dine, and 2',3',5'-triacetyluridine were purchased from the Sigma Chemical Co. Immediately prior to use chloroform was washed with water, dried over K_2CO_2, refluxed with P_2O_5, distilled, and passed through a column of activated alumina.

^1H and ^{13}C NMR spectra of chloroform-*d* solutions were recorded on a General Electric QE-300 instrument at 300 MHz unless specified otherwise. Chemical shifts are reported in parts per million (ppm) with TMS as an internal reference, and coupling constants are reported in hertz (Hz). Mass spectra were obtained on a Finnigan AT CH-5 or MAT-731 spectrometer. Elemental analyses were performed at the University of Illinois School of Chemical Sciences. The ^1H NMR titrations were monitored by a General Electric GN 500-MHz instrument. The UV-visible titrations were monitored on either a Shimadzu 160U or a Hewlett Packard 8451A diode array spectrophotometer. In both cases the temperature of the samples was maintained at 298 ± 1 K.

4-Amino-7-propylpyrazolo[3,4-*d*]pyrimidine (9). With use of the procedure of Itaya et al.[28] 405 mg of 4-aminopyrazolo[3,4-d]pyrimidine gave 84 mg (15%) of **9** as colorless needles (from ethyl acetate): mp 164-165 °C; ^1H NMR δ 8.40 (s, 1 H, H-2), 7.92 (s, 1 H, H-9), 5.50 (br s, 2 H, NH), 4.38 (t, J = 7.1, 2 H, NCH_2), 1.96 (m, 2 H, CH_2), 0.93 (t, J = 7.4, 3 H, CH_3); ^{13}C NMR (500 MHz) δ 157.46, 155.61, 153.32, 130.15, 100.52, 48.84, 23.01, 11.16; MS (EI, 70 eV), m/z 177 (M^+, 51), 149 (64), 148 (100). Anal. Calcd for $C_8H_{11}N_5$: C, 54.22; H, 6.26; N, 39.52. Found: C, 54.09; H, 6.25; N, 39.21.

2',3',5'-Tripentanoylguanosine (13). With use of the procedure of Matsuda,[29] 6.38 g of guanosine gave 5.95 g (56%) of compound **13** as a white solid (ether trituration): mp 237-238 °C; ^1H NMR δ 12.07 (br s, 1 H, H-5), 7.65 (s, 1 H, H-8), 6.08 (br s, 2 H, 6-NH_2), 5.97 (d, $J_{1',2'}$ = 5.3, 1 H, H-1'), 5.87 (m, 1 H, H-2' or H-3'), 5.70 (m, 1 H, H-2' or H-3'), 4.40 (m, 3 H, H-4', H-5'), 2.36 (m, 6 H, CH_2), 1.66 (m, 6 H, CH_2), 1.37 (m, 6 H, CH_2), 0.92 (m, 9 H, CH_3); ^{13}C NMR (500 MHz) δ 173.41, 172.39, 172.13, 159.09, 153.90, 151.37, 136.42, 117.41, 86.15, 80.15, 72.59, 70.48, 62.95, 33.69, 33.55, 33.39, 26.76, 26.66, 22.15, 22.06, 13.64, 13.58; MS (EI, 70 eV), m/z 535 (M^+, 1) 85 (100). Anal. Calcd for $C_{25}H_{37}N_5O_8$: C, 56.06; H, 6.96; N, 13.08. Found: C, 56.02; H, 6.96; N, 13.10.

Job Plot. The stoichiometry of the complex between **1** and **4** was determined by Job's method.[18b,19] Stock solutions 5×10^{-4} M in **1** and **4** in $CDCl_3$ were prepared. In eleven separate NMR tubes portions of the two solutions were added such that their ratio changed from 0 to 1 while maintaining a total volume of 500 μL. A ^1H NMR spectrum was taken for each tube and the change in chemical shift of the anthracene H-10 resonance of **1** was used to calculate the complex concentration (taking $\Delta\delta_{max}$ = 0.62; see Table II). The complex concentration was plotted against the mole fraction of **1** (Figure 2).

^1H NMR Titrations. For a specific example, the titration of **1** with **7** is described here. A 0.025 M solution of **1** and a 0.050 M solution of **7** in $CDCl_3$ were prepared. In 13 separate NMR tubes 10 μL of the solution of **1** and 0, 1, 2, 5, 10, 20, 30, 40, 60, 80, 100, 200, and 400 μL of the solution of **7** were added, respectively. The total volume in each NMR tube was increased to 500 μL by adding $CDCl_3$. ^1H NMR spectra were taken for each tube and $\Delta\delta$ values were calculated by substracting the chemical shift of interest in the spectrum of the mixtures (δ_x) from the appropriate resonance in the spectrum of pure **1** (δ_0). Thus, a titration curve of $\Delta\delta$ vs $[G_0]$ could be plotted. In each case calculation of association constants used data up to 80-90% of saturation.

UV-Visible Titrations. A chloroform solution ca. 0.025 M in 9-propyladenine (**4**) was prepared and its exact concentration determined by its absorbance at λ_{max} = 262 nm ($\epsilon = 1.15 \times 10^{-4}$) following a 600-fold dilution. A chloroform solution ca. 4×10^{-5} M in **2** was prepared in a 1-cm UV cuvette. For **3** the solution was ca. 4×10^{-6} M and it was prepared in a 10-cm UV cell. The exact concentrations were determined by UV-vis with λ_{max} = 386 nm ($\epsilon = 1.96 \times 10^4$) for **2** and λ_{max} = 406 nm ($\epsilon = 1.62 \times 10^4$) for **3**. Small aliquots (ca. 10 μL) of the solution of **4** were added to the receptor solution until the absorbance at λ_{max} = 386 nm (**2**) or λ_{max} = 406 nm (**3**) no longer decreased. The concentration of **4** was thus varied as follows: for **2**, [**4**] ≈ 5-30 × 10^{-5} M, and for **3**, [**4**] ≈ 5-60 × 10^{-6} M. Data from ca. 20-30% to 80-90% saturation were used in the calculation of K_{assoc} and $\Delta\epsilon$.

Acknowledgment. Funding from the NIH (GM 38010) and the NSF (CHE 58202) is gratefully acknowledged. Contributions from the Monsanto Company are acknowledged with gratitude. S.C.Z. acknowledges a Dreyfus Teacher-Scholar Award, an Eli Lilly Granteeship, and an NSF Presidential Young Investigator Award. Z.Z. thanks the University of Illinois for a Departmental Fellowship.

(29) Matsuda, A.; Shinozaki, M.; Suzuki, M.; Watanabe, K.; Miyasaka, T. *Synthesis* **1986**, 385-386.

Convergent Functional Groups. 10. Molecular Recognition of Neutral Substrates

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Abstract: In this paper synthetic molecular clefts with functional groups complementary to adenines, diketopiperazines, and barbiturates are described. Lactams and imides are compared for hydrogen-bonding affinites toward each other and to the heterocycles mentioned above. Titrations in $CDCl_3$ using NMR show association constants vary by factors of 10^4 for adenines, 10^2 for diketopiperazines, and 10 for barbiturates with the new receptors. Enantioselective recognition of *cyclo*-L-Leu-Leu is observed, corresponding to $\Delta\Delta G$ = 2.7 kcal/mol. The relative strengths of hydrogen-bonding arrays are interpreted in terms of secondary interactions such as defined in the following paper in this issue by Jorgensen and Severance.

Introduction

How does one choose the optimal complement to functional groups in a given structure? Patterns of hydrogen bond donors and acceptors are easily and intuitively visualized, but what other factors, less visible, contribute to the intermolecular forces between functional groups? In previous disclosures from these laboratories, we have shown that cleft-like shapes offer a number of advantages for the study of molecular recognition.[1] Here their abilities to probe subtle effects in hydrogen bonding are described particularly in the context of the questions posed above. Their capacities to act as synthetic receptors for neutral, biorelevant targets is further developed.

The cleft-like structures are readily made from Kemp's triacid[2] **1**. The U-shaped relationship between any two carboxyl functions in this subunit permits the construction of molecules which fold back upon themselves, and, in conjunction with suitable spacer

(1) For a recent review, see: Rebek, J., Jr. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 245-255.

(2) Kemp, D. S.; Petrakis, K. S. *J. Org. Chem.* **1981**, *46*, 5140. Commercially available from the Aldrich Chemical Co. For a convenient synthesis, see: Rebek, J., Jr.; Askew, B.; Killoran, M.; Nemeth, D.; Lin, F.-T. *J. Am. Chem. Soc.* **1987**, *109*, 2426-2431.

0002-7863/91/1513-201$02.50/0

Scheme I

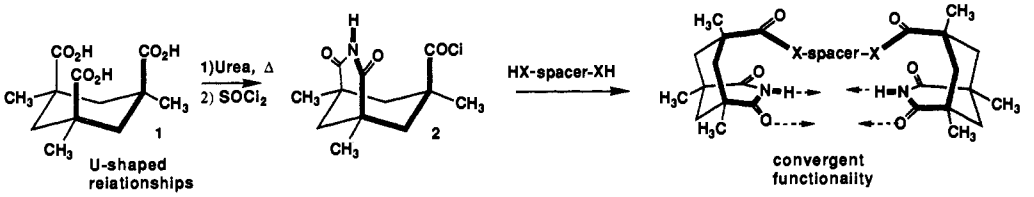


Table I. Cyclization Data, $CDCl_3$, 25 °C

				imide–imide (Scheme II)		lactam–lactam (Scheme III)		lactam–imide (Chart II)		
	ν free			7.42		5.1		5.1, 7.42		
	ν cyclic			10.40		8.6		7.54, 11.93		
	imide–imide (Scheme II)				lactam–lactam (Scheme III)			lactam–imido (Chart II)		
n	ν_{obs}	% cyclic	K_{obs}	K_c(corr)	ν_{obs}	% cyclic	K_c	ν_{obs}	% cyclic	K_c
2	9.29	63	1.7	0.85	8.11	86	6.1	6.92/10.87	75	3
3	9.90	83	5.2	2.6	8.47	96	24	7.23/11.47	87–90	8
4	8.36	32	0.45	0.22	6.76	48	0.92	5.75/9.42	27–44	0.43–0.78
5	8.59	39	0.64	0.32	7.04	55	1.2	6.06/9.46	39–45	0.66–0.82

Chart I

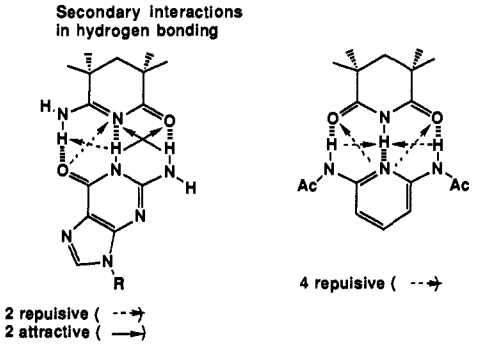
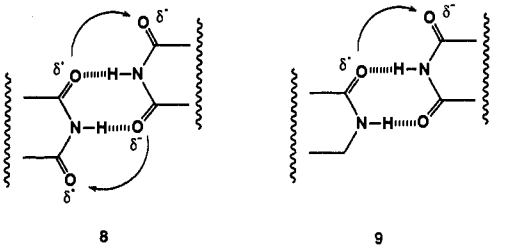


Chart II



elements, cleft-like structures are assembled in efficient, modular fashion (Scheme I). The lining of the cleft presents convergent functional groups that may be tailored for complementarity to the target structures.

A further refinement for recognition, the remarkable mnemonic due to Jorgensen,[3] has recently emerged from his calculations of hydrogen-bonding interactions. The results are presented for two cases in Chart I, in which *secondary* interactions determine the relative strengths of hydrogen bonds in cyclic arrays. The initial objective of this study was to measure the extent to which the results of Jorgensen's calculations influence binding in solution, particularly in $CDCl_3$, a solvent that offers a bridge between water and the gas phase.

The initial question concerned the relative "stickiness" of imides and lactams as hydrogen-bonding partners. Earlier work by a number of researchers[4] had established that in $CDCl_3$ the self-association, or dimerization of such structures, is quite weak with association constants in the single digits and quite difficult to measure. Our approach was to enhance these associations by promoting them to an *intramolecular* system. Within the context of the convergent molecules, this could be accomplished by the use of flexible spacers or tethers that allow the collapse of hydrogen bond donors and acceptors on opposite ends of the structures upon each other. The synthesis of these structures (Scheme II) was uneventful, as it followed previous work[5] in this area.

The extent of intramolecular self-association of these structures was monitored by NMR. The chemical shifts of the exchangeable protons were found to be concentration independent in the diimides, dilactams, or the imide lactams. Thus, intermolecular interactions in this series are small and generally negligible at these concentrations. Even so, two points must be considered. The first is a statistical one: the diimides have two equivalent modes of cyclization and are therefore at an advantage when compared to the corresponding dilactams or imide lactam hybrids. Secondly, the diastereomeric forms of the dilactams separated by these relatively short tethers confers upon the racemic isomers the ability to form cyclic hydrogen-bonded arrays (Scheme III). The meso isomers, however, are unable to achieve more than one-point attachments. This was reflected in the NMR chemical shifts of the lactam NH resonances. In the racemic forms, these varied considerably in accord with their degrees of cyclization, whereas the meso diastereomer resonances occurred between 5.26 and 6.0 ppm. That they varied at all suggests that some cyclization involving a single hydrogen-bonded contact was possible in the meso compounds. The general and reasonable promise was that hydrogen bonds occurred in pairs for the systems that showed a high tendency to cyclize.

The cyclization data is given in Table I along with the limiting chemical shifts observed for the four types of compounds.[6] The results show that the most stable cyclic arrays involve the lactams interacting with lactams, whereas the imide–imide interactions are the least stable. This is quite understandable and is a corollary of the Jorgensen analysis. For any of the imides, each spectator carbonyl destabilizes the nearby hydrogen-bonded array by ~0.4 kcal/mol (Chart II).

At first glance, this would indicate that lactams should be superior hydrogen-bonding partners for complementary donor–acceptor molecules. Yet this is not the case when the partners are adenine derivatives. For example, the imide structure bearing a naphthalene stacking surface **10** was shown[5] to bind adenine derivatives such as **12** with a K_a of 220 M^{-1} (Scheme IV).

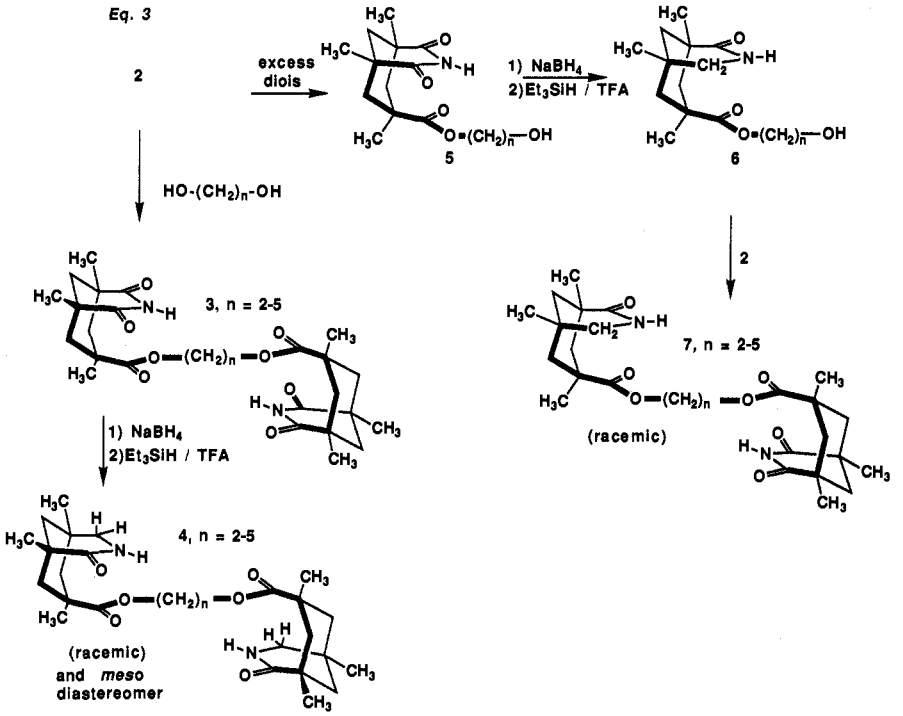
(3) Jorgensen, W.; Pranata, J. *J. Am. Chem. Soc.* **1990**, *112*, 2008–2010.

(4) Hine, J.; Hahn, S.; Hwang, S. *J. Org. Chem.* **1988**, *53*, 884–887. Gentric, E.; Lauransan, J.; Roussel, C.; Metzger, J. *Nouv. J. Chim.* **1980**, *4*, 743–746. Krikorian, S. E. *J. Phys. Chem.* **1982**, 1875. For a discussion of the high self-affinity of pyridones, see: Ducharme, Y.; Wuest, J. D. *J. Org. Chem.* **1988**, *53*, 5787–5789, and references therein. For intramolecular amide–amide interactions, see: Gellman, S. H.; Adams, B. R. *Tetrahedron Lett.* **1989**, *30*, 3381–3384.

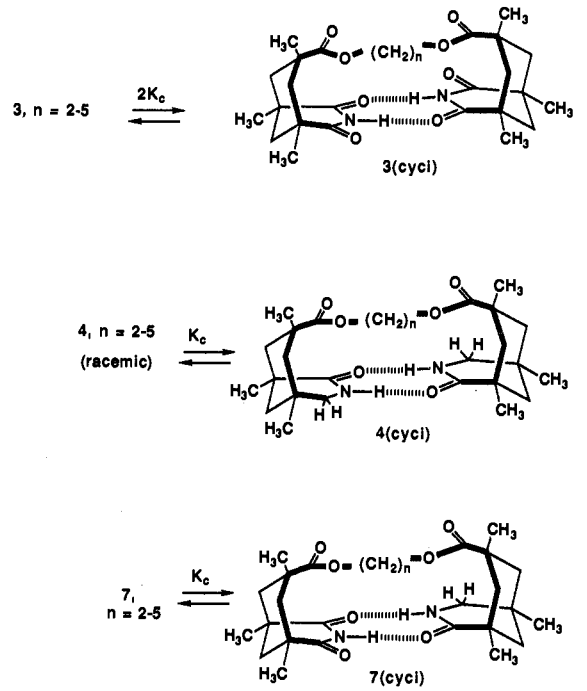
(5) Askew, B.; Ballester, P.; Buhr, C.; Jeong, K. S.; Jones, S. Parris, K.; Williams, K.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1989**, *111*, 1082–1090. The permethylated analogue of **20b** showed insufficient solubility in $CDCl_3$ and gave a K_a of 11 000 M^{-1} in $CD_3CN/CDCl_3$.

(6) For a preliminary account of these results, see: Jeong, K. S.; Tjivikua, T.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1990**, *112*, 3215–3217.

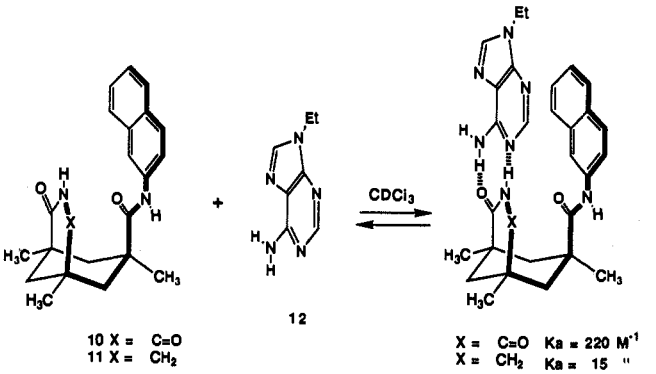
Scheme II



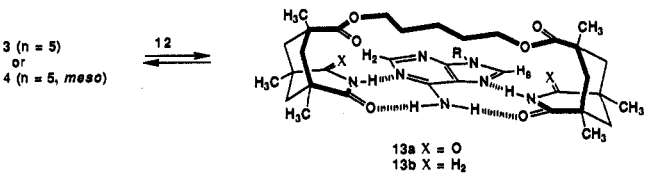
Scheme III



Scheme IV



Scheme V



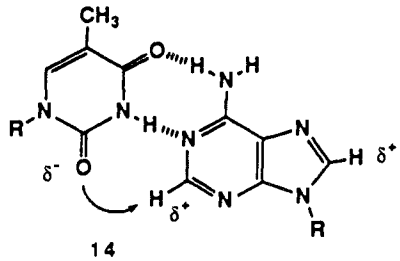
However, there are two ways to bind adenine with **10** (either of the imide oxygens can be involved), so the statistically corrected value is 110 M^{-1}. When the imide was reduced to the corresponding lactam **11**, the titration, under identical conditions, gave a K_a of 15 M^{-1}.

The effect could be magnified: the flexible diimide **3** ($n = 5$) was shown to bind adenine **12** with an association constant of 4800 M^{-1}, which results from simultaneous Watson–Crick and Hoogsteen binding to the adenine as shown in **13**. Again, a statistical correction gives K_a 2400 M^{-1}. The corresponding meso dilactam **4** ($n = 5$), however, which presents the same hydrogen-bonding pattern, was found to bind adenine with an association constant of only 52 M^{-1} (Scheme V).

A third system, involving greater rigidity or preorganization was also examined in this context. The highly soluble, propylated derivatives with a 2,7-naphthalene spacer were prepared (their synthesis is described later). Titrations of **12** (Scheme VI) with diimide **20b** and the meso dilactam **23b** gave an uncorrected K_a of 102 000 M^{-1} (±10%) for the former and only 290 M^{-1} for the latter.

Is it the enhanced acidity of the imide that leads to higher affinity to the purine base, or does some other factor operate? The answer appears to come from a peculiar *reverse* secondary interaction observed by Jorgensen[7] through calculational methods. In the Watson–Crick base pair, the H_2 of the adenine becomes highly polarized in contact with the imide function, as in **14**. This interaction may be regarded as a weak hydrogen bond between this atom and the otherwise non participating carbonyl oxygen. Presumably, a similar situation exists with H_8 on the Hoogsteen edge. This is consistent with earlier reports of similar contacts, such as hydrogen bonds to CH hydrogens involved in these positions in caffeine.[8] Thus, subtle local effects are seen to be a

(7) Jorgensen, W.; Severance, D. Manuscript submitted for publication.



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significant determinant of optimal hydrogen bonding, i.e., an intermolecular version of neighboring group participation is involved. Even so, acidity *does* contribute to adenine binding. Recent results with carboxylic acid derivatives by Zimmerman[9] and Wilcox[10] have shown that such functions are among the most effective binders of adenine under these conditions. These studies suggest there is still more to be learned about this subject.

In order to reduce acid–base interactions as a driving force for complexations, the neutral targets, diketopiperazines, were studied. From the considerations above, it was anticipated that lactams would show higher affinity for diketopiperazines than would imides. Preliminary results[11] with these structures and their notorious insolubility led us to enhance the lipophilicity of our synthetic receptors. Thus, a new triacid **7b** was prepared in which the peripheral functions were propyl rather than methyl groups. This was accomplished by alkylation of the hexahydrotrimesic esters **15** with allyl bromide. The hydrolysis and hydrogenation of the product **16a** (in either order) gave the new propyl derivatives (Scheme VII). While the yield of the alkylation reaction was somewhat lower with allyl bromide vs dimethyl sulfate, the cis,trans isomer was not observed, and qualitatively the reactions of the new triacid resembled those of Kemp's triacid. For example, condensation with urea gave the imide **18a** which could be converted to the acid chloride **18b** with $SOCl_2$.

A number of aromatic diamines were used as spacers, including the 2,6-disubstituted anthracene **19a**, the corresponding dihydroanthracene **19b**, and both the 2,6- and 2,7-disubstituted naphthalene derivatives **20**. Reduction to the lactams followed a two-step procedure (Scheme VIII) in which the initial product of the $NaBH_4$ treatment, the hydroxy lactam, was cyclized to the dilactam through acidic workup. The diastereomers were then separated by flash chromatography.[12] The meso and the racemic forms of **21** were then further reduced (Et_3SiH/TFA) to give the appropriate dilactams **22** and **23**. The dilactams **22** were resolved on a Pirkle column[13] by HPLC.

All of the isomers showed excellent solubility in organic solvents, particularly in $CDCl_3$. Distinguishing between the meso and the racemic forms could also be easily accomplished by their relative affinities for diketopiperazines and quinoxaline-2,3-dione. For example, as shown in Table II, the meso form solubilizes quinoxaline-2,3-dione (**29**) to a considerably greater extent than does the racemic form. In a complementary sense, the racemic dilactam solubilizes glycine anhydride **24** better than it does quinoxalinedione. The results of solubilization experiments are given in Table II, and these give a qualitative picture of the affinities. Note especially that the diimides consistently solubilized less of either heterocycle than the dilactams.

The promising affinity of the 2,6-dinaphthyl lactam suggested its nearly ideal fit to diketopiperazines, and this was borne out by titrations with the soluble L-leucylglycine **25** and L-leucyl-L-leucine (Scheme VIII). The association constants are given in Table III, however, with association so high, that is $>10^4$, errors

Table II. Solid–Liquid Extractions into $CDCl_3$ of Glycine Anhydride **24**, Quinoxalinedione **29**, and Barbituric Acid (**31**)

host	equiv **24** dissolved	equiv **29** dissolved	equiv **31** dissolved
19a	<0.05		
19b	0.4		
20a	0.7	0.5	0.16
20b		0.28	0.75
22ab	0.8	0.32	
22cd			
23a	0.45	0.65	0.35
23b		0.4	1.0

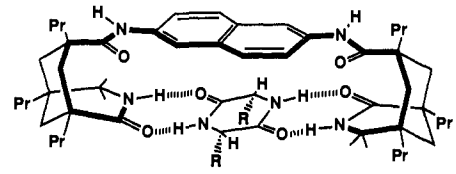
Table III. Association Constants with Diketopiperazines (K_a, M^{-1}, 296 K, $CDCl_3$)

	Hosts				
guests	**19b**	**20a**	**22a**	**22b**	**23a**
cyclo-L-Leu-Gly **25**	4800	50000	2900	73000	6700
cyclo-L-Leu-L-Leu **26**		12000	840	82000	

Table IV. Association Constants with Barbiturate **32** (M^{-1}, 296 K, $CDCl_3$)

	hosts		
	20b	**23a**	**23b**
K_a	17000	890	32400

Chart III



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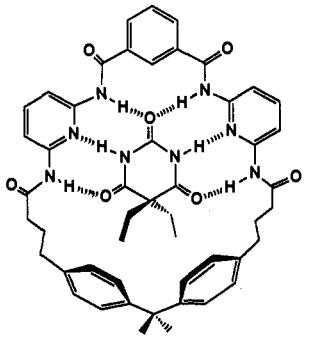
inherent in the NMR saturation titrations grow and the numbers are less certain. Nonetheless, it was possible to show through direct competition experiments that the relative affinities are in the order shown. One dividend from these studies was yielded by the high chiral recognition of the two enantiomeric lactams. The value was 25-fold for *cyclo*-L-leucylglycine, a 1.9 kcal/mol difference in binding affinities. The corresponding value for *cyclo*-L-leucyl-L-leucine is 97-fold and indicates a $\Delta\Delta G$ of 2.7 kcal/mol. For the binding of neutral substrates, these values represent some of the highest enantioselectivities seen to date.[14] Even the more competitive solvent, CD_3OD, permitted titrations of **22b** with *cyclo*-L-Leu-Gly; the K_a observed was 46 M^{-1}.

The stereochemical preferences are seen quite clearly in **27** and **28** (Chart III and Scheme IX, respectively), in which complementarity of shape and hydrogen-bonding patterns are expressed in an ideal fashion between substrate and receptor. For a mismatched fit, at best three hydrogen bonds can be formed, and even these require distortions on the rest of the skeleton as shown by molecular mechanics calculations using MacroModel.

Finally, we have examined complexes of barbiturate derivatives with these structures. Excellent complexing agents for this class of heterocycles have been developed by Hamilton;[15] for example, the macrocyclic complex **30** shows a dissociation constant in the micromolar range in $CDCl_3$. For our systems, the 2,6- and 2,7-disubstituted naphthalenes were used as spacers, while the lining was either the diimide or the meso dilactam. The first protocol involved the solid–liquid extraction of barbituric acid **31** into $CDCl_3$, and, as shown in Table III, the 2,7-derivatives were quite

(8) For a discussion, see: Donohue, J. In *Structural Chemistry and Molecular Biology*, Rich, A., Davidson, N. Eds.; W. H. Freeman: New York, 1968; pp 459–465.
(9) Zimmerman, S. C.; Wu, W. *J. Am. Chem. Soc.* **1989**, *111*, 8054.
(10) Adrian, J. C.; Wilcox, C. S. *J. Am. Chem. Soc.* **1989**, *111*, 8055.
(11) Jeong, K. S.; Muehldorf, A.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1990**, *112*, 6144–6145.
(12) Still, W. C.; Khan, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.
(13) Pirkle, W. H.; Pochapsky, T. *Chem. Rev.* **1989**, 347–362. (Regis Chemical Co.).
(14) Castro, P. D.; Georgiadis, T. M.; Diederich, F. *J. Org. Chem.* **1989**, *54*, 5835–5838. Sanderson, P. E.; Kilburn, J. D.; Still, W. C. *J. Am. Chem. Soc.* **1989**, *111*, 8314–8315.
(15) Chang, S. K.; Hamilton, A. D. *J. Am. Chem. Soc.* **1988**, *110*, 1318–1319.



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effective. In fact the meso dilactam **23b** was capable of extracting ~0.7 equiv of barbituric acid from its aqueous 1 N HCl solution into $CDCl_3$. A reasonable structure for the complex is proposed in **33** (Scheme X).

The second protocol involved titrations with the *n*-butyl barbiturate **32**. Both diimide and dilactam showed high affinity for this material in the 2,7-series, while the 2,6-derivatives were poorly matched. The results are shown in Table IV and are depicted in complex **33**. These again underscore the importance of complementarity of size and shape for effective molecular recognition.

We are currently investigating the use of related structures for the molecular recognition of simple peptide derivatives, and we will report on these results in due course.

Experimental Section

Titrations. Typically, a 2 mM solution of host in dry $CDCl_3$ was prepared, a 500-mL aliquot was transferred to a 5-mm NMR tube, and a spectrum was recorded. Aliquots of a 3 mM $CDCl_3$ solution of guest were added (20 mL at first and then 50 mL close to saturation), and a spectrum was recorded after each addition. The addition of guest was continued until the chemical shift of the host signals remained constant (at 800 mL total guest). Association constants were obtained by nonlinear least-squares fit of the saturation plot to the 1:1 binding isotherm. The complete numerical analysis is given in ref 16. The titration data were well-matched by the theoretically generated curves (see Figure 1), and all cases showed $10^{-6} < R^2 < 10^{-3}$ ppm.

Extractions. (a) Solubilization of glycine anhydride **24** and barbituric acid (**31**) in $CDCl_3$: To a 3 mM solution of receptor in dry $CDCl_3$ (1 mL) was added **24** (3 mg) or **31** (3 mg). The mixture was sonicated for 10 min at room temperature and filtered. The amount of **24** and **31** dissolved was calculated by integration of the appropriate ^1H NMR signals of the filtrate. (b) Extraction of **31** from aqueous solution: 2,7-Naphthalenediamide dilactam **23b** (1.5 mg) was dissolved in $CDCl_3$ (1 mL). Barbituric acid **31** (0.5 g) was suspended in 5 mL of neutral or acidic (1 N HCl) water, stirred for 10 min at room temperature, and filtered. The aqueous solution was combined with the $CDCl_3$ solution, and the mixture was shaken for 5 min. The organic layer was separated, dried over anhydrous Na_2SO_4, and filtered. The amount of **31** dissolved was calculated by integration of the appropriate ^1H NMR signals of the filtrate. (c) Solubilization of quinoxalinedione **29**: To a 2 mM solution of receptor in dry $CDCl_3$ (1 mL) was added **29** (6–8 mg). The mixture was sonicated for 10 min at room temperature and filtered. To this solution was added ca. 50 μL of DMSO-d_6 to resolve the signal of the complex. The amount of **29** dissolved was calculated by integration of the appropriate ^1H NMR signals of the filtrate.

General Procedure for the Preparation of Alkane Diester Diimide Systems 3, *n* = 2–5. The syntheses of **1** and **2** were previously described,[2,5] and experimental details for **3** have recently been published.[16]

General Procedure for the Preparation of Alkane Diester Dilactams 4, *n* = 2–5. A solution of alkane diester diimides **3**, *n* = 2–5 (0.1 g), and $NaBH_4$ (10–20 equiv) in EtOH was stirred at 0 °C for 6–12 h. The solution was poured into cold brine, and the aqueous solution was extracted with $CHCl_3$. The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo to give a white solid. The solid was dissolved in dry CH_2Cl_2, and excess CF_3CO_2H and Et_3SiH were added. The solution was stirred for 2–5 h at ambient temperature and concentrated in vacuo. The resulting oily liquid was taken up in CH_2Cl_2, and the organic layer was washed with saturated $NaHCO_3$ and brine and then dried over anhydrous Na_2SO_4. The crude mixture (racemic/meso 50/50) was subjected to flash chromatography to give pure dilactams as white solids. The racemic forms of **4**, *n* = 2–5, were less polar than the meso forms of **4**, *n* = 2–5. Total yields of **4**, *n* = 2–5, from **3**, *n* = 2–5, were in the range of 85–94%.

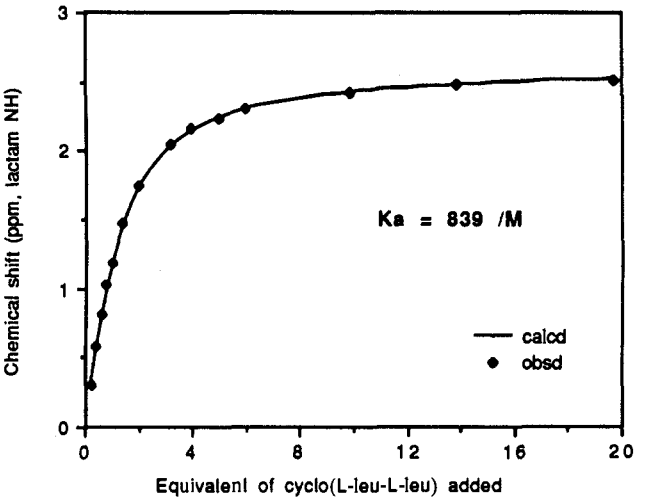


Figure 1. Saturation plot of **22a** titrated with **26**.

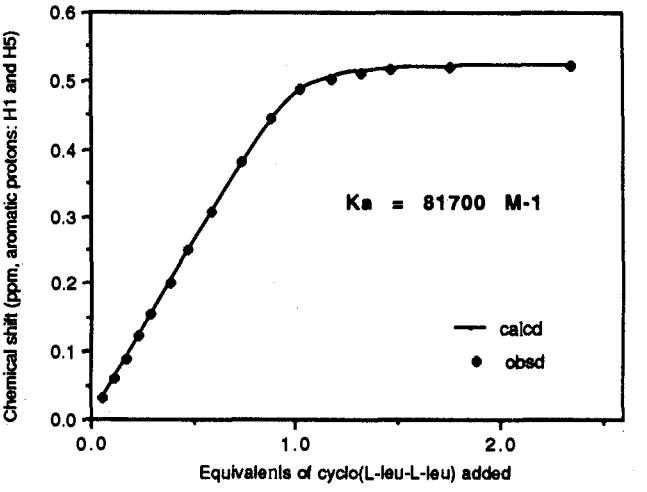


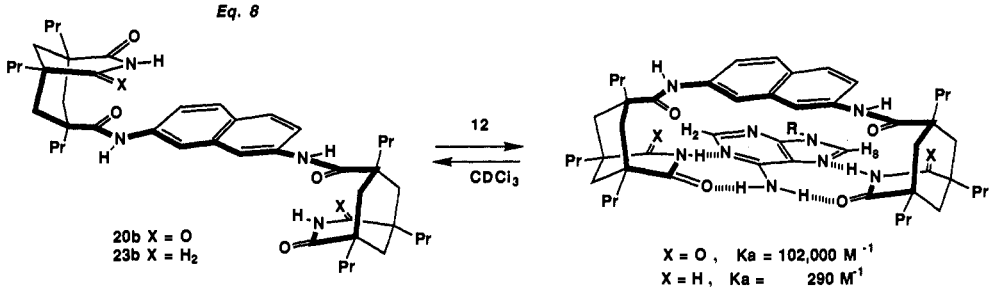
Figure 2. Saturation plot of **22b** titrated with **26**.

1,2-Ethanediyl diester dilactams 4, *n* = 2 (racemic, less polar): mp 223–226 °C; IR (NaCl, neat) 3197, 2954, 2928, 1724, 1663, 1491, 1456, 1241, 1175, 1089 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.11 (s, 2 H), 4.25–4.09 (m, 4 H), 3.19 (d, *J* = 12.1 Hz, 2 H), 2.97 (d, *J* = 12.1 Hz, 2 H), 2.53 (d, *J* = 13.7 Hz, 4 H), 1.69 (d, *J* = 12.7 Hz, 2 H), 1.23–0.99 (m, 6 H), 1.17 (s, 6 H), 1.07 (s, 6 H), 0.94 (s, 6 H); HRMS *m/z* for $C_{26}H_{40}N_2O_6$ (M^+) calcd 476.2886, obsd 476.2885. **(Meso, more polar):** mp >280 °C; IR (NaCl, neat) 3197, 2953, 2912, 1715, 1688, 1646, 1440, 1261 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.41 (s, 2 H), 4.36 (m, 4 H), 4.10 (m, 2 H), 3.17 (d, *J* = 11.7 Hz, 2 H), 3.03 (d, *J* = 11.7 Hz, 2 H), 2.70 (d, *J* = 13.9 Hz, 2 H), 2.50 (d, *J* = 14.1 Hz, 2 H), 1.73 (d, *J* = 12.8 Hz, 2 H), 1.25–1.02 (m, 6 H), 1.18 (s, 6 H), 1.15 (s, 6 H), 0.98 (s, 6 H); HRMS *m/z* for $C_{26}H_{40}N_2O_6$ (M^+) calcd 476.2886, obsd 476.2885.

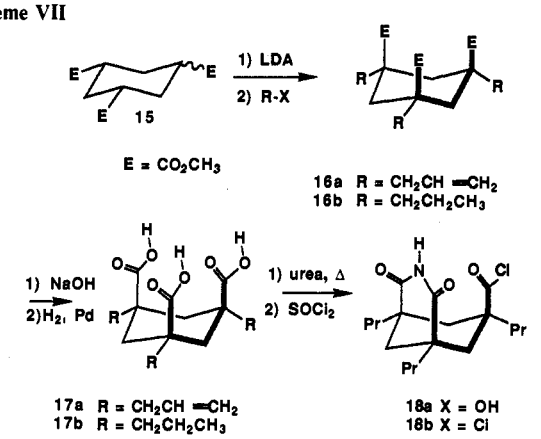
1,3-Propanediyl diester dilactams 4, *n* = 3 (racemic, less polar): mp 213–215 °C; IR (NaCl, neat) 3209, 2955, 2927, 1723, 1666, 1471, 1456, 1257, 1174, 1105 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.47 (s, 2 H), 4.33 (m, 2 H), 4.18 (m, 2 H), 3.24 (d, *J* = 12.1 Hz, 2 H), 2.99 (d, *J* = 12.1 Hz, 2 H), 2.59–2.51 (m, 4 H), 2.03 (m, 2 H), 1.69 (d, *J* = 12.5 Hz, 2 H), 1.21–1.00 (m, 6 H), 1.14 (s, 6 H), 1.10 (s, 6 H), 0.95 (s, 6 H); HRMS *m/z* for $C_{26}H_{40}N_2O_6$ (M^+) calcd 476.2886, obsd 476.2885. **(Meso, more polar):** mp 185–187 °C; IR (NaCl, neat) 3300, 2954, 2924, 1723, 1663, 1491, 1456, 1273, 1257, 1175 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.01 (s, 2 H), 4.21–3.98 (m, 4 H), 3.18 (d, *J* = 11.5 Hz, 2 H), 3.03 (d, *J* = 11.5 Hz, 2 H), 2.63 (d, *J* = 13.9 Hz, 2 H), 2.51 (d, *J* = 14.0

(16) Tjivikua, T.; Deslongchamps, G.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1990**, *112*, 8408–8414.
(17) For a general procedure, see: von Braun, J.; Bayer, O. *Justus Liebigs Ann. Chem.* **1929**, *472*, 90.
(18) Drake, N. L. In *Organic Reactions*; John Wiley & Sons: New York, 1942; Vol. 1, Chapter 5.
(19) Chatt, J.; Wynne, P. *J. Chem. Soc.* **1943**, 33.
(20) For a synthesis of barbituric acid, see: Dickey, J. B.; Gray, A. R. *Organic Syntheses*; Wiley: New York, 1943; Collect. Vol. II, p 60.

Scheme VI



Scheme VII



Hz, 2 H), 1.72 (d, J = 12.9 Hz, 2 H), 1.25–1.01 (m, 6 H), 1.16 (s, 6 H), 1.14 (s, 6 H), 0.97 (s, 6 H); HRMS m/z for $C_{26}H_{40}N_2O_6$ (M^+) calcd 476.2886, obsd 476.2885.

1,4-Butanediyl diester dilactams 4c (racemic, less polar): mp 172–174 °C; IR (NaCl, neat) 3223, 2950, 2927, 1715, 1653, 1472, 1448, 1174, 1089 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.76 (s, 2 H), 4.20 (m, 2 H), 3.91 (m, 2 H), 3.19 (d, J = 11.7 Hz, 2 H), 2.99 (d, J = 11.7 Hz, 2 H), 2.63–2.50 (m, 4 H), 1.80–1.55 (m, 4 H), 1.25–1.00 (m, 6 H), 1.15 (s, 6 H), 1.12 (s, 6 H), 0.96 (s, 6 H); HRMS m/z for $C_{28}H_{44}N_2O_6$ (M^+) calcd 504.3199, obsd 504.3198. **(Meso, more polar)**: mp 201–203 °C; IR (NaCl, neat) 3197, 2952, 2916, 1717, 1645, 1439, 1258, 1177 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.64 (s, 2 H), 4.09–3.93 (m, 4 H), 3.17 (d, J = 11.5 Hz, 2 H), 3.00 (d, J = 11.5 Hz, 2 H), 2.65 (d, J = 14.1 Hz, 2 H), 2.51 (d, J = 13.9 Hz, 2 H), 1.75–1.57 (m, 4 H), 1.25–1.01 (m, 6 H), 1.16 (s, 6 H), 1.15 (s, 6 H), 0.97 (s, 6 H); HRMS m/z for $C_{28}H_{44}N_2O_6$ (M^+) calcd 504.3199, obsd 504.3198.

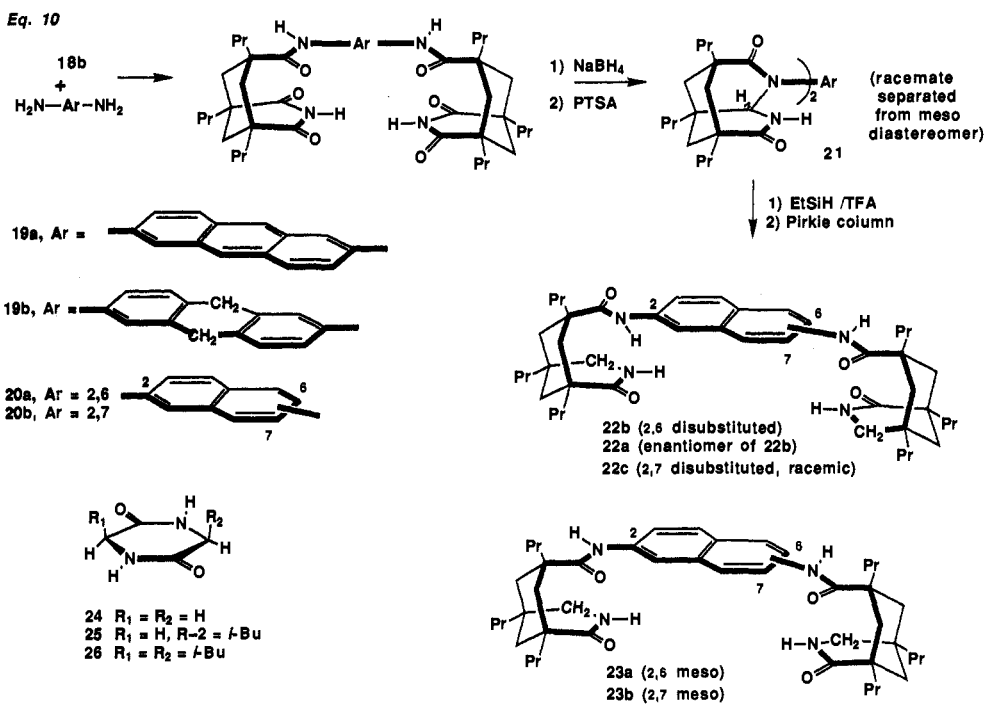
1,5-Pentanediyl diester dilactams 4, n = 5 (racemic, less polar): mp 161–163 °C; IR (NaCl, neat) 3206, 2954, 2925, 1719, 1655, 1448, 1257, 1186, 1089 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.98 (s, 2 H), 3.97 (m, 4 H), 3.19 (d, J = 11.8 Hz, 2 H), 2.96 (d, J = 11.8 Hz, 2 H), 2.58–2.50 (m, 2 H), 1.75–1.65 (m, 4 H), 1.39 (t, J = 7.0 Hz, 2 H), 1.22–0.97 (m, 6 H), 1.15 (s, 6 H), 1.11 (s, 6 H), 0.96 (s, 6 H); HRMS m/z for $C_{29}H_{46}N_2O_6$ (M^+) calcd 518.3356, obsd 518.3357. **(Meso, more polar)**: mp 178–180 °C; IR (NaCl, neat) 3193, 2953, 2927, 1723, 1668, 1448, 1257, 1175, 1105 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.23 (s, 2 H), 4.07 (m, 2 H), 3.90 (m, 2 H), 3.17 (d, J = 11.5 Hz, 2 H), 3.01 (d, J = 11.5 Hz, 2 H), 2.60 (d, J = 13.9 Hz, 2 H), 2.50 (d, J = 14.0 Hz, 2 H), 1.74–1.60 (m, 6 H), 1.41–1.00 (m, 8 H), 1.16 (s, 6 H), 1.15 (s, 6 H), 0.98 (s, 6 H): HRMS m/z for $C_{29}H_{46}N_2O_6$ (M^+) calcd 518.3356, obsd 518.3357.

General Procedure for the Preparations of Alkane Monoester Imides 5, n = 2–5. A solution of imide acid chloride **2** (0.15 g, 1 equiv), diol (10 equiv), DMAP (0.5 equiv), and excess Et_3N in dry CH_2Cl_2 was heated at reflux overnight under N_2 atmosphere. The solution was washed with 1 N HCl and brine and dried over anhydrous Na_2SO_4. The crude product **5** was purified by flash chromatography.

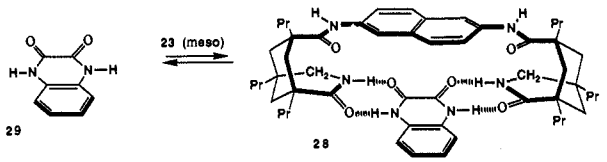
2-Hydroxyethyl ester imide 5, n = 2: white solid (67% yield); mp 140–142 °C; IR (NaCl, neat) 3410, 3077, 2977, 2873, 1728, 1691, 1464, 1317, 1196, 1179, 1078 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.17 (s, 1 H), 4.17 (m, 2 H), 3.79 (m, 2 H), 3.34 (t, J = 6.8 Hz, 1 H), 2.71 (d, J = 14.1 Hz, 2 H), 2.01 (d, J = 13.4 Hz, 1 H), 1.38 (d, J = 13.4 Hz, 1 H), 1.27 (s, 6 H), 1.23 (s, 3 H), 1.19 (d, J = 14.1 Hz, 2 H).

3-Hydroxypropyl ester imide 5, n = 3: white solid (80% yield); mp 133–135 °C; IR (NaCl, neat) 3510, 3203, 3097, 2967, 2933, 1727, 1697, 1463, 1382, 1318, 1199, 1056 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.70 (s, 1 H), 4.12 (t, J = 5.3 Hz, 2 H), 3.69 (m, 2 H), 2.69 (d, J = 14.1 Hz,

Scheme VIII



Scheme IX



2 H), 2.57 (t, J = 6.5 Hz, 1 H), 1.99 (d, J = 13.2 Hz, 1 H), 1.38 (d, J = 13.2 Hz, 1 H), 1.26 (s, 6 H), 1.23 (s, 3 H), 1.19 (d, J = 13.9 Hz, 2 H).

4-Hydroxybutyl ester imide 5, n = 4: oily liquid (81% yield); IR (NaCl, neat) 3462, 3220, 3099, 2964, 2933, 1729, 1697, 1463, 1381, 1318, 1208 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.81 (s, 1 H), 4.05 (t, J = 6.1 Hz, 2 H), 3.67 (q, J = 5.7 Hz, 2 H), 2.69 (d, J = 14.2 Hz, 2 H), 1.97 (d, J = 13.3 Hz, 1 H), 1.70–1.61 (m, 3 H, including OH), 1.36 (d, J = 13.3 Hz, 1 H), 1.24 (s, 6 H), 1.21 (s, 3 H), 1.17 (d, J = 14.2 Hz, 2 H).

5-Hydroxyethyl ester imide 5, n = 5: a white solid (86% yield); mp 142–144 °C; IR (NaCl, neat) 3445, 2961, 2931, 1727, 1696, 1448, 1318, 1196, 1207 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.72 (s, 1 H), 4.02 (t, J = 6.3 Hz, 2 H), 3.67 (q, J = 5.9 Hz, 2 H), 2.70 (d, J = 14.5 Hz, 2 H), 1.97 (d, J = 13.4 Hz, 1 H), 1.82–1.28 (m, 8 H), 1.25 (s, 6 H), 1.22 (s, 3 H), 1.17 (d, J = 14.5 Hz, 2 H).

General Procedure for the Preparation of Alkane Monoester Lactams 6, n = 2–5. The reductions of **5**, n = 2–5, were performed following the same procedure as that described for the preparation of **3**, n = 2–5. Yields of **6**, n = 2–5, from **5**, n = 2–5, were in the 80–93% range.

2-Hydroxyethyl ester lactam 6, n = 2: oily liquid; IR (NaCl, neat) 3403, 2959, 2931, 1724, 1653, 1189, 1082 cm^{-1} ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.44 (s, 1 H), 3.89–3.65 (m, 4 H), 3.16 (d, J = 11.6 Hz, 1 H), 3.06 (d, J = 11.6 Hz, 1 H), 2.63 (d, J = 14.0 Hz, 2 H), 2.55 (d, J = 13.9 Hz, 1 H), 1.73 (d, J = 12.7 Hz, 1 H), 1.30–1.02 (m, 3 H), 1.19 (s, 3 H), 1.18 (s, 3 H), 1.00 (s, 3 H).

3-Hydroxypropyl ester lactam 6, n = 3: white solid; mp 123–125 °C; IR (NaCl, neat) 3321, 2958, 2931, 1722, 1654, 1457, 1258, 1188 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.48 (s, 1 H), 4.30 (s, 1 H), 4.14 (m, 1 H), 4.10 (m, 1 H), 3.75–3.51 (m, 2 H), 3.22 (d, J = 11.6 Hz, 1 H), 3.01 (d, J = 11.6 Hz, 1 H), 2.61–2.50 (m, 2 H), 1.81–1.70 (m, 3 H), 1.27–1.01 (m, 6 H), 1.18 (s, 3 H), 1.16 (s, 3 H), 0.99 (s, 3 H).

4-Hydroxybutyl ester lactam 6, n = 4: white solid; mp 155–157 °C, IR (NaCl, neat) 3403, 3203, 2960, 2929, 1719, 1652, 1242, 1190, 1083 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.37 (s, 1 H), 4.24 (m, 1 H), 3.92 (m, 1 H), 3.77 (m, 1 H), 3.58 (m, 1 H), 3.21 (d, J = 11.6 Hz, 1 H), 3.01 (d, J = 11.6 Hz, 1 H), 2.62 (d, J = 13.9 Hz, 1 H), 2.53 (d, J = 13.9 Hz, 1 H), 1.78–1.55 (m, 3 H), 1.27–1.01 (m, 3 H), 1.17 (s, 3 H), 1.15 (s, 3 H), 0.99 (s, 3 H).

5-Hydroxypentyl ester lactam 6, n = 5: white solid; mp 103–105 °C; IR (NaCl, neat) 3312, 2952, 2931, 1723, 1663, 1458, 1188, 1088 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.32 (s, 1 H), 4.15–3.91 (m, 2 H), 3.71–3.60 (m, 2 H), 3.20 (d, J = 11.6 Hz, 1 H), 3.01 (d, J = 11.6 Hz, 1 H), 2.61 (d, J = 14.0 Hz, 1 H), 2.53 (d, J = 13.9 Hz, 1 H), 1.74–1.40 (m, 7 H), 1.17 (s, 3 H), 1.14 (s, 3 H), 0.98 (s, 3 H).

General Procedure for the Preparations of Alkane Diester Imide Lactams 7, n = 2–5. A solution of imide acid chloride **2** (0.50 g, 1.1 equiv), **6**, n = 2–5 (1 equiv), DMAP (0.5 equiv), and excess Et_3N in dry CH_2Cl_2 was heated at reflux overnight under N_2 atmosphere. The solution was washed with 1 N HCl and brine and dried over anhydrous Na_2SO_4. The crude product was purified by flash chromatography to give a white solid.

1,2-Ethanediyl diester lactam imide 7, n = 2: white solid (64% yield); mp 248–250 °C; IR (NaCl, neat) 3303, 3252, 2965, 2932, 2872, 1728, 1697, 1652, 1464, 1197, 1175 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 10.87 (s, 1 H), 6.91 (s, 1 H), 4.30–4.04 (m, 4 H), 3.19 (d, J = 11.7 Hz, 1 H), 2.98 (d, J = 11.7 Hz, 1 H), 2.77–2.49 (m, 4 H), 1.93 (d, J = 13.3 Hz, 1 H), 1.69 (d, J = 13.6 Hz, 1 H), 1.36–1.01 (m, 18 H), 0.96 (s, 3 H); HRMS m/z for $C_{26}H_{38}N_2O_7$ (M^+) calcd 490.2679, obsd 490.2678.

1,3-Propanediyl diester lactam imide 7, n = 3: white solid (83% yield); mp 222–224 °C; IR (NaCl, neat) 3292, 3244, 2965, 2930, 1726, 1693, 1650, 1453, 1176 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 11.47 (s, 1 H), 7.22 (s, 1 H), 4.27–4.15 (m, 2 H), 3.98–3.84 (m, 2 H), 3.22 (d, J = 11.6 Hz, 1 H), 2.97 (d, J = 11.6 Hz, 1 H), 2.77–2.50 (m, 6 H), 2.00–1.90 (m, 3 H), 1.67 (d, 1 H, J = 12.7 Hz), 1.38–0.84 (m, 24 H); HRMS m/z for $C_{27}H_{40}N_2O_7$ (M^+) calcd 504.2835, obsd 504.2833.

1,4-Butanediyl diester lactam imide 7, n = 4: white solid; mp 178–180 °C; IR (NaCl, neat) 3218, 2965, 2933, 1728, 1697, 1665, 1464, 1183 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.42 (s, 1 H), 5.75 (s, 1 H), 4.07–3.98 (m, 4 H), 3.20 (d, J = 11.6 Hz, 1 H), 3.00 (d, J = 11.6 Hz, 1 H), 2.73–2.50 (m, 4 H), 1.96 (d, J = 13.3 Hz, 1 H), 1.76–1.55 (m, 5 H), 1.36–0.96 (m, 24 H); HRMS m/z for $C_{28}H_{42}N_2O_7$ (M^+) calcd 518.2992, obsd 518.2990.

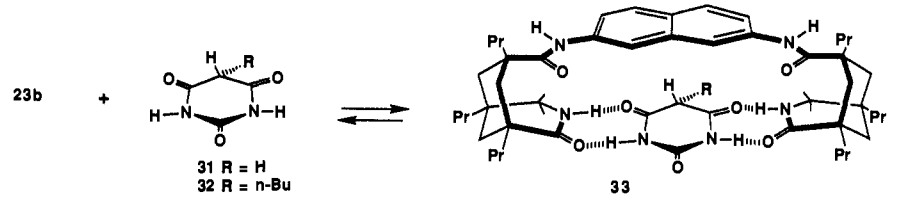
1,5-Pentanediyl diester lactam imide 7, n = 5: white solid (86% yield); mp 175–177 °C; IR (NaCl, neat) 3247, 2962, 2931, 1727, 1697, 1654, 1462, 1184 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.45 (s, 1 H), 6.06 (s, 1 H), 4.04–3.93 (m, 4 H), 3.20 (d, J = 11.6 Hz, 1 H), 2.97 (d, J = 11.6 Hz, 1 H), 2.75–2.49 (m, 4 H), 1.95 (d, J = 13.3 Hz, 1 H), 1.76–0.96 (m, 30 H); HRMS m/z for $C_{29}H_{44}N_2O_7$ (M^+) calcd 532.3148, obsd 532.3149.

2-Naphthalenamide Lactam 11. The synthesis of 2-naphthalenamide imide **10** was previously described.[5] A solution of 2-naphthalenamide imide **10** (0.20 g, 0.55 mmol) and excess $NaBH_4$ (0.4 g) in absolute EtOH (50 mL) was stirred for 5 h. The cooled solution was poured into ice-water (300 mL) and extracted with $CHCl_3$ (3 × 100 mL). The $CHCl_3$ solution was washed with brine, dried over anhydrous Na_2SO_4, and evaporated in vacuo. The crude product was purified by flash chromatography (2:1 EtOAc/$CHCl_3$) affording 0.19 g (95%) of the corresponding hydroxy lactam as colorless crystals: mp 186–189 °C dec; IR (NaCl, neat), 3280, 2959, 2924, 1716, 1650, 1600, 1576, 1558, 1506, 1471, 1392 cm^{-1}; ^{1}H NMR ($CDCl_3$), δ 8.03 (d, 1 H, J = 2 Hz), 7.80 (m, 3 H), 7.68 (s, 1 H, NH), 7.46 (m, 3 H), 5.56 (s, 1 H, NH), 5.15 (d, 1 H, OH, J = 13 Hz), 4.56 (d, 1 H, J = 13 Hz), 2.96 (d, 1 H, J = 15 Hz), 2.33 (d, 1 H, J = 15 Hz), 1.82 (d, 1 H, J = 13 Hz), 1.54 (d, 1 H, J = 15 Hz), 1.38 (s, 3 H), 1.36 (d, 1 H, J = 13 Hz, 1 H), 1.24 (s, 3 H), 1.09 (s, 3 H), 0.96 (d, 1 H, J = 15 Hz); HRMS m/z for $C_{22}H_{26}N_2O_3$ (M^+) calcd 366.1943, found 366.1944.

A solution of 2-naphthyl hydroxy lactam (0.15 g, 0.41 mmol) in dry CH_2Cl_2 (5 mL) containing CF_3CO_2H (0.5 mL) and Et_3SiH (0.1 mL) was stirred for 2 h at room temperature. The reaction mixture was carefully washed with saturated $NaHCO_3$ and brine and then dried (Na_2SO_4). The solvent was removed in vacuo to yield pure **11** in quantitative yield as a white solid: mp 214–216 °C; IR (NaCl, neat) 3427, 3276, 3190, 2957, 2908, 2868, 1663, 1539, 1469, 1193, 754 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 8.08 (d, 1 H, J = 1.8 Hz), 7.77 (m, 3 H), 7.57 (s, 1 H, NH), 7.51–7.38 (m, 3 H), 5.39 (s, 1 H, NH), 3.18 (dd, 1 H, J_1 = 11.5 Hz, J_2 = 1.3 Hz), 2.97 (d, 1 H, J = 11.5 Hz), 2.88 (d, 1 H, J = 13.9 Hz), 2.31 (d, 1 H, J = 15.2 Hz), 1.76 (d, 1 H, J = 12.8 Hz), 1.44 (d, 1 H, J = 12.8 Hz), 1.34 (s, 3 H), 1.30 (dd, 1 H, J_1 = 15.1 Hz, J_2 = 1.3 Hz), 1.25 (s, 3 H), 1.04 (dd, 1 H, J_1 = 13.9 Hz, J_2 = 1.3 Hz), 0.99 (s, 3 H); HRMS m/z for $C_{22}H_{26}N_2O_2$ (M^+) calcd 350.1994, found 350.1994.

***cis,cis*-Trimethyl 1,3,5-Triallylcyclohexane-1,3,5-tricarboxylate (16a).** The synthesis of **15** was previously described.[2] To a solution of diisopropylamine (15 mL, 107 mmol) in toluene (100 mL) stirred at 0 °C was syringed in 10 M n-butyllithium (10 mL, 100 mmol) over 5 min under Ar. The solution was allowed to stir for 20 min at 0 °C. Trimethyl 1,3,5-cyclohexanetricarboxylate (**15**) (8 g, 31 mmol) was dissolved in 300 mL of toluene and cannulated over 1 h to the stirred LDA solution. After the addition was complete, the suspension was stirred at 0 °C for 15 min after which allyl bromide (9 mL, 104 mmol) was added in a single portion. The ice bath was removed, and the temperature was slowly raised to 75 °C over 1 h and maintained for 30 min. After cooling to room temperature, the mixture was concentrated in vacuo. The residue was dissolved in ether (100 mL) and washed with 1 N HCl (2 × 75 mL) and brine. The organic phase was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was distilled at 0.5 mmHg with a Kugelrohr apparatus to yield **16a** as a pale yellow oil (8.9 g, 76%): mp 78–79 °C (needles from hexanes); IR ($CHCl_3$) 3078, 2951, 2914, 1737, 1430, 1211, 1156, 991 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 5.51 (m,

Scheme X



3 H), 5.00 (m, 6 H), 3.57 (s, 9 H), 2.59 (d, 3 H, J = 14.0 Hz), 2.24 (d, 6 H, J = 8 Hz), 0.94 (d, 3 H, J = 14.0 Hz); HRMS m/z for $C_{21}H_{30}O_6$ (M^+) calcd 378.2042, found 378.2040.

***cis,cis*-Trimethyl 1,3,5-Tripropylcyclohexane-1,3,5-tricarboxylate (16b).** Distilled triallyl compound **16a** (16.1 g, 43 mmol) was dissolved in ethyl acetate (50 mL) and briefly refluxed with 5% Pd/C (1.0 g). The solution as filtered and placed in a Parr apparatus along with 10% Pd/C (0.5 g). Hydrogenation was complete at room temperature under 50 psi H_2 for 3 h. The catalyst was filtered off through Celite, and the solvent was evaporated to yield a pale yellow semisolid. This was recrystallized from hexanes (75 mL) to give more tripropyl ester **16b** as large blocky crystals (12.1 g, 73% from crude **16a**): mp 115.5 °C; IR ($CHCl_3$) 2952, 2852, 1732, 1433, 1177, 1115 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 3.94 (s, 9 H), 2.83 (s, 6 H), 1.43 (m, 6 H), 1.16 (m, 6 H), 0.90 (d, 3 H, J = 14.0 Hz), 0.84 (t, 9 H, J = 8.0 Hz); HRMS m/z for $C_{20}H_{33}O_5$ ($M - OCH_3$) calcd 353.2328, found 353.2326.

***cis,cis*-1,3,5-Triallylcyclohexane-1,3,5-tricarboxylic Acid (17a).** Triallyl triester **16a** (crude product from a 0.31 mol allylation; 100 g) was dissolved in ethanol (500 mL). Potassium hydroxide (100 g, 1.5 mol) in water (100 mL) was added, and the dark brown mixture was refluxed for 4 h. The ethanol was removed in vacuo, and the residue was cooled in an ice bath while concentrated HCl was slowly added until pH = 2. The mixture was extracted with ethyl acetate (2 × 600 mL). The solvent was removed in vacuo, and the residue was dissolved in ether (300 mL), precipitating triacid **17a**. Triacid **17a** was collected by filtration and washed with ether and then hexanes: yield 46.1 g (46% overall); mp 210–215 °C dec; IR (NaCl, neat) 3500–2500, 3075, 2905, 1685, 1456, 1231, 915 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 8.30 (vb, 3 H), 5.80–5.60 (m, 3 H), 5.09 (m, 6 H), 2.72 (d, 3 H, J = 14.0 Hz), 2.29 (d, 6 H, J = 7.0 Hz), 1.01 (d, 3 H, J = 14.0 Hz); HRMS m/z for $C_{18}H_{22}O_5$ ($M - H_2O$) calcd 318.1467, found 318.1467.

***cis,cis*-1,3,5-Tripropylcyclohexane-1,3,5-tricarboxylate (17b). From Tripropyl Triester 16b.** Tripropyl triester **16b** (12 g, 31 mmol) was suspended in ethanol (150 mL). Potassium hydroxide (10 g, 150 mmol) in water (40 mL) was added, and the mixture was heated at reflux for 12 h. The ethanol was removed in vacuo, and the aqueous residue was diluted with water (60 mL) and carefully acidified to pH < 2 with concentrated HCl in an ice bath. The mixture was filtered, and a white solid was dried in vacuo to give pure tripropyl triacid **17b** (10.4 g, 97%).

From Triallyl Triacid 17a. Triallyl triacid **17a** (10 g, 30 mmol) was dissolved in tetrahydrofuran (THF, 75 mL) with 10% Pd/C (0.5 g), and the mixture was hydrogenated under 40 psi H_2 for 2 h with a Parr apparatus. The catalyst was filtered off through Celite and washed with acetone. The solution was concentrated and dried in vacuo to yield pure tripropyl triacid **17b**: mp 205–210 °C dec; IR (NaCl, neat) 3500–2500, 2960, 2874, 1707, 1467, 1457, 1404, 1255, 1237, 1178, 759 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 2.80 (d, 3 H, J = 14.6 Hz), 1.48 (m, 6 H), 1.30 (m, 6 H), 0.96 (d, 3 H, J = 14.6 Hz), 0.88 (t, 9 H, J = 7.0 Hz); HRMS m/z for $C_{18}H_{29}O_5$ (M − OH) calcd 325.2015, found 325.2012.

Tripropyl Imide Acid 18a. Tripropyl triacid **17b** (4.5 g, 13.2 mmol) in triglyme (20 mL) was heated with urea (1.5 g, 25 mmol) at 180 °C for 2 h under N_2 atmosphere. The hot solution was poured into 1 N HCl aqueous solution (200 mL) and cooled to room temperature with stirring. After filtration, a white solid was dried in vacuo to yield pure **18a** (4.1 g, 96%): mp 262–263 °C; IR (NaCl, neat) 3145, 3071, 2949, 2910, 2875, 1707, 1661, 1465, 1367, 1202, 1177, 872, 760 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 10.61 (s, 1 H, NH), 2.62 (d, 2 H, 13.3 Hz), 2.18 (d, 1 H, J = 13.1 Hz), 1.94 (m, 2 H), 1.49–1.13 (m, 13 H), 0.93–0.81 (m, 9 H); HRMS m/z for $C_{18}H_{29}NO_4$ (M^+) calcd 323.2096, found 323.2095.

Tripropyl Imide Acid Chloride 18b. Tripropyl imide acid **18a** (4.1 g, 12.7 mmol) was heated at reflux in thionyl chloride ($SOCl_2$, 10 mL) under N_2 atmosphere for 2 h. Excess $SOCl_2$ was removed in vacuo to give an off-white solid which was recrystallized from carbon tetrachloride/hexanes to yield pure **18b** (4.1 g, 95%): mp 157.5–158.5 °C; IR (NaCl, neat) 3194, 3100, 2962, 2918, 2876, 1785, 1696, 1440, 1200, 818 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 7.61 (s, 1 H, N H), 2.66 (d, 2 H, J = 13.6 Hz), 2.21 (d, 1 H, J = 13.1 Hz), 1.93 (m, 2 H), 1.57 (m, 2 H), 1.40–1.15 (m, 11 H), 0.92 (m, 9 H); HRMS m/z for $C_{18}H_{28}NO_3Cl$ (M^+) calcd 341.1758, found 341.1757.

2,6-Anthracenediamide Diimide 19a. 2,6-Diaminoanthracene and 9,10-dihydro-2,6-diaminoanthracene were prepared by reduction[17] of 2,6-diaminoanthraquinone with zinc dust in 5% NaOH solution at 80 °C. A solution of 2,6-diaminoanthracene (44 mg, 0.21 mmol), imide acid chloride **18b** (0.15 g, 0.44 mmol), and a catalytic amount of DMAP in dry pyridine (20 mL) was heated at reflux for 7 h under N_2 atmosphere. The solution was concentrated in vacuo, the residue was taken up in CH_2Cl_2 (30 mL), and the organic phase was washed with 1 N HCl solution and brine and then dried with anhydrous Na_2SO_4. The crude product was purified by flash chromatography using 20% EtOAc in $CHCl_3$ to yield a pure **19a** (0.12 g, 69%) as a yellow solid: mp > 300 °C; IR (NaCl, neat) 3450, 3189, 2955, 2934, 2871, 1725, 1689, 1553, 1507, 1448, 1385, 1181, 869 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 8.29 (d, 2 H, J = 1.9 Hz), 8.25 (s, 2 H), 7.88 (d, 2 H, J = 9.1 Hz), 7.60 (s, 2 H, NH), 7.32 (s, 2 H, NH), 7.30 (dd, 2 H, J_1 = 9.1 Hz, J_2 = 1.9 Hz), 2.64 (d, 2 H, J = 14.3 Hz), 2.23 (d, 2 H, J = 13.0 Hz), 1.99 (m, 4 H), 1.56–1.24 (m, 44 H); HRMS m/z for $C_{50}H_{66}N_4O_6$ (M^+) calcd 818.4982, found 818.4979.

9,10-Dihydro-2,6-anthracenediamide Diimide 19b. The preparation of **19b** is the same as that described for **19a** except that 9,10-dihydro-2,6-diaminoanthracene (33 mg, 0.16 mmol) was used instead of 2,6-diaminoanthracene. The crude product was purified by flash chromatography (33% EtOAc/CH_2Cl_2) to yield pure **19b** (0.11 g, 78%) as a white solid: mp > 300 °C; IR (NaCl, neat) 3378, 2958, 2933, 2871, 1700, 1521, 1496, 1180 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 7.48 (d, 2 H, J = 1.8 Hz), 7.47 (s, 2 H, NH), 7.17 (s, 4 H), 7.11 (s, 2 H), 3.85 (s, 4 H), 2.58 (d, 2 H, J = 15.2 Hz), 2.22 (d, 2 H, J = 13.0 Hz), 1.99 (m, 4 H), 1.56–1.24 (m, 44 H); HRMS m/z for $C_{50}H_{68}N_4O_6$ (M^+) calcd 820.5138, found 820.5135.

2,7-Naphthalenediamide Diimide 20b. A solution of 2,7-diaminonaphthalene[18] (46 mg, 0.29 mmol), imide acid chloride **18b** (0.20 g, 0.58 mmol), and a catalytic amount of DMAP in dry pyridine (10 mL) was heated at reflux overnight under N_2 atmosphere. The solution was concentrated in vacuo, the residue was taken up in CH_2Cl_2 (30 mL); and the organic phase was washed with 1 N HCl solution and brine and then dried with anhydrous Na_2SO_4. The crude product was purified by flash chromatography using 33% EtOAc in $CHCl_3$ to yield pure **20b** (0.18 g, 81%) as a white solid: mp 329–331 °C; IR (NaCl, neat) 3447, 3360, 3155, 2962, 2934, 2875, 1700, 1652, 1539, 1520, 1496, 1457, 1387, 1381, 1188, 1017 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 7.86 (d, 2 H, J = 1.8 Hz), 7.66 (d, 2 H, J = 8.9 Hz), 7.53 (s, 2 H), 7.39 (dd, 2 H, J_1 = 8.9 Hz, J_2 = 1.8 Hz), 7.30 (s, 2 H), 2.63 (d, 4 H, J = 14.3 Hz), 2.24 (d, 2 H, J = 13.1 Hz), 1.98 (m, 4 H), 1.52–0.85 (m, 44 H); HRMS m/z for $C_{46}H_{64}N_4O_6$ (M^+) calcd 768.4825, found 768.4825.

2,7-Naphthalenediamide Dilactams 22c and 23b. A solution of 2,7-naphthalenediamide diimide **20b** (0.14 g, 0.18 mmol) in ethanol (20 mL) was stirred with $NaBH_4$ (0.13 g) at room temperature for 23 h under Ar atmosphere. The ethanolic solution was poured into water (250 mL) and extracted with $CHCl_3$. The organic phase was dried with anhydrous $MgSO_4$, and the solvent was removed in vacuo. The residue was taken up in CH_2Cl_2 (10 mL), and a catalytic amount of *p*-TsOH was added. The mixture was stirred for 2.5 h and diluted with CH_2Cl_2 (70 mL). The mixture was washed with saturated $NaHCO_3$ and brine and then dried with anhydrous $MgSO_4$. The diastereomeric mixture was separated by flash chromatography (16% EtOAc/CH_2Cl_2) to yield a meso (less polar, 48 mg, 37%) and a racemic tricyclic compound (more polar, 54 mg, 40%). Each isomer was dissolved in CH_2Cl_2 (2 mL), and CF_3CO_2H (1 mL) and Et_3SiH (81 mg) were added to the solution. The mixture was stirred for 18 h at room temperature and concentrated in vacuo. The residue was taken up in CH_2Cl_2 (30 mL), and the solution was washed with saturated $NaHCO_3$ and brine and then dried with anhydrous $MgSO_4$. The solvent was removed to yield the desired products in quantitative yield as white solids. Racemic isomer **22c**: mp 175–177 °C; IR (NaCl, neat) 3154, 2961, 2932, 2921, 2874, 1653, 1648, 1471, 1457, 1381, 1096, 1033, 1012 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 8.04 (d, 2 H, J = 1.8 Hz), 7.67 (d, 2 H, J = 8.8 Hz), 7.57 (s, 2 H, NH), 7.38 (dd, 2 H, J_1 = 8.8 Hz, J_2 = 1.8 Hz), 5.44 (s, 2 H, NH), 3.19 (d, 2 H, J = 11.3 Hz), 2.99 (d, 2 H, J = 11.3 Hz), 2.90 (d, 2 H, J = 14.3 Hz), 2.24 (d, 2 H, J = 15.6 Hz), 1.99 (m, 2 H), 1.84 (d, 2 H, J = 12.7 Hz), 1.61–0.88 (m, 46 H); HRMS m/z for $C_{46}H_{68}N_4O_4$ (M^+) calcd 740.5240, found 740.5240. Meso isomer **23b**: mp 308–310 °C; IR (NaCl, neat) 3393, 3155, 2961, 2933, 2920, 2874, 1653, 1624, 1506, 1491, 1448, 1380, 1095, 1033, 1010, 667 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 8.03 (d, 2 H, J = 1.8 Hz), 7.67 (d, 2 H, J = 8.8 Hz), 7.58 (s, 2 H, NH), 7.38 (dd, 2 H, J_1 = 8.8 Hz, J_2 = 1.8 Hz), 5.38 (s, 2 H, NH), 3.18 (d, 2 H, J = 11.3 Hz), 2.99 (d, 2 H, J = 11.3 Hz), 2.90 (d, 2 H, J = 14.3 Hz), 2.23 (d, 2 H, J = 15.6 Hz), 1.99 (m, 2 H), 1.84 (d, 2 H, J = 12.7 Hz), 1.61–0.88 (m, 46 H); HRMS m/z for $C_{46}H_{68}N_4O_4$ (M^+) calcd 740.5240, found 740.5240.

2,6-Naphthalenediamide Diimide 20a. 2,6-Diaminonaphthalene was prepared from 2,6-dihydroxynaphthalene.[19] The preparation of **20** is the same as that described for **19a** except that 2,6-diaminonaphthalene (0.22 g, 1.39 mmol) was used instead of 2,6-diaminoanthracene. The crude product was purified by flash chromatography (20% EtOAc/CH_2Cl_2) to yield pure **20a** (0.92 g, 86%) as a thin white solid: mp >300 °C; IR (NaCl, neat) 3454, 3201, 3073, 2957, 2934, 2872, 1717, 1689, 1539, 1461, 1180, 875 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 8.06 (d, 2 H, J = 1.7 Hz), 7.70 (d, 2 H, J = 8.8 Hz), 7.49 (s, 2 H, NH), 7.31 (dd, 2 H, J_1 = 8.8 Hz, J_2 = 1.7 Hz), 7.26 (s, 2 H, NH) 2.61 (d, 2 H, J = 14.1 Hz), 2.24 (d, 2 H, J = 13.0 Hz), 1.99 (m, 4 H), 1.56–1.24 (m, 44 H);

HRMS m/z for $C_{46}H_{64}N_4O_6$ (M^+) calcd 768.4825, found 768.4825.

2,6-Naphthalenediamide Tricyclic Dilactams 21. A solution of **20a** (0.70 g, 0.91 mmol) in EtOH (60 mL) and THF (60 mL) was stirred with $NaBH_4$ (1.40 g) at room temperature for 24 h. The solution was poured into water (200 mL), and the aqueous solution was extracted with $CHCl_3$ (2 × 200 mL). The organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed in vacuo, the residue was taken up in CH_2Cl_2 (50 mL), a catalytic amount of *p*-TsOH was added, and the mixture was stirred for 3 h at room temperature. The solution was washed with saturated $NaHCO_3$ and brine and then dried with anhydrous Na_2SO_4. The solvent was evaporated in vacuo, and the resulting mixture of two diastereomers was separated by flash chromatography (16% EtOAcCH_2Cl_2) to yield a less polar diastereomer **21** (0.30 g, 45%) and a more polar diastereomer **21** (0.26 g, 39%) as white solids. Less polar diastereomer (meso) **21**: mp 298-300 °C; IR (NaCl, neat) 3220, 2958, 2931, 2871, 1676, 1440, 1376, 1259, 1084, 743 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 7.89 (d, 2 H, J = 8.9 Hz), 7.70 (d, 2 H, J = 1.8 Hz), 7.31 (dd, 2 H, J_1 = 8.9 Hz, J_2 = 1.8 Hz), 5.88 (d, 2 H, NH, J = 3.1 Hz), 4.70 (d, 2 H, J = 3.1 Hz), 2.22 (d, 2 H, J = 14.1 Hz), 2.09-0.80 (m, 50 H); HRMS m/z for $C_{46}H_{64}N_4O_4$ (M^+) calcd 736.4927, found 736.4927. More polar diastereomer (racemic) **21**: mp > 300 °C; IR (NaCl, neat) 3345, 2957, 2929, 2872, 1693, 1646, 1457, 1383, 1235, cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 7.89 (d, 2 H, J = 8.9 Hz), 7.70 (d, 2 H, J = 1.8 Hz), 7.31 (dd, 2 H, J_1 = 8.9 Hz, J_2 = 1.8 Hz), 5.88 (d, 2 H, NH, J = 3.1 Hz), 4.68 (d, 2 H, J = 3.1 Hz), 2.22 (d, 2 H, J = 14.1 Hz), 2.09-0.80 (m, 50 H): HRMS m/z for $C_{46}H_{64}N_4O_4$ (M^+) calcd 736.4927, found 736.4927.

2,6-Naphthalenediamide Dilactams 22a and 22b. Racemic tricyclic dilactam **21** (0.20 g, 0.27 mmol) was dissolved in CF_3CO_2H (3 mL) and Et_3SiH (0.2 mL). The mixture was stirred overnight at room temperature. The mixture was concentrated in vacuo and the residue was taken up in CH_2Cl_2 (15 mL), the organic phase was washed with saturated $NaHCO_3$, brine, then dried with anhydrous Na_2SO_4. The crude product was purified by flash chromatography (80% EtOAc/CH_2Cl_2) to yield pure **22** (racemic, 0.13 g, 64%) as a white solid. mp 174-176 °C; IR (NaCl, neat) 3432, 3197, 2957, 2917, 2871, 1684, 1662, 1585, 1525, 1457, 1393, 1269, 1156 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 8.00 (d, 2 H, J = 1.7 Hz), 7.71 (d, 2 H, J = 8.7 Hz), 7.60 (s, 2 H, NH), 7.46 (dd, 2 H, J_1 = 8.7 Hz, J_2 = 1.7 Hz), 5.34 (s, 2 H, NH), 3.17 (d, 2 H, J = 11.9 Hz), 2.99 (d, 2 H, J = 11.9 Hz), 2.89 (d, 2 H, J = 13.6 Hz), 2.24 (d, 2 H, J = 15.1 Hz), 2.00 (m, 2 H), 1.85 (d, 2 H, J = 12.2 Hz), 1.61-0.88 (m, 46 H); HRMS m/z for $C_{46}H_{68}N_4O_4$ (M^+) calcd 740.5240, found 740.5240.

Racemic **22** was chromatographed on a Pirkle column (L-3,5-dinitrophenylglycine, Regis Chem. Co.) to yield a less polar enantiomer **22b** ($[\alpha]_D$ = -77.6°, c 1.13 in CH_2Cl_2) and a more polar enantiomer **22a** ($[\alpha]_D$ = +77.4°, c 1.31 in CH_2Cl_2).

2,6-Naphthalenediamide Dilactam 23a (meso). The preparation of **23** is the same as that described for **22a** and **22b** except that the less polar diastereomer **21** (0.20 g, 0.27 mmol) was used instead of the more polar diastereomer **21**: a white solid (0.12 g, 60%); mp > 300 °C; IR (NaCl, neat) 3438, 3174, 2956, 2845, 1675, 1635, 1605, 1539, 1456, 1283 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 8.00 (d, 2 H, J = 1.7 Hz), 7.71 (d, 2 H, J = 8.7 Hz), 7.60 (s, 2 H, NH), 7.46 (dd, 2 H, J_1 =8.7 Hz, J_2 = 1.7 Hz), 5.34 (s, 2 H, NH), 3.17 (d, 2 H, J = 11.9 Hz), 2.99 (d, 2 H, J = 11.9 Hz), 2.89 (d, 2 H, J = 13.6 Hz), 2.24 (d, 2 H, J = 15.1 Hz), 2.00 (m, 2 H), 1.85 (d, 2 H, J = 12.2 Hz), 1.61-0.88 (m, 46 H); HRMS m/z for $C_{46}H_{68}N_4O_4$ (M^+) calcd 740.5240, found 740.5240.

***N*-Butylbarbituric Acid 32.**[20] A solution of diethyl butylmalonate (1.00 g, 4.62 mmol), urea (0.28 g, 4.63 mmol), and sodium ethoxide (9.25 mmol) in absolute ethanol (40 mL) was refluxed for 6 h under N_2 atmosphere. The mixture was concentrated in vacuo, and the residue was triturated with 1 N HCl (100 mL) and filtered to yield a white solid. The mother liquid was saturated with NaCl and extracted with $CHCl_3$ (2 × 100 mL). The organic phase was dried with anhydrous Na_2SO_4 and concentrated in vacuo. Combined crude product was recrystallized from hot $CHCl_3$ to yield a white solid (0.53 g, 63%): mp 211-212 °C; IR (NaCl, neat) 3227, 2960, 2926, 2863, 1684, 1419, 1337, 1209 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 6.05 (s, 2 H, NH), 3.99 (d, 2 H, J = 9.5 Hz), 1.93-1.60 (m, 6 H), 1.00 (d, 6 H, J = 6.2 Hz), 0.95 (d, 6 H, J = 6.2 Hz); HRMS m/z for $C_8H_{12}N_2O_3$ (M^+) calcd 350.1994, found 350.1994.

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Chemical Chameleons: Hydrogen Bonding with Imides and Lactams in Chloroform

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Abstract: Monte Carlo statistical mechanics simulations have been used to elucidate the origin of the novel variations in complex formation observed for imides and lactams. The OPLS potential functions were employed in conjunction with statistical perturbation theory to calculate relative association constants for the dimerization of succinimide and butyrolactam as well as for their cross complex in chloroform. The solution environment significantly dampens the gas-phase preference for the hydrogen bonding with butyrolactam. Consistent with recent experimental results for related intramolecular associations, the symmetry-corrected K_a ratios for lactam-lactam over imide-lactam and imide-lactam over imide-imide are both computed to be about 3, while the differences in optimal gas-phase interactions are nearly 2 kcal/mol. However, the remarkable observations of stronger association of imides rather than lactams with adenines also emerges from similar simulations for complexes of succinimide and butyrolactam with 9-methyladenine. The symmetry-corrected K_a ratios favoring the imide are now ca. 2 and 6 for the Watson-Crick and Hoogsteen orientations. The origin of these variations is shown to arise in a straightforward way from secondary electrostatic interactions.

Introduction

Amido groups are the most common sites for molecular recognition through hydrogen bonding in natural systems. Consequently, it is important to understand the energetic and structural details of such interactions which can often be subtle. A case in point is the notable variation in preferences for association with imides and lactams that has been observed. The self-association of lactams is greater than for related imides. Typical association constants, K_a, in carbon tetrachloride are 100-300 M^{-1} for lactams and 10-60 M^{-1} for imides including butyrolactam and 2-ethyl-2-methylsuccinimide.[1-3] It should be realized that the imide

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