a 5-mL flask, and 0.7 mL of 70% perchloric acid was added. The mixture was stirred at 70 °C under nitrogen for 4 h. After cooling of the mixture slightly, 2 mL of ethanol was added, forming a thick, orange slurry. The mixture was filtered and the orange powder was suspended in 20 mL of CH_2Cl_2 and 20 mL of ammonia-saturated methanol. After stirring of the mixture overnight, the volume of solvent was reduced by ca. 50%, and the solid was filtered off to afford 165 mg (24%) of **7d** as a pale orange solid: mp >280 °C; ^1H NMR δ 8.453* (s, 1 H, H-1), 8.452* (s, 1 H, H-1), 8.37* (d, $J_{5',6'}$ = 10.6, 1 H, H-5'), 8.35* (d, $J_{5',6'}$ = 9.5, 1 H, H-5'), 7.74 (m, 2 H, H-8'), 7.62 (m, 2 H, H-6'), 7.51 (s, 2 H, H-16), 7.38 (d, J = 6.5, 2 H, H-3), 7.31 (m, 2 H, H-4), 7.31 (m, 2 H, H-7'), 7.17 (m, 2 H, H-1'), 7.12 (d, $J_{16,18}$ = 1.2, 1 H, H-18), 6.98 (m, 2 H, H-2'), 6.83 (m, 2 H, H-3'), 4.17* (s, 3 H, OMe), 4.15* (s, 3 H, OMe), 2.98 (m, 4 H, H-6), 2.86 (m, 4 H, H-5), 1.41 (s, 18 H, 17-tBu); MS, *m/e* (FD) 886 (M + H, 100), (70 eV, EI) 885 (M^+, weak; *m/e* calcd for $C_{63}H_{55}N_3O_2$ 885.42940, measured 885.43176.

7-(3,5-Di-*tert*-butylphenyl)-2,12-bis(2,5-dimethoxyacridin-9-yl)-5,6,8,9-tetrahydrodibenz[*c*,*h*]acridine (7e). Tetralone **4e** (160.9 mg, 0.42 mmol) and 350 mg (0.60 mmol) of benzylidene **5e** were combined in a 5-mL flask, and 0.6 mL of 70% perchloric acid was added. The mixture was stirred at 70 °C under nitrogen for 4 h. After cooling of the mixture slightly, 2 mL of ethanol was added, forming a homogeneous, dark red solution. After further cooling to room temperature, 20 mL of CH_2Cl_2 and 20 mL of ammonia-saturated methanol were added, and the mixture was stirred for 3 h. The volume of the solvent was reduced by ca. 50%, and the mixture was filtered to afford 169 mg (43%) of **7e** as an orange-brown solid: mp >280 °C; ^1H NMR δ 8.48 (s, 2 H, H-1), 8.26* (d, $J_{3',4'}$ = 9.5, 1 H, H-4'), 8.23* (d, $J_{3',4'}$ = 9.2, 1 H, H-4'), 7.51 (d, $J_{16,18}$ = 1.3, 1 H, H-18), 7.39 (d, $J_{3,4}$ = 7.6, 2 H, H-3), 7.30 (m, 2 H, H-4), 7.30 (m, 2 H, H-3'), 7.20 (d, $J_{7',8'}$ = 9.3, 2 H, H-8'), 7.13 (d, $J_{16,18}$ = 1.3, 2 H, H-16), 7.03* (t, $J_{6',7'}$ = 8.0, $J_{7',8'}$ = 8.0, 1 H, H-7'), 6.96* (t, $J_{6',7'}$ = 8.0, $J_{7',8'}$ = 8.0, 1 H, H-7'), 6.87* (d, $J_{1',3'}$ = 2.5, 1 H, H-1'), 6.84* (d, $J_{1',3'}$ = 2.6, 1 H, H-1'), 6.81 (d, $J_{6',7'}$ = 7.7, H-6'), 4.16* (s, 3 H, 5-OMe), 4.12* (s, 3 H, 5-OMe), 3.48* (s, 3 H, 2-OMe), 3.47* (s, 3 H, 2-OMe), 2.99 (m, 4 H, H-6), 2.86 (m, 4 H, H-5), 1.41 (s, 18 H, 17-tBu); MS, *m/e* (70 eV, EI) 945 (M^+, 80); *m/e* calcd for $C_{65}H_{59}N_3O_4$ 945.45052, measured 945.45139.

7-(3,5-Di-*tert*-butylphenyl)-2,12-bis[2-(dimethylamino)acridin-9-yl]-5,6,8,9-tetrahydrodibenz[*c*,*h*]acridine (7f). Tetralone **4f** (227 mg, 0.62 mmol) and 500 mg (0.88 mmol) of benzylidene **5f** were combined in a 5-mL flask, and 1 mL of 70% perchloric acid was added. After stirring the mixture at 135 °C for 4 hr, it was cooled slightly and 2 mL of ethanol was added. The dark mixture was refluxed for 5 min and cooled to room temperature, and the solvent was removed at reduced pressure. The residue was dissolved in 25 mL of CH_2Cl_2 and 35 mL of ammonia-saturated methanol was added. After stirring overnight, the mixture was partitioned between chloroform and 2 N aqueous potassium hydroxide solution. The aqueous layer was washed once with chloroform, and the

combined organic layers were dried over magnesium sulfate and filtered, and the solvent was removed at reduced presure. The residue was flash chromatographed (5% MeOH–CH_2Cl_2) and rechromatographed (50% acetone–CH_2Cl_2) to afford 179 mg (32%) of **7f** as a deep purple, crystalline solid: mp >280 °C; δ ^{1}H NMR 8.22–8.15 (m, 6 H, H-4′, H-5′, H-8), 7.65–7.48 (m, 10 H, H-5, H-6, H-6′, H-7′, H-8′), 7.34 (m, 2 H, H-3′), 6.47 (d, $J_{1',3'}$ = 2.6, 2 H, H-1′), 3.16 (m, 4 H, H-4), 2.96 (s, 6 H, NMe_2), 2.78 (m, 2 H, H-2), 2.30 (m, 2 H, H-3), 1.42 (s, 18 H, 17-tBu); MS, *m/e* (FD) 945 (M^+, 100); *m/e* calcd for $C_{65}H_{61}N_5$ 911.49267, measured 945.49539.

7-(3,5-Di-*tert*-butylphenyl)-2,12-bis(2-chloro-7-*tert*-butylacridin-9-yl)-5,6,8,9-tetrahydrodibenz[*c*,*h*]acridine (7g). Tetralone **4g** (40 mg, 0.10 mmol) and 80 mg (0.13 mmol) of benzylidene **5g** were combined in a 5-mL flask, and 2.0 mL of 70% perchloric acid was added. The mixture was stirred at 90–95 °C under nitrogen for 2 h. After cooling of the mixture slightly, 15 mL of ethanol was added, and the mixture was heated at 80 °C for 1.5 h. The solvent was removed at reduced pressure, and the residue was treated with ammonia-saturated methanol until basic. The resulting mixture was stirred overnight and concentrated to a crude solid, which was triturated with CH_2Cl_2. The organic extracts were flash chromatographed (30% EtOAc–petroleum ether) to afford 165 mg (36%) of **7g** as a cream-colored solid: mp >280 °C; ^{1}H NMR δ 8.53* (d, $J_{1,3}$ = 1.1, 1 H, H-1), 8.48* (d, $J_{1,3}$ = 1.2, 1 H, H-1), 8.08–8.01 (m, 4 H, H-4′, H-5′), 7.71–7.27 (m, 12 H, H-1′, H-3, H-3′, H-4, H-6′, H-8′), 7.55 (d, $J_{16,18}$ = 1.0, 1 H, H-18), 7.15 (d, $J_{16,18}$ = 1.0, 2 H, H-16), 3.01 (m, 4 H, H-6), 2.89 (m, 4 H, H-5), 1.42 (s, 18 H, 17-tBu), 1.05* (s, 9 H, 7′-tBu), 0.94* (s, 9 H, 7′-tBu); MS, *m/e* (FD) 1006 (M^+, 100); *m/e* calcd for $C_{69}H_{65}N_3Cl_2$ 1005.45552, measured 1005.45651.

7-(3,5-Di-*tert*-butylphenyl)-2,12-bis(2-*tert*-butylacridin-9-yl)dibenz[*c*,*h*]acridine (1b). To a solution of 185 mg (0.20 mmol) of **7b** in 6 mL of chlorobenzene was added 134 mg (0.59 mmol) of DDQ. The dark mixture was heated to reflux under a nitrogen atmosphere for 8 h. The mixture was partitioned between 100 mL of saturated aqueous sodium bicarbonate solution and 100 mL of chloroform. The aqueous layer was washed once with 75 mL of chloroform, and the combined organic layers were dried over magnesium sulfate and filtered, and the solvent was removed at reduced pressure. ^{1}H NMR of the residue showed ca. 50% conversion. The material was redissolved in chlorobenzene and 100 mg (0.4 mmol) of DDQ was added. The mixture was refluxed for 4 h and worked up as described above. Flash chromatography (20% EtOAc–petroleum ether) afforded 138 mg (75%) of **1b** as an amber, crystalline solid: mp 225 °C, dec; ^{1}H NMR δ 9.70* (s, 1 H, H-1), 9.69* (s, 1 H, H-1), 8.17 (m, 2 H, H-5′), 8.13 (m, 2 H, H-4′), 7.87 (d, $J_{5,6}$ = 9.2, 2 H, H-6), 7.8–7.6 (m, 11 H, H-1′, H-3, H-4, H-6′, H-8′, H-18), 7.78 (d, $J_{5,6}$ = 9.2, 2 H, H-5), 7.75 (d, $J_{3',4'}$ = 8.1, 2 H, H-3′), 7.41 (s, 2 H, H-16), 7.19* (t, $J_{6',7'}$ = 7.5, $J_{7',8'}$ = 7.5, 1 H, H-7′), 7.15* (t, $J_{6',7'}$ = 7.5, $J_{7',8'}$ = 7.5, 1 H, H-7′), 1.47* (s, 4.5 H, 16-tBu), 1.465* (s, 9 H, 16-tBu), 1.455* (s, 4.5 H, 16-tBu), 1.11* (s, 9 H, 2-tBu), 0.97 (s, 9 H, 2-tBu); MS, *m/e* (70 EV, EI) 933 (M^+, 100); *m/e* calcd for $C_{69}H_{63}N_3$ 933.50216, measured 933.50370.

7-(3,5-Di-*tert*-butylphenyl)-2,12-bis(2-chloro-7-*tert*-butylacridin-9-yl)dibenz[*c*,*h*]acridine (1g). By the procedure for **1b**, 7.5 mg (51%) of **1g** was obtained as a brown solid: ^{1}H NMR δ 9.75 (s, 2 H, H-1), 8.14 (d, $J_{5',6'}$ = 7.6, 2 H, H-5′), 8.12 (d, $J_{3',4'}$ = 6.8, 2 H, H-4′), 7.90 (d, $J_{5,6}$ = 9.4, 2 H, H-6), 7.81 (d, $J_{5,6}$ = 9.4, 2 H, H-5), 7.72 (m, 12 H, H-1′, H-3′, H-6′, H-8′, H-3, H-4), 7.58 (s, 1 H, H-18), 7.42 (d, $J_{16,18}$ = 1.7, 2 H, H-16), 1.47 (s, 18 H, 17-tBu), 1.08* (s, 9 H, 7′-tBu), 0.98* (s, 9 H, 7′-tBu).

7-(3,5-Di-*tert*-butylphenyl)-2-(2-*tert*-butylacridinyl-9-yl)-12-(2,5-dimethoxyacridin-9-yl)-5,6,8,9-tetrahydrodibenz[*c*,*h*]acridine (8). Tetralone **4e** (106 mg, 0.28 mmol) and 200 mg (0.35 mmol) of benzylidene **5b** were combined with 0.4 mL of boron trifluoride etherate, and the mixture was heated to 110 °C for 2.5 h. The homogeneous, maroon solution was transferred to a larger flask with 10 mL of CH_2Cl_2, and 20 mL of ammonia-saturated methanol was added. The clear brown solution was stirred at room temperature overnight and the solvent removed under reduced pressure. The residue was partitioned between 70 mL of CH_2Cl_2 and 100 mL of a saturated aqueous solution of sodium bicarbonate. The organic layer was dried over $MgSO_4$ and filtered, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (EtOAc to 5% MeOH–CH_2Cl_2) to afford 143.5 mg (55%) of **8** as an amber, crystalline solid: mp 255 °C dec; ^{1}H NMR δ 8.51 (s, 1 H, H-13), 8.48 (s, 1 H, H-1), 8.24–8.12 (m, 3 H, H-4′, H-4″, H-5″), 7.77–7.56 (m, 4 H, H-1″, H-3″, H-6″, H-8″), 7.52 (s, 1 H, H-18), 7.41–7.15 (m, 6 H, H-3′, H-8′, H-3, H-4, H-10, H-11), 7.13 (s, 2 H, H-16), 7.12–6.73 (m, 4 H, H-1′, H-6′, H-7′, H-7″), 4.15* (s, 1.5 H, 5′-OMe), 4.13* (s, 1.5 H, 5′-OMe), 3.51* (s, 1.5 H, 2′-OMe), 3.44* (s, 1.5 H, 2′-OMe), 1.42 (s, 18 H, 17-tBu), 1.10* (s, 4.5 H, 2″-tBu), 1.05* (s, 4.5 H, 2″-tBu); MS, *m/e* (70 eV, EI) 941 (M^+, 100); *m/e* calcd for $C_{67}H_{63}N_3O_2$ 941.49120, measured 941.49263.

Acknowledgment. We thank Prof. R. Foster for helpful correspondence. Funding from the Research Corporation, American Cancer Society (Junior Faculty Award to S.C.Z.), the National Institutes of Health (Grant No. GM38010-01), and the National Science Foundation (PYI Award) is gratefully acknowledged.

(Dialkoxymethyl)lithiums: Generation, Stability, and Synthetic Transformations

Christopher S. Shiner,* Tetsuto Tsunoda, Burton A. Goodman, Stephen Ingham, Shi-hung Lee, and Paul E. Vorndam

Contribution from the Department of Chemistry and Biochemistry, University of Colorado, Boulder, Colorado 80309-0215. *Received July 14, 1986. Revised Manuscript Received September 16, 1988*

Abstract: (Dialkoxymethyl)lithium reagents, $(RO)_2CHLi$, can be generated simply and efficiently and employed as synthetically useful one-carbon nucleophiles. Reductive lithiation of phenylthio-substituted precursors, $(RO)_2CHSPh$, at −95 °C or transmetalation of tri-*n*-butylstannyl compounds, $(RO)_2CHSn(n\text{-}Bu)_3$, at −110 to −111 °C afforded the acyclic species $(MeO)_2CHLi$ (**4**) and $(EtO)_2CHLi$ (**5**). The cyclic reagents, 2-lithio-1,3-dioxolane (**6**) and 2-lithio-1,3-dioxane (**7**), were similarly prepared at −78 °C by reductive lithiation or transmetalation. Reactions of (dialkoxymethyl)lithiums with electrophiles, including aldehydes, ketones, 2-cyclohexen-1-one (1,2- or 1,4-addition as desired), dimethyl sulfate, primary alkyl bromides, epoxides, oxetane, and $n\text{-}Bu_3SnCl$, afforded structurally diverse, functionalized acetals. In these experiments, which emphasized transformations of lithiodioxane **7**, yields of products generally exceeded 90%. The thermal stability of each reagent was investigated at several temperatures. The acyclic compounds **4** and **5** decompose rapidly even at −95 °C, whereas lithiodioxolane **6** and dioxane derivative **7** are relatively stable at −78 and −45 °C, respectively. These striking differences in solution lifetimes can be rationalized in terms of alternative decomposition pathways and steric and stereoelectronic factors. The primary products of thermal decomposition of **7** can be ascribed to formation of a reactive carbene or carbenoid via α-elimination. Equilibration experiments established that (dialkoxymethyl)lithium **7** is more stable thermodynamically than the α-monoalkoxy species [(benzyloxy)methyl]lithium, in accord with previous ab initio calculations.

α-Heterosubstituted organometallics serve as versatile, effective reagents for the preparation of organic structures.[1] Whereas α-alkoxy organolithiums[2] (**1**) and bis(α-alkylthio) organolithium compounds[3,4] (**2**) have been widely employed in synthesis, no viable

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