# Relative Binding Affinity of Carboxylate and Its Isosteres: Nitro, Phosphate, Phosphonate, Sulfonate, and δ-Lactone

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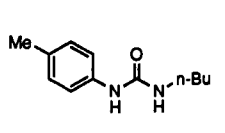
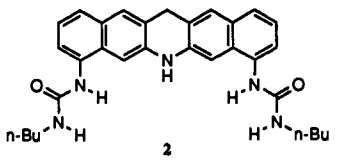
**Abstract:** Using the mono and ditopic receptors **1** and **2** (*N*-*n*-butyl-*N'*-*p*-tolylurea and 4,8-bis[((*n*-butylamino)carbonyl)amino]dibenz[*b*, *i*]acridan), the relative binding affinities of the title functional groups were determined to be $ArOPO_3^{2-} \geq ArPO_3^{2-} > ArCOO^- \geq ArP(OH)O_2^- > ArOP(OH)O_2^- > ArSO_3^- >$ δ-lactone $> ArNO_2$. No evidence of hydrogen bonding of nitrobenzene to **1** was detected in either $CDCl_3$ or DMSO-$d_6$, but in $CCl_4$, $K_{assoc} = 180\ M^{-1}$. Ditopic receptor **2** was designed as a receptor for *meta*-disubstituted aromatic substrates and binds some (isophthalate and 1,3-$C_6H_4(P(OH)O_2^-)_2$) with high affinity ($K_{assoc} > 10^4\ M^{-1}$) in DMSO-$d_6$. In contrast, the isosteric *m*-dinitrobenzene is not bound by **2** in that solvent, which further illustrates the relatively poor hydrogen bonding ability of nitro groups.

Binding interactions figure prominently in myriad chemical and biochemical processes. The consequences of such fundamental events in molecular recognition are as disparate as cellular self-assembly, enzyme/substrate affinity, host/guest association, crystallization, and the formation of new materials. It is widely recognized that carboxylate, phosphate, and nitro groups are often involved in binding interactions, where they act as bidentate participants. Less commonly remarked are that the neutral nitro, the mono anionic carboxylate, and the mono-, di-, or trianionic phosphate groups are approximately isosteric and that other isosteres include sulfonates, phosphonates, and lactones. Moreover, despite the structural similarity of those units and the prominence of several in various aspects of molecular recognition, to date no direct assessment of the relative affinity of all of these isosteres toward a common partner has been described.[1] We now provide such an assessment and include a partial survey of the effects of three solvents, $CDCl_3$, DMSO, and $CCl_4$, on binding affinity.

Monourea **1** and bisurea **2** were selected as the initial binding partners; unsymmetrical monourea **1** was chosen instead of a symmetrical variant in order to facilitate comparison of binding studies involving **1** and **2** with the various substrates. It has been demonstrated[2] that *N*, *N'*-disubstituted ureas preferentially adopt the *trans*,*trans* geometry reflected in the drawings of **1** and **2**.




**1**




**2**

The binding constants for benzoate and its isosteres with **1** are shown in Table 1. The initial use of a relatively nonpolar solvent such as $CDCl_3$ was intended to favor hydrogen bonding and electrostatic interactions, but the insolubility of some of the anionic substrates required the use of a more polar solvent; DMSO served the purpose. In some instances it was possible to carry out binding studies of the same partners in both DMSO-$d_6$ and $CDCl_3$ in order to gauge the effect of solvent polarity. Again, for solubility reasons, anionic substrates were generally studied as their tetrabutylammonium salts, but in the case of benzenesulfonate, the sodium salt was also sufficiently soluble to carry out the control study, showing that the counterion ($Na^+$ versus $Bu_4N^+$) did not affect the strength of the binding interaction.

Examination of the data in Table 1 is revealing. Table 1 lists the substrates in order of increasing binding strength (except for the last two entries). The values of the association constants ($K_{assoc}$) correlate relatively well with the net charge on the substrate. Thus, in DMSO, all of the anionic species bind more tightly than their neutral counterparts. But in contrast to lactone **4**, nitrobenzene does not significantly bind to **1**, even in $CDCl_3$, despite the much greater concentration of negative charge on the oxygens in nitrobenzene compared to lactone **4** (a lactone rather than an ester was chosen because esters preferentially adopt[3] an *s-trans* conformation which would not be compatible with two-point binding to **1**). That the nitro group was such a poor binder was surprising to us. The lack of binding between **1** and **3** is not

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(1) For a less extensive comparison, see: Smith, P. J.; Reddington, M. V.; Wilcox, C. S. *Tetrahedron Lett.* **1992**, *33*, 6085.

(2) Mido, Y. *Bull. Chem. Soc. Jpn.* **1974**, *47*, 1833.

(3) Cf. Sutherland, I. O. In *Comprehensive Organic Chemistry*; Barton, D., Ollis, W. D., Eds.; Pergamon: Oxford, 1979; Vol 2., p 869.

(4) For the $pK_a$ values from which the $pK_b$ values were calculated, see the following. (a) Benzoic acid: Fischer, A.; Mann, B. R.; Vaughan, J. *J. Chem. Soc.* **1961**, 1093. (b) Phenylphosphonic acids: Jaffe, H. H.; Freed, L. D.; Doak, G. O. *J. Am. Chem. Soc.* **1953**, *75*, 2209. (c) Phenyl mono- and dihydrogen phosphate: Chanley, J. D.; Feageson, E. *J. Am. Chem. Soc.* **1955**, *77*, 4002. (d) Benzenesulfonic acid: Cerfontain, H.; Telder, A. K.; Kruk, G. C. *Tetrahedron Lett.* **1975**, 3639. (e) Nitrobenzene and aromatic esters: Arnett, E. M. *Prog. Org. Chem.* **1963**, *1*, 223.

(5) The dimensions quoted are either taken directly from the data in the following papers or estimated using that data. (a) For *N*,*N'*-disubstituted ureas, see: Coiro, V. M.; Giacomello, P.; Giglio, E. *Acta Crystallogr.* **1971**, *B27*, 2112. Dannecker, W.; Kopf, J.; Rust, H. *Cryst. Struct. Commun.* **1979**, *8*, 429. Lind, M. D. *Acta Crystallogr.* **1970**, *B26*, 590. (b) For benzoate see: Kashino, S.; Kataoka, S.; Haisa, M. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 1717. Oxton, I. J.; Cameron, T. S.; Knop, O. *Can. J. Chem.* **1977**, *55*, 3831. Kashino, S. *Acta Crystallogr.* **1973**, *B29*, 1836. Skinner, J. M.; Stewart, G. M. D.; Speakman, J. C. *J. Chem. Soc.* **1954**, 180. (c) For sulfonate, see: Couldwell, J. O.; Prout, K.; Robey, D.; Taylor, R. *Acta Crystallogr.* **1978**, *B34*, 1491. Lundgren, J. O.; Williams, J. M. *J. Chem. Phys.* **1973**, *58*, 788. Arora, S. K.; Sundaralingam, M. *Acta Crystallogr.* **1971**, *B27*, 1293. Hargreaves, A. *Acta Crystallogr.* **1957**, *10*, 191. Broomhead, J. M.; Nicol, A. D. I. *Acta Crystallogr.* **1948**, *1*, 88. (d) For nitro compounds, see: Mayerle, J. J.; Clarke, T. C.; Bredfeldt, K. *Acta Crystallogr.* **1979**, *B35*, 1519. Kimura, M.; McCluney, R. E.; Watson, W. H. *Acta Crystallogr.* **1979**, *B35*, 483. Talberg, H. J. *Acta Chem. Scand.* **1978**, *A32*, 373. Lolapietro, M.; Domenicano, A. *Acta Crystallogr.* **1977**, *B33*, 2240. Barve, J. V.; Pant, L. M. *Acta Crystallogr.* **1971**, *B27*, 1158. Trotter, J. *Tetrahedron* **1960**, *8*, 13. (e) For phosphate monoanions see: Caughlan, C.N.; Li, C.-T. *Acta Crystallogr.* **1965**, *19*, 637. (f) For phosphate dianions see: Caughlan, C.N.; Ul-Haque, M. *Inorg. Chem.* **1967**, *6*, 1998. (g) For phosphonate monoanions see: Sheldrick, V. W. S.; Morr, M. *Acta Crystallogr.* **1981**, *B37*, 733. Barnett, B. L.; Strickland, L. C. *Acta Crystallogr.* **1979**, *B35*, 1212. Jones, P. G.; Kennard, O. *Acta Crystallogr.* **1978**, *B34*, 2309. Collins, A. J.; Fraser, G. W.; Perkins, P. O. *J. Chem. Soc., Dalton Trans.* **1974**, 960. Philippot, E.; Jumas, J. C.; Brun, G.; Maurin, M. *Cryst. Struct. Commun.* **1972**, *1*, 103. (h) For phosphonate dianions see; Hanson, J. C.; Jensen, L. H.; Herriott, J. R. *Acta Crystallogr.* **1972**, *A28*, s40. Herriott, J. R.; Love, W. *Acta Crystallogr.* **1968**, *B24*, 1014. Beard, L. N.; Lenhert, P. G. *Acta Crystallogr.* **1968**, *B24*, 1529.

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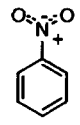
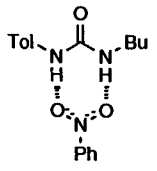
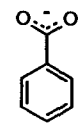
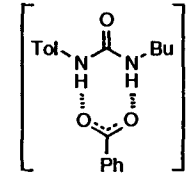
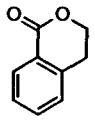
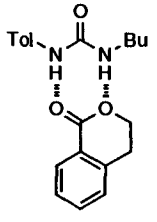
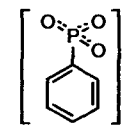
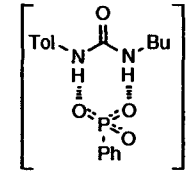
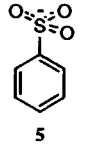
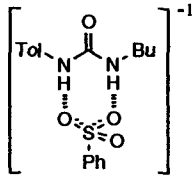
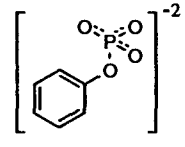
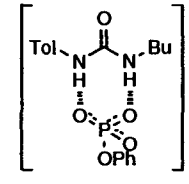
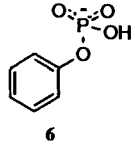
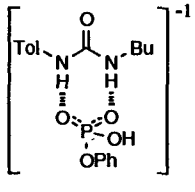
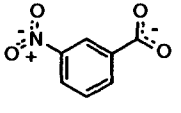
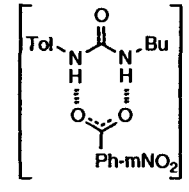
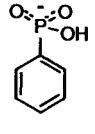
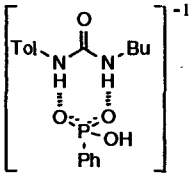
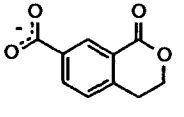
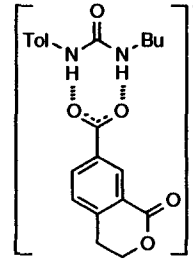
**Table 1.** Binding of **1** with Various Substrates[a]

| Substrate | Presumed complex | Solvent | $K_{assoc}$ $M^{-1}$ | Basicity ($pK_b$) of substrate (approx)[c] | Å[d] | Substrate | Presumed complex | Solvent | $K_{assoc}$ $M^{-1}$ | Basicity ($pK_b$) of substrate (approx.) | Å[d] |
|---|---|---|---|---|---|---|---|---|---|---|---|
|  **3** |  | $CDCl_3$ | binding not detected[e] | 25 | 2.15 |  **8** |  | $CDCl_3$ | 1300 (±200) | 10 | 2.23 |
| | | DMSO | binding not detected[e] | | | | | DMSO | 150 (±3) | | |
| | | $CCl_4$ | 180 (±40) | | | | | | | | |
|  **4** |  | $CDCl_3$ | 13 (±1) | 21 | 2.22[f] |  **9** |  | $CDCl_3$ | not soluble | 7 | 2.55 |
| | | DMSO | binding not detected[e] | | | | | DMSO | 2500 (±800) | | |
| | | $CCl_4$ | 330 ( ±120) | | | | | | | | |
|  **5** |  | $CDCl_3$ | not soluble | 20 | 2.42 |  **10** |  | $CDCl_3$ | not soluble | 8 | 2.57 |
| | | DMSO | 13[b](±3) | | | | | DMSO | 3600 (±1000) | | |
|  **6** |  | $CDCl_3$ | not soluble | 13 | 2.55 |  **11** |  | DMSO | 163 (±16) | | 2.23 |
| | | DMSO | 27 (±4) | | | | | | | | |
|  **7** |  | $CDCl_3$ | not soluble | 12 | 2.55 |  **12** |  | DMSO | 160 (±7) | | 2.23 |
| | | DMSO | 140 (±13) | | | | | | | | |

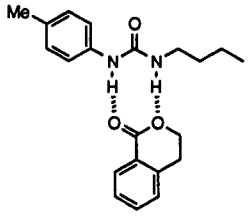
[a] Anions were studied as their $n$-$Bu_4N^+$ salts unless otherwise indicated. [b] The $Na^+$ salt and the $n$-$Bu_4N^+$ salt have exactly the same $K_{assoc}$ value. [c] See ref 4 for sources of $pK_b$ data. [d] See ref 5 for sources of dimensions. [e] A $K_{assoc}$ of ≥1 would have been detected. [f] Calculated value (PCMODEL).

due to some competing $\pi$–$\pi$ interaction: a control study (in $CDCl_3$) shows that nitrobenzene does not bind detectably to *N,N'*-di(*n*-butyl)urea either.

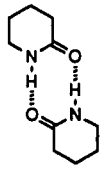
The most recent monograph[6] on hydrogen bonding does not list the nitro group as a hydrogen bonding partner (and Pimentel and McClellan's classic text *The Hydrogen Bond*[7] makes no mention of nitro groups). Vinogradov and Linnell's book *hydrogen bonding*,[8] published in 1971, rates nitro groups as "borderline" hydrogen bonding partners. Nonetheless, the recent work of Etter[9] and the undergraduate organic experiment[10] that separates *o*- and *p*-nitrophenol by steam distillation document the ability of nitro groups to serve as hydrogen bond acceptors. Evidently, however, despite the near perfect isosterism of nitrobenzene for benzoate, the data in Table 1 indicate that nitro and carboxylate are in different leagues so far as their hydrogen bonding ability is concerned.

As noted above, there is a reasonably good correlation of the relative hydrogen bonding abilities of the isosteres with their net charge, but that correlation does not explain the difference among species with the same charge. The exact distance between the two oxygens (see Table 1) does not appear very important since the interoxygen distance most similar to the H–H distance in the urea (2.1 Å[2,5a]) is that of nitrobenzene, which is the weakest binder. The best correlation we have found for the binding strengths of isosteres **3–12** is with their Brönsted basicity,[3,4] as tabulated in Table 1. Thus, nitrobenzene, which is the weakest base, is the weakest binder, and the phosphate and phosphonate dianions, which are the strongest bases, are the strongest binders.[11]

We find it interesting to note that the $K_{assoc}$ for the lactone/urea complex **13** in $CDCl_3$ is stronger than that for the dimer (**14**) of $\gamma$-valerolactam.[12] Since the components of **13** and **14** are all uncharged, the smaller $K_{assoc}$ of **14** may result from operation of negative secondary hydrogen bonding interactions, as proposed by Jorgensen.[13]




13

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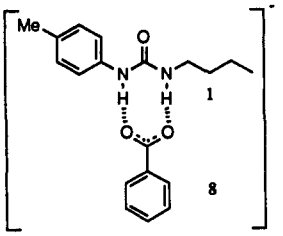
Thermodynamic parameters for the complex **15** in $CDCl_3$ and DMSO were obtained by titrations of **1** with **8** over a temperature range of 298–328 K. Plots of R ln $K$ versus $1/T$ gave a straight line ($R > 0.99$), from which $\Delta H_{assoc}$ and $\Delta S_{assoc}$ values were derived.[14] In $CDCl_3$, $\Delta G = -4.4$ kcal·mol$^{-1}$, $\Delta H = -3.1$ kcal·mol$^{-1}$ and $\Delta S = 4.5$ cal·mol$^{-1}$·K$^{-1}$; in DMSO-$d_6$, $\Delta G = -3.0$ kcal·mol$^{-1}$, $\Delta H = -2.8$ kcal·mol$^{-1}$, and $\Delta S = 0.7$ cal·mol$^{-1}$·K$^{-1}$. As expected from the less polar nature of $CDCl_3$ and its lesser ability to compete

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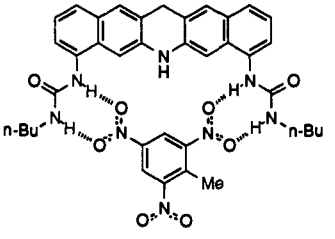
as a hydrogen bonding partner, binding of **1** with **8** is stronger in $CDCl_3$ than in DMSO. The difference in binding affinity in the two solvents is due primarily to entropic rather than enthalpic factors since the $\Delta H$ of binding is approximately the same in the two solvents. Net entropy changes are small in DMSO-$d_6$ but substantially positive in $CDCl_3$.[15]

The superiority of chloroform over carbon tetrachloride as a solvent and the present ubiquity of deuterium-lock NMR spectrometers have made $CDCl_3$ the standard solvent when using NMR to measure binding affinities of hydrogen bonding partners in a (relatively) nonpolar medium. Earlier workers who toiled without the benefit (or myopia?) of NMR regarded $CCl_4$ as superior to $CHCl_3$ ($CDCl_3$), since hydrogen bonding interactions are stronger in $CCl_4$ because $CHCl_3$ can compete as a hydrogen bond partner.[16] Accordingly, the binding of nitrobenzene (**3**) and urea **1** was assayed in $CCl_4$. In contrast with $CDCl_3$, in $CCl_4$, substantial binding ($K_{assoc} = 180$ M$^{-1}$) is, in fact, observed. Thus, in the absence of a competing solvent, the nitro group does function effectively as a hydrogen bond partner. Similarly, urea **1** binds lactone **4** with considerably greater affinity in $CCl_4$ than in $CDCl_3$.

The studies with **1** were conducted concurrently with the synthesis and evaluation of the ditopic[17] receptor **2**. The latter was of interest for two reasons. First, space-filling models suggested that **2** was ideally contoured to serve as a receptor (see **16**) for *meta*-dinitro-substituted benzenes. Such a receptor might

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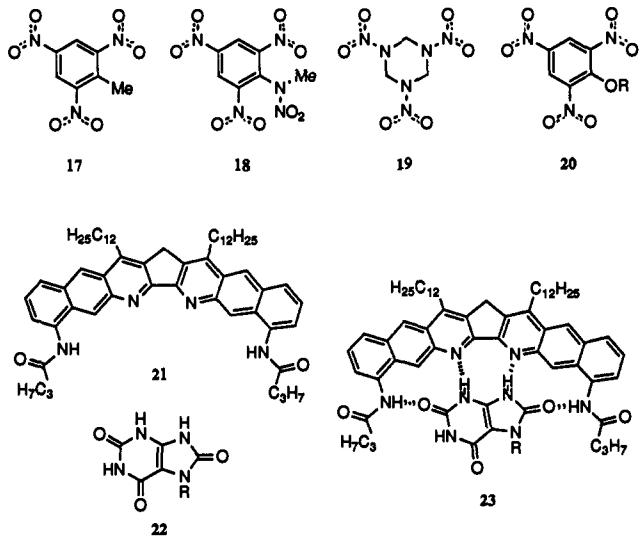
find use, for instance, in a sensor designed to detect explosives such as TNT (**17**), nitramine (tetryl, **18**), cyclonite (RDX, **19**), and picrates (**20**), all of which share as a common feature a *meta*-dinitro-substituted, six-membered ring. The relative rigidity/preorganization[18] of **2** was expected to confer selectivity and foster strong binding. We previously[19] showed that **21**, whose degree of preorganization is similar to that of **2**, binds uric acids (**22**) and related compounds with very high affinity: the dissociation constant for complex **23** is 1 $\mu$M ($K_{assoc} = 10^6$ M$^{-1}$).

The second reason for studying **2** was that it offered a possible way of evaluating the strength of binding interactions too weak to assess using the monotopic urea **1**. For example, in the event that the binding ability of nitro groups was not strong enough to allow significant formation of a **15**-like complex in $CDCl_3$ or

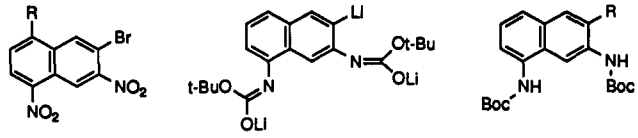
(6) Jeffrey, G. A.; Saenger, W. *Hydrogen Bonding in Biological Structures*; Springer Verlag: Berlin, 1991.
(7) Pimentel, G. C.; McClellan, A. L. *The Hydrogen Bond*; W. H. Freeman & Co.: San Francisco, CA, 1960.
(8) Vinogradov, S. N.; Linnell, R. H. *hydrogen bonding*; Van Nostrand Reinhold Co.: New York, 1971; p 14. See also: Baitinger, W. F.; Schleyer, P. von R.; Murty, T. S. S. R.; Robinson, L. *Tetrahedron* **1964**, *20*, 1635.
(9) Etter, M. C. *Acc. Chem. Res.* **1990**, *23*, 120.
(10) Cf. Moore, J. A.; Dalrymple, D. L. *Experimental Methods in Organic Chemistry*, 2nd ed.; W. B. Saunders Co.: Philadelphia, PA, 1976; p 192.
(11) For an earlier discussion of the relevance of Brönsted acidity and basicity to hydrogen bonding, see: Hine, J. *Structural Effects on Equilibria in Organic Chemistry*; Wiley Interscience: New York, 1975; p 200.
(12) Jeong, K. S.; Tjivikua, T.; Muehldorf, A.; Deslongchamps, G.; Famulok, M.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1991**, *113*, 201 and references therein.
(13) Jorgensen, W. L.; Pranata, J. *J. Am. Chem. Soc.* **1990**, *112*, 2008. Pranata, J.; Wieischke, S. G.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1991**, *113*, 2810.
(14) Kim, M. H. Ph.D. Thesis, Boston College, Chestnut Hill, MA, 1993.
(15) Cf. Garcia-Tellado, F.; Goswami, S.; Chang, S. K.; Hamilton, A. D. *J. Am. Chem. Soc.* **1990**, *112*, 7393.
(16) See, for example, ref 7, p 218.
(17) For a survey of ditopic receptors, see Sutherland, I. O. In *Advances in Supramolecular Chemistry*; Gokel, G. W., Ed.; JAI Press: Greenwich, CT, 1990; p 65.
(18) Cram. D. J. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1039.
(19) Kelly, T. R.; Maguire, M. P. *J. Am. Chem. Soc.* **1987**, *109*, 6549.




DMSO, comparison of the binding of benzoate and *m*-nitrobenzoate to **2** might provide a more exact measure of the hydrogen bonding ability of nitro groups, since the carboxylate/urea binding would position the nitro group proximate to its presumed hydrogen bonding partner.

Receptor **2** was synthesized as shown in Scheme 1 using naphthalene **25** as a key building block. Achievement of a 2,3-disubstitution pattern in naphthalenes is usually a synthetically exacting challenge, since electrophilic aromatic substitution reactions normally occur at $\alpha$- and not $\beta$- positions. However, the Hyman laboratory's[20] development of the chemistry of the bis(hexachlorocyclopentadiene) adduct of naphthalene provided easy access to **25**. In fact, **25** is available in a single step from the inexpensive, commercially available precursor **24**.

Attempted nitration of **25** under conditions where **25** reacted led primarily to **36**, the product of dinitration, rather than the desired **37**. In contrast, nitration of amine **26** (as the ammonium

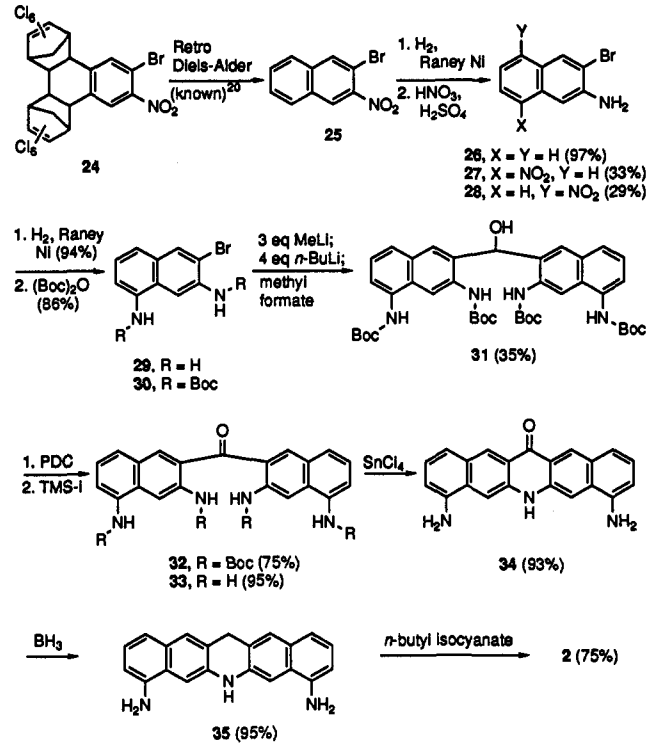



ion under the conditions of the reaction), which had been obtained cleanly from **25** by Raney nickel-catalyzed reduction, gave the desired **27** in 33% yield, along with a similar amount of the isomer **28**, which was separated by chromatography. Reduction of **27** to **29** and reaction of the latter with di-*tert*-butyl pyrocarbonate then afforded bromide **30**.

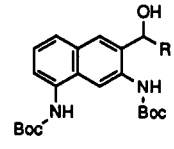
It had been our plan to treat **30** with 3 equivalents of butyllithium with the expectation that the first 2 equiv of BuLi would deprotonate the acidic -N*H* groups and that the third equivalent of BuLi would then effect halogen/metal exchange to give **38**. Reaction of **38** with a double-barreled electrophile such as methyl formate should then give **31**, but attempts to achieve that end gave largely **39** after workup. Use of other electrophiles such as TMS-Cl and MeSSMe gave only small yields of the expected products. Quenching of the reaction mixture with $D_2O$ gave (after an aqueous workup that exchanged N*D* to N*H*) primarily **39**, not the deuterated analog **40**. Those and related studies led us to conclude that halogen/metal exchange was occurring with **30** before both N*H*s had been deprotonated and that a remaining N*H* was quenching the carbanionic site.

(20) Danish, A. A.; Silverman, M.; Tajima, Y. A. *J. Am. Chem. Soc.* **1954**, *76*, 6144. See, also: Look, M. In *Selections from the Aldrich. Acta*; Aldrich Chemical Co., Inc.: Milwaukee, WI, 1984; p 40.

**Scheme 1**




Extensive experimentation was then aimed at identifying a base for deprotonating the N*H*s prior to halogen/metal exchange. Use of NaH, KH or LiN(*i*-Pr)$_2$, followed by treatment with *n*-, *sec*-, or *tert*-butyllithium and reaction with electrophiles, gave unsatisfactory results. An acceptable solution was eventually found which involved treating **30** first with 3 equiv of methyllithium, followed by transmetalation with 4 equiv of *n*-butyllithium and slow addition of methyl formate. The use of methyllithium to selectively deprotonate the N*H*s (but not to effect transmetalation of the bromide) was based on Gilman's[21] generalization that, unlike butyllithium, methyllithium is not effective in transmetalations. Slow addition of methyl formate was preferable to fast addition since fast addition gave more of the unwanted mixed methyl naphthyl and butyl naphthyl carbinols **41** and **42**, respectively, at the expense of the desired bis(naphthyl) carbinol **31**. Addition of the lithiated material to methyl formate gave a very poor yield of **31**, in part because remaining *n*-BuLi/MeLi competed to give **41**/**42**. Alcohol **31** was then oxidized to ketone

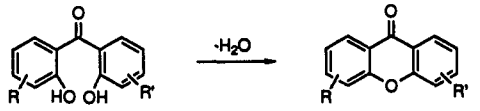



**32** with pyridinium dichromate (attempts to convert **30** to **32** in one step by replacing the methyl formate with carbon dioxide[22] or ethyl *N*,*N*′-diethylcarbamate[23] gave no **32**). Cleavage of the BOC group was then achieved cleanly with trimethylsilyl iodide.[24]

Despite its close mechanistic parallel to the widely employed synthesis of xanthones by cyclization of 2,2′-dihydroxybenzophe-

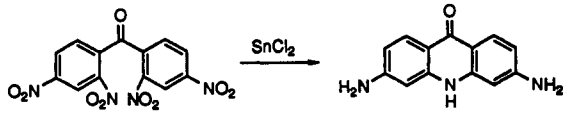
(21) Langham, W.; Brewster, P. Q.; Gilman, H. *J. Am. Chem. Soc.* **1941**, *63*, 545.
(22) Gilman, H.; Parker, H. H. *J. Am. Chem. Soc.* **1924**, *46*, 2816.
(23) Scilly, N. F. *Synthesis* **1973**, 160.
(24) Lott, R. S.; Chauhan, V. S.; Stammer, C. H. *J. Chem. Soc., Chem. Commun.* **1979**, 495.

nones (eq 1),[25] there are very few examples in the literature of the preparation of acridones by the analogous cyclization of 2,2′-diaminobenzophenones. However, Spalding et al.[26] reported that




(1)

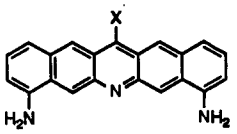
3,6-diaminoacridone itself can be prepared (eq 2) from 2,2′,4,4′-tetranitrobenzophenone using $SnCl_2$. We could not achieve




(2)

cyclization of **33** to **34** with $SnCl_2$, and use[27] of $H_3PO_4$ was also not very effective in producing **34**. Since Sn(IV) is a stronger Lewis acid than Sn(II), $SnCl_4$ would be expected to be a stronger activator of the carbonyl group in **33** than $SnCl_2$. In fact, it was eventually found that treatment of **33** with $SnCl_4$ generates the desired pentacyclic compound **34** in excellent yield. This result points toward an Sn(IV) species being the actual active catalyst in Spalding's cyclization[26] in eq 2, since some of the Sn(II) from the $SnCl_2$ used in the reaction would be converted to Sn(IV) during the process of the reduction of the nitro groups to amino groups.

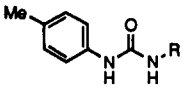
Dibenzacridone **34** is a very insoluble substance. We had anticipated that **34** would be poorly soluble, and the original plan had been to solve the solubility problem by converting the central pyridone ring of **34** to an alkoxypyridine unit as in **43** (in our experience, alkoxypyridines are generally more soluble than the corresponding pyridones) or, possibly, to the chloro derivative **44**. We were, however, not able to achieve the conversion of **34**



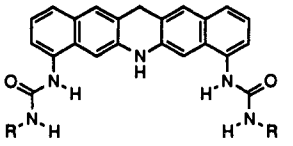

**43**, X = OR
**44**, X = Cl

to **43** or **44** in the limited number of reactions we attempted. Instead, **34** was reduced to **35** in high yield with diborane; as expected, **35** was considerably more soluble than **34** in all solvents examined. The two primary amine groups were then simultaneously converted to their *n*-butylurea derivatives with *n*-butyl isocyanate.

Bisurea **2** is adequately soluble in DMSO, but it is not sufficiently soluble in $CDCl_3$ or $CCl_4$ to conduct binding studies with putative binding partners. The selection of the *n*-butyl group was based on the results of a survey of the effect of the R group on the solubility of ureas **1** and **45-49** in $CHCl_3$. When R = benzyl, 1-adamantyl, or 1-dodecyl, the ureas were only partially soluble. When R = *n*-butyl, *tert*-butyl, or β-tritylethyl (-$CH_2$-$CH_2CPh_3$), the ureas exhibited good solubility. In studies leading to the development of a receptor for uric acids, workers in this laboratory[19] previously showed that attachment of a β-tritylethyl unit to the $N^7$ nitrogen of uric acid was sufficient to confer some solubility of uric acid in nonpolar solvents; the β-tritylethyl unit has also solved solubility problems for others.[28] Unfortunately,




**45**, R = benzyl
**46**, R = dodecyl
**47**, R = 1-adamantyl
**48**, R = *t*-butyl
**49**, R = β-tritylethyl
**1**, R = *n*-butyl




**50**, R = β-tritylethyl
**51**, R = *t*-butyl
**2**, R = *n*-butyl

neither the bis(β-tritylethyl)urea **50** nor **51** nor **2** was sufficiently soluble in $CDCl_3$ to carry out binding studies. All three are adequately soluble in DMSO. Because *n*-butyl isocyanate is commercially available, **2** was chosen over **50**. The *n*-butyl derivative **2** was chosen over the *tert*-butyl isomer **51** because the yield of the synthesis of the former is better.

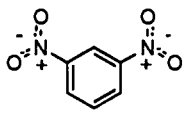
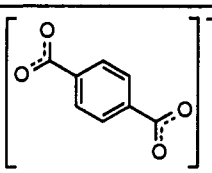
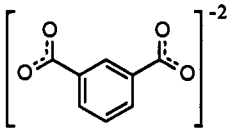
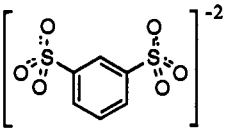
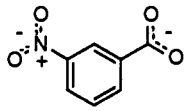
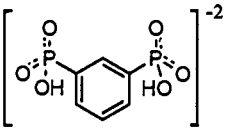
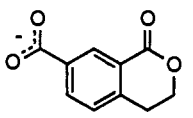
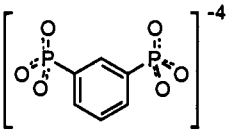
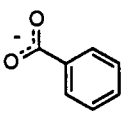
The binding of bisurea **2** with the various putatively ditopic partners **8**, **11**, **12**, and **52-57** in DMSO-$d_6$ was then examined (Table 2). To our surprise, *m*-dinitrobenzene (**52**), chosen as a nonexplosive stand-in for the more dangerous **17-20**, exhibited no evidence of binding to **2**. That binding does not occur despite the possibility for forming four N—H···O hydrogen bonds demonstrates clearly how poor nitro groups are as intermolecular hydrogen bond acceptors in solution. It also suggests that the forces that operate to orient molecules in crystals designed to involve nitro groups in hydrogen bonding are relatively weak, even though they are adequate for imposing order in the crystalline state.

Two controls were done to ensure that the failure of **2** to bind **52** was not due to misdesign or to the possibility that binding was occurring but that we were unable to detect it. Substitution of isophthalate (**53**) for **52** results in a very tightly bound complex.[29] On the other hand, the replacement of one of the carboxylate residues in isophthalate with a nitro group results in a reduction of binding affinity even below that of monotopic benzoate. At least in this system, nitro is actually counterproductive. It is not clear why nitro is deleterious. One might argue that the nitro group reduces the basicity of the carboxylate (**11** is approximately 0.7 $pK_b$ units less basic[30] than benzoate), but the nitro group does not diminish the affinity of **11** for monourea **1** (see Table 1).

The remaining ditopic substrates tabulated in Table 2 exhibit binding constants with bisurea **2** qualitatively in agreement with the affinities given in Table 1, although the binding of disulfonate **54** is a little lower than what one might expect on the basis of the $K_{assoc}$ = 13 for benzenesulfonate with monourea **1**. Perhaps the diminished binding of **54** reflects the consequences of an imperfect fit with a receptor (**2**) that is quite rigid and not able to adopt a geometry most complementary to **54**. Were that the case, one might expect binding of **55** to be similarly impaired, but it is not. Possibly the difference in binding between **54** and **55** is that the P–O and C–P bond lengths[5] in **55** are 0.10 and 0.04 Å longer, respectively, than the S–O and C–S bonds[5] in **54** and that **55** fits **2** slightly better.

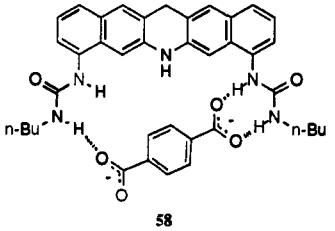
(25) Hepworth, J. D. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A.R., Rees, C. W., Eds.; Pergamon: Oxford, 1984; Vol. 3 (Boulton, A. J.; McKillop, A., Eds.), p 737.
(26) Spalding, D. P.; Moersch, G. W.; Mosher, H. S.; Whitmore, F. C. *J. Am. Chem. Soc.* **1946**, *68*, 1596.
(27) Parfitt, J. *J. Chem. Soc.* **1966**, 87.
(28) Whitesides, G. M.; Seto, C. T. *J. Am. Chem. Soc.* **1993**, *115*, 905.
(29) For a partial listing of papers describing other ditopic receptors that bind dicarboxylic acids (or their salts) see, inter alia: (a) Schiessl, P.; Schmidtchen, F. P. *Tetrahedron Lett.* **1993**, *34*, 2449. (b) Raposo, C.; Crego, M.; Partearroyo, A.; Mussons, L.; Caballero, C.; Moran, J. R. *Tetrahedron Lett.* **1993**, *34*, 1995. (c) Alcazar, V.; Diederich, F. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1521. (d) Fan, E.; Van Arman, S. A.; Kincaid, S.; Hamilton, A. D. *J. Am. Chem. Soc.* **1993**, *115*, 369. (e) Rebek, J., Jr.; Nemeth, D.; Ballester, P.; Lin, F.-T. *J. Am. Chem. Soc.* **1987**, *109*, 3474 and ref 15. A number of the so-called "Kemp triacid"-derived receptors reported by Rebek and colleagues (cf. Rebek, J., Jr.; Askew, B.; Killoran, M.; Nemeth, D.; Lin, F. T. *J. Am. Chem. Soc.* **1987**, *109*, 2426) are dicarboxylic acids or their salts. Whether they are receptors or substrates depends on one's point of view. Among recent reports of the use of ureas to bind carboxylate ions, see ref 1 and the following: Albert, J. S.; Hamilton, A. D. *Tetrahedron Lett.* **1993**, *34*, 7362. Hamann, B. C.; Branda, N. R.; Rebek, J., Jr. *Tetrahedron Lett.* **1993**, *34*, 6836. Note also: Etter, M. C.; Urbaficzyk-Lipkowska, Z.; Zia-Ebrahimi, M; Panunto, T. W. *J. Am. Chem. Soc.* **1990**, *112*, 8415
(30) Bolton, P. D.; Fleming, K. A.; Hall, F. M. *J. Am. Chem. Soc.* **1972**, *94*, 1033. Clark, R. T. H.; Ellis, A. J. J. *Chem. Soc.* **1960**, 247. Fischer, A.; Mann, B. R.; Vaughan, J. *J. Chem. Soc.* **1961**, 1093.

**Table 2.** Binding of Bisurea **2** with Various Substrates in DMSO[a]

| Substrate | $K_{assoc}$ ($M^{-1}$) | Substrate | $K_{assoc}$ ($M^{-1}$) |
|---|---|---|---|
|  **52** | no binding observed |  **56** | 745 (±60) |
|  **53** | 63000 (±7800) |  **54** | 30[b](±6) |
|  **11** | 86 (±16) |  **55** | 34000 (±4200) |
|  **12** | 87 (±10) |  **57** | receptor **2** decomposed |
|  **8** | 104 (±25) | | |

[a] Anions were studied as their $n$-$Bu_4N^+$ salts unless otherwise indicated. [b] $Na^+$ salt.

Shape selectivity of **2** for isophthalate (**53**) over terephthalate (**56**) is, as expected, very substantial, reflecting the rigidity of the receptor. That **2** binds **56** somewhat more strongly than benzoate may reflect **56**'s slightly greater (0.3 p$K_b$ units) basicity[31] or statistics (either carboxylate of **56** can bind), but probably it is mostly due to the involvement of a third hydrogen bond (see **58**), which models indicate is feasible.



**58**

**Conclusion.** The relative hydrogen bonding affinities of carboxylate and its isosteres for urea **1** have been measured. They establish the following ranking: $ArOPO_3^{2-} \geq ArPO_3^{2-} > ArCOO^- \geq ArP(OH)O_2^- \geq ArOP(OH)O_2^- > ArSO_3^- >$ $\delta$-lactone $> ArNO_2$ in DMSO. In the binding of benzoate with urea **1**, the difference between using DMSO-$d_6$ and $CDCl_3$ as solvent is about 1 order of magnitude in $K_{assoc}$; the $\Delta H$ of binding is approximately the same in those two solvents, but the $\Delta S$ of binding is substantially more positive in $CDCl_3$. The nitro group is an abysmal hydrogen bond partner in DMSO and even in $CDCl_3$, but in the less competitive solvent $CCl_4$, the nitro group's hydrogen bonding affinity toward urea **1** is substantial.

Results of studies using the pentacyclic, ditopic receptor **2** show the same relative binding affinities of the various functional groups as obtained with **1**. The inability of **2** to bind *m*-dinitrobenzene despite the potential to form four hydrogen bonds is noteworthy.

## Experimental Section[32]

**General Procedure for NMR Titrations and Determination of Association Constants. Method A (Titration Method).** For a specific example, the titration of monourea receptor **1** with benzoate **8** will be described here. A 0.013 M solution of **1** in DMSO-$d_6$ (1.3 mg in 0.50 mL) was prepared in a 5-mm NMR tube. A 0.199 M solution of **8** in DMSO-$d_6$ (247 mg in 2.00 mL) was prepared in a 2-mL volumetric flask under nitrogen. An initial NMR spectrum of the solution of **1** was taken, and the initial chemical shift of the urea N*H* proton was determined to be 8.39 ppm (control studies indicated that in the absence of binding partner, the chemical shift of the urea N*H* protons was not concentration dependent). The solution of substrate **8** was then added, initially in 10-$\mu$L portions, and the chemical shift of the urea N*H* proton was recorded after each addition. After ~1 equiv of guest had been added, the aliquot size was increased to 20 $\mu$L. After a total of 100 $\mu$L had been added, the aliquot size was increased to 40 $\mu$L until a total of 300 $\mu$L was added, and then 100-$\mu$L aliquots were added until a total of 1000 $\mu$L of guest

(31) Willi, A. V.; Stocker, J. F. *Helv. Chim. Acta* **1955**, *38*, 1279. Dondon, M. L. *J. Chim. Phys.* **1957**, *54*, 304.

(32) For general experimental procedures, see: Kelly, T. R.; Bridger, G. J.; Zhao, C. *J. Am. Chem. Soc.* **1990**, *112*, 8024.

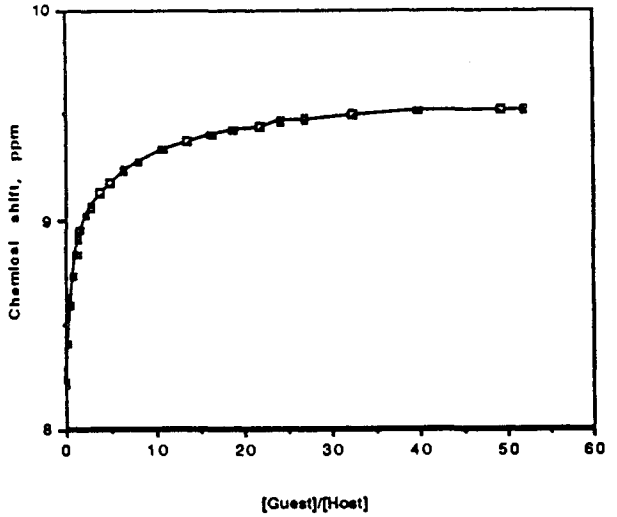



**Figure 1.** Plot of chemical shift versus [guest]/[host] obtained using method A. Guest and host concentrations for each point take into account the changes in volume.

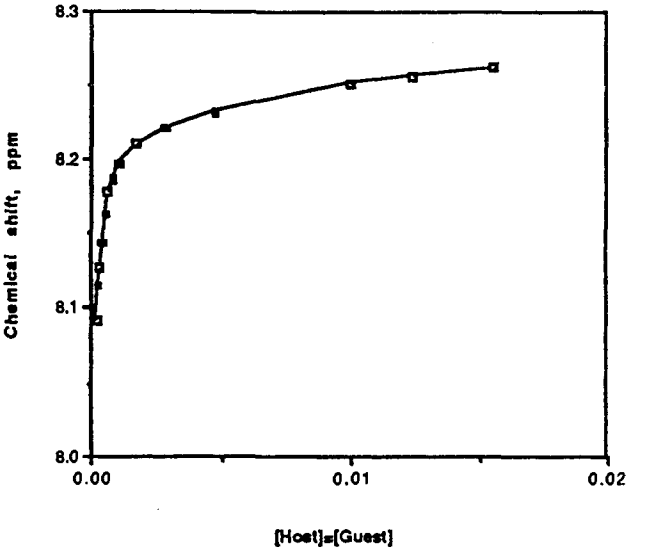



**Figure 2.** Plot of chemical shift versus concentration of host or guest obtained using method B.

had been added. Finally, 200-$\mu$L portions were added until no further change in the chemical shift of the urea N*H* proton was observed (usually ~2000 $\mu$L). The chemical shift of the urea N*H* proton at this saturation point was 10.88 ppm. The temperature of the NMR probe was 20–21 °C.

A graph was then plotted of chemical shift versus [guest]/[host] (Figure 1).

The association constant was obtained using the equation below:[33]

$$K_{assoc} = \alpha/[(1-\alpha)([G]-\alpha[H])]$$

where $\alpha = (\delta-\delta_0)/(\delta_{max}-\delta_0)$, $\delta_0$ is the initial chemical shift (host only), $\delta$ is the chemical shift at each titration point, and $\delta_{max}$ is the chemical shift when the receptor is entirely bound.

Values for the association constant were calculated for those cases where the amount of receptor bound ranged from 20 to 80%.[34] The average for those measurements was calculated, and the standard deviation was determined to give the $K_{assoc}$ values (and error limits) reported in Tables 1 and 2.

**Method B (Dilution Method).** For a specific example, the binding of bisurea receptor **2** with isophthalate dianion **53** will be described here. A 0.016 M solution of **2** and **53** (each) in DMSO-$d_6$ was prepared to give a 1.0:1.0 molar ratio of the binding partners in an NMR tube. An initial NMR spectrum of this solution was recorded. Progressively more dilute solutions were made by removing 100-$\mu$L aliquots of the original solution and diluting with the same amount of DMSO-$d_6$. Typically, spectra of 15–20 different solutions with concentrations ranging from 0.017 to ~0.0002 M (lower limit of NMR sensitivity) were recorded. A graph was then plotted of chemical shift versus concentration of host (or guest) (Figure 2). *Note*: a control study showed that in the absence of a guest, the chemical shift of the host **2** was changed very little (< 0.01 ppm) by variation of the concentation. The association constant was obtained using the equation below:[33]

$$K_{assoc} = \alpha/(1-\alpha)^2[c]$$

where $\alpha = (\delta-\delta_0)/(\delta_{max}-\delta_0)$, $\delta_0$ is the initial chemical shift (host only) obtained from method A, $\delta$ is the chemical shift at each titration point, $\delta_{max}$ is the chemical shift when the receptor is entirely bound (obtained from method A), and [*c*] = concentration of the host and guest.

The reported value of $K_{assoc}$ was calculated by averaging the values of $K_{assoc}$ obtained for each data point (20–80% bound). Errors are standard deviations.

Most substrates were available commercially as the acids, which were then converted to their tetrabutylammonium salts (see below). 3,4-Dihydro-1-oxo-1*H*-2-benzopyran-7-carboxylic acid (for **12**) was prepared using a procedure based on that of Bhide.[35] *m*-Phenylenediphosphonic acid was prepared by hydrolysis[36] (6 N HCl, 24 h reflux) of tetraethyl *m*-phenylenediphosphonate.[37]

**Preparation of Tetrabutylammonium Salts.** To a stirred solution of the acid (10.0 mmol) in dry methanol (10 mL) under nitrogen was added 1.0 equiv of a 1.0 M solution of tetrabutylammonium hydroxide in methanol (Aldrich) in one portion. The resulting mixture was stirred for 2 h at room temperature. The solvent was evaporated *in vacuo*, and the resulting solid was further dried for 24 h under high vacuum (<0.005 Torr) over $P_2O_5$. The resulting tetrabutylammonium salt was stored under anhydrous conditions.

***N*-*n*-Butyl-*N*'-*p*-tolylurea (1).** A mixture of *p*-toluidine (58 mg, 0.54 mmol), triethylamine (0.10 mL, 0.89 mmol), and *n*-butyl isocyanate (0.10 mL, 0.72 mmol) in dry THF (10 mL) was stirred at room temperature for 24 h under nitrogen. The solvent was evaporated, and the residue was further dried under high vacuum to give **1** (111 mg, 0.54 mmol, 100%) as a white solid: $^1$H NMR ($CDCl_3$) $\delta$ 0.90 (3 H, t, $J$ = 7.2 Hz), 1.33 (2 H, m), 1.45 (2 H, m), 2.31 (3 H, s), 3.24 (2 H, m), 4.93 (1 H, br s), 6.54 (1 H, br s), 7.10 (2 H, d, $J$ = 8.7 Hz), 7.15 (2 H, d, $J$ = 8.7 Hz); MS *m/z* (relative intensity) 206 (19, $M^+$), 108 (10), 107 (100); IR (KBr) $\nu$ 3318 (br), 2959, 2931, 2861, 1631, 1574, 1452 cm$^{-1}$. An analytical sample was obtained as a white solid, mp 112–113 °C, after recrystallization from $Et_2O$. Anal. Calcd for $C_{12}H_{18}N_2O$: C, 69.87; H, 8.80; N, 13.58. Found: C, 69.84; H, 8.79; N, 13.60.

**2-Bromo-3-nitronaphthalene (25).** The following procedure is a modification of one by Fenyes.[38] 2-Bromo-3-nitronaphthalene–bis(hexachlorocyclopentadiene) adduct (**24**, 204 g, 257 mmol, Aldrich) was placed in a 250-mL round-bottomed flask, and the flask was fitted with a distillation apparatus. A vacuum (0.05–0.1 Torr) was applied to the apparatus, and the flask was then heated at ~220 °C (internal temperature) using a heating mantle. The resulting distillate consisted essentially of a slurry of **25** with hexachlorocyclopentadiene. The solid was collected by filtration

(33) Horman, I.; Dreux, B. *Anal. Chem.* **1983**, *55*, 1219.
(34) Deranleu, D. A. *J. Am. Chem. Soc.* **1969**, *91*, 4044.
(35) Bhide, B. H. *Chem. Ind.* **1974**, 75.
(36) Bigge, C. F.; Johnson, G.; Ortwine, D. F.; Drummond, J. T.; Retz, D. M.; Brahce, L. T.; Coughenour, L. L.; Marcoux, F. W.; Probert, A. W., Jr. *J. Med. Chem.* **1992**, *35*, 1371.
(37) Tavs, P. *Chem. Ber.* **1970**, *103*, 2428.
(38) Fenyes, J. G. E. *J. Org. Chem.* **1962**, *27*, 2614.

and washed three times with hexane (30 mL portions). The solid was recrystallized from hexane to give **25** (54.1 g, 215 mmol, 84%) as yellow crystals: mp 73–75 °C (lit.[38] mp 84 °C); $^1$H NMR ($CDCl_3$) $\delta$ 7.67 (2 H, m), 7.84 (1 H, d, $J$ = 4.1 Hz), 7.94 (1 H, d, $J$ = 3.8 Hz), 8.22 (1 H, s), 8.40 (1 H, s); MS *m/z* (relative intensity) 253 (31, $M^+$), 251 (31, $M^+$), 195 (19), 193 (19), 126 (100); IR (KBr) $\nu$ 3058, 1623, 1588, 1525, 1434, 1342 cm$^{-1}$.

**2-Amino-3-bromonaphthalene (26).** A mixture of 2-bromo-3-nitronaphthalene (**25**, 5.00 g, 19.8 mmol) and approximately 6 g (dry weight) of Raney nickel (from a 50% slurry in water, Aldrich no. 22,167-8, which was freed from as much water as possible by decanting the $H_2O$ and then rinsed twice with absolute ethanol) in ethyl acetate (120 mL) was stirred under an atmosphere of hydrogen (balloon pressure) at room temperature for 2 h. The reaction mixture was freed from catalyst by filtration through Celite, and the solvent was evaporated to give **26** (4.25 g, 19.1 mmol, 96%) as an off-white solid, which was ordinarily used without further purification: $^1$H NMR ($CDCl_3$) $\delta$ 4.20 (2 H, br s), 7.09 (1 H, s), 7.23 (1 H, t, $J$ = 5.1 Hz), 7.37 (1 H, t, $J$ = 5.1 Hz), 7.56 (1 H, d, $J$ = 5.1 Hz), 7.61 (1 H, d, $J$ = 5.1 Hz), 7.98 (1 H, s); MS *m/z* (relative intensity) 223 (14, $M^+$), 221 (15, $M^+$), 115 (100); IR (KBr) $\nu$ 3466, 3374, 3051, 1623, 1602, 1497 cm$^{-1}$. An analytical sample was obtained as white plates, mp 165–166 °C, after recrystallization from petroleum ether. Anal. Calcd for $C_{10}H_8NBr$: C, 54.08; H, 3.63; N, 6.31. Found: C, 54.33; H, 3.53; N, 6.22.

**3-Amino-2-bromo-5-nitronaphthalene (27) and 2-amino-3-bromo-5-nitronaphthalene (28).** To a stirred mixture of 2-amino-3-bromonaphthalene (**26**, 6.76 g, 30.4 mmol) and concentrated $H_2SO_4$ (100 mL) at 0 °C was added a solution of fuming nitric acid (90%, 2.35 g, 33.5 mmol) dropwise over 30 min. After 1 h the ice bath was removed, and the reaction mixture was stirred for a further 2 h at room temperature. The reaction mixture was poured into ice/water (1.5 L), and the resulting mixture was basified to pH 9 with solid $Na_2CO_3$. This mixture was then filtered to give a brick red solid. Preliminary purification of the solid to eliminate polar impurities by vacuum filtration of a solution of it through a 5-in. × 3-in. pad of silica gel eluting with 1:1 ethyl acetate/petroleum ether gave a dark red solid. This was then further purified by flash column chromatography on a 2-in. × 10-in. column eluting with 1:5 ethyl acetate/petroleum ether to give first **27** (2.68 g, 10.0 mmol, 33%) and then the unwanted isomer **28** (2.39 g, 8.95 mmol, 29%) as a red solid. **27**: $^1$H NMR ($CDCl_3$) $\delta$ 4.65 (2 H, br s), 7.27 (1 H, t, $J$ = 7.7 Hz), 7.88 (1 H, dd, $J$ = 7.7, 1.2 Hz), 8.02 (1 H, s), 8.08 (1 H, s), 8.29 (1 H, dd, $J$ = 7.7, 1.2 Hz); MS *m/z* (relative intensity) 268 (36, $M^+$), 266 (38, $M^+$), 157 (39), 141 (100); IR (KBr) $\nu$ 3466, 3367, 1623, 1511 cm$^{-1}$. An analytical sample of **27** was obtained as a red powder, mp 180–182 °C, after recrystallization from 1:1 $Et_2O$/petroleum ether. Anal. Calcd for $C_{10}H_7N_2O_2Br$: C, 44.97; H, 2.64; N, 10.49. Found: C, 45.41; H, 2.34; N, 10.22. **28**: $^1$H NMR ($CDCl_3$) $\delta$ 4.47 (2 H, br s), 7.15 (1 H, s), 7.42 (1 H, t, $J$ = 7.8 Hz), 7.83 (1 H, dd, $J$ = 7.8, 0.9 Hz), 8.29 (1 H, dd, $J$ = 7.8, 0.9 Hz), 8.83 (1 H, s).

**2-Bromo-3,5-diaminonaphthalene (29).** A mixture of 3-amino-2-bromo-5-nitronaphthalene (**27**, 2.10 g, 7.86 mmol) and approximately 5 g (dry weight) of Raney nickel (from a 50% slurry in water, Aldrich no. 22,167-8, which was freed from as much water as possible by decanting the $H_2O$ and then rinsed twice with absolute ethanol) in ethyl acetate (150 mL) was stirred under an atmosphere of hydrogen (balloon pressure) at room temperature for 1.5 h. The reaction mixture was freed from catalyst by filtration through Celite, and the solvent was evaporated to give **29** (1.70 g, 7.17 mmol, 91%) as a gray solid which was ordinarily used without further purification: $^1$H NMR ($CDCl_3$) $\delta$ 3.92 (2 H, br s), 4.25 (2 H, br s), 6.71 (1 H, dd, $J$ = 7.4, 1.2 Hz), 7.06 (1 H, s), 7.07 (1 H, t, $J$ = 7.4 Hz), 7.13 (1 H, dd, $J$ = 7.4, 1.2 Hz), 7.94 (1 H, s); MS *m/z* (relative intensity) 238 (65, $M^+$), 236 (68, $M^+$), 130 (100); IR (KBr) $\nu$ 3423, 3346, 1623, 1574, 1497 cm$^{-1}$ An analytical sample was obtained as pale brown needles, mp 102–103 °C, after recrystallization from 1:1 $Et_2O$/petroleum ether. Anal. Calcd for $C_{10}H_9N_2Br$: C, 50.66; H, 3.83; N, 11.81. Found: C, 50.95; H, 3.59; N, 11.76.

**2-Bromo-3,5-bis-[((1,1-dimethylethoxy)carbonyl)amino]-naphthalene (30).** A stirred solution of 2-bromo-3,5-diaminonaphthalene (**29**, 4.87 g, 20.5 mmol) and di-*tert*-butyl dicarbonate (50.0 g, 229 mmol) in dry THF (100 mL) was refluxed for 5 days under nitrogen. After the solution cooled to room temperature, the solvent was evaporated, and the resulting residue was dissolved in ethyl acetate (250 mL) and washed with 1 M citric acid (150 mL) and then brine (150 mL). The organic phase was dried ($MgSO_4$), and the ethyl acetate was evaporated. The residue was purified by flash column chromatography on a 2-in. × 13-in. column eluting with 1:5 $Et_2O$/petroleum ether to give **30** (7.36 g, 16.8 mmol, 82%) as a white solid: $^1$H NMR ($CDCl_3$) $\delta$ 1.57 (9 H, s), 1.59 (9 H, s), 6.89 (1 H, br s), 7.22 (1 H, br s), 7.36 (1 H, t, $J$ = 8.1 Hz), 7.45 (1 H, apparent d, $J$ = 8.1 Hz), 7.90 (1 H, dd, $J$ = 8.1, 0.3 Hz), 8.04 (1 H, s), 8.59 (1 H, s); MS *m/z* (relative intensity) 439 (8, $M^+$), 437 (9, $M^+$), 326 (16), 324 (16), 287 (87), 285 (87), 130 (100); IR (KBr) $\nu$ 3452, 3416, 3304, 2981, 2931, 1736, 1715, 1546, 1511 cm$^{-1}$. An analytical sample was obtained as pale yellow needles, mp 141–142 °C, after recrystallization from petroleum ether. Anal. Calcd for $C_{20}H_{25}N_2O_4Br$: C, 54.93; H, 5.76; N, 6.41. Found: C, 55.23; H, 5.79; N, 6.39.

**Bis[2-[3,5-bis[((1,1-dimethylethoxy)carbonyl)amino]naphthyl]]-methanol (31).** To a stirred solution of 2-bromo-3,5-bis[((1,1-dimethylethoxy)carbonyl)amino]naphthalene (**30**, 1.83 g, 4.18 mmol) in dry THF (80 mL) under nitrogen was added methyllithium (9.0 mL of a 1.4 M solution in $Et_2O$, 13 mmol; Aldrich) at −78 °C. The reaction mixture was then warmed to −23 °C and stirred for 1 h at that temperature. The reaction mixture was recooled to −78 °C, *n*-butyllithium (6.7 mL of a 2.5 M solution in hexane, 17 mmol; Aldrich) was added in one portion, and the reaction mixture was stirred for 30 min at this temperature. The reaction mixture was warmed to 0 °C and stirred for 40 min, and then methyl formate (8.5 mL of a 1.0 M solution in THF, 8.5 mmol) was added dropwise over 10 min. After the mixture was stirred another 10 min, additional methyl formate solution (2.0 mL, 2.5 mmol) was added dropwise over 10 min. The reaction mixture was stirred for a further 15 min, and then the ice bath was removed. The reaction was stirred for a further 30 min before being quenched by water (20 mL) and then extracted with $Et_2O$ (3 × 60 mL). The combined organic phases were dried ($MgSO_4$), and the solvent was evaporated. The residue was purified by flash column chromatography on a 1.5-in. × 12-in. column eluting with 1:1 $Et_2O$/petroleum ether to give **31** (0.57 g, 0.76 mmol, 36%) as a yellow glass: $^1$H NMR ($CDCl_3$) $\delta$ 1.46 (18 H, s), 1.59 (18 H, s), 4.38 (1 H, br s), 6.18 (1 H, d, $J$ = 1.5 Hz), 6.92 (2 H, s), 7.27 (2 H, d, $J$ = 7.2 Hz), 7.34 (2 H, t, $J$ = 7.2 Hz), 7.37 (2 H, s), 7.84 (2 H, d, $J$ = 7.2 Hz), 8.01 (2 H, s), 8.30 (2 H, s); IR (KBr) $\nu$ 3416, 3311 (br), 2981, 2931, 1729, 1680, 1546, 1511 cm$^{-1}$. An analytical sample was obtained as pale yellow needles, mp 202–204 °C, after recrystallization from 5:1 petroleum ether/$Et_2O$. Anal. Calcd for $C_{41}H_{52}N_4O_9$: C, 66.13; H, 7.04; N, 7.52. Found: C, 66.25; H, 6.82; N, 7.40.

**Bis[2-[3,5-bis[((1,1-dimethylethoxy)carbonyl)amino]-naphthyl]] Ketone (32).** To a stirred suspension of pyridinium chlorochromate (2.00 g, 9.29 mmol) in $CH_2Cl_2$ (30 mL) at room temperature under nitrogen was added a solution of bis[2-[3,5-bis[(1,1-dimethylethoxy)carbonyl)amino]naphthyl]]methanol (**31**, 0.51 g, 0.68 mmol) in $CH_2Cl_2$ (30 mL) in one portion. The resulting mixture was stirred for 1 h at room temperature. The reaction mixture was diluted with $Et_2O$ (100 mL) and stirred for 30 min. The supernatant was decanted, and the residue was washed with $Et_2O$ (2 × 50 mL). The combined supernatant and

washes were concentrated, and the resulting solid was purified by flash column chromatography on a 1.5-in. × 10-in. column eluting with 1:1 $Et_2O$/petroleum ether to give **32** (0.37 g, 0.50 mmol, 73%) as a yellow solid: $^1H$ NMR ($CDCl_3$) $\delta$ 1.57 (18 H, s), 1.60 (18 H, s), 6.99 (2 H, s), 7.38 (2 H, t, $J$ = 8.0 Hz), 7.46 (2 H, dd, $J$ = 8.0, 0.3 Hz), 7.99 (2 H, s), 8.04 (2 H, dd, $J$ = 8.0, 0.3 Hz), 8.75 (2 H, s), 9.28 (2 H, s); IR (KBr) $\nu$ 3363, 2977, 2931, 1722, 1636, 1535, 1511 $cm^{-1}$. An analytical sample was obtained as pale yellow needles, mp 175–177 °C, after recrystallization from 5:1 petroleum ether/$Et_2O$. Anal. Calcd for $C_{41}H_{50}N_4O_9$: C, 66.29; H, 6.78; N, 7.54. Found: C, 66.09; H, 6.70; N, 7.29.

**Bis(3,5-diamino-2-naphthyl) Ketone (33).** To a stirred solution of bis[2-[3,5-bis[((1,1-dimethylethoxy)carbonyl)amino]naphthyl]] ketone (**32**, 452 mg, 0.608 mmol) in dry $CH_2Cl_2$ (30 mL) at room temperature under nitrogen was added iodotrimethylsilane (0.80 mL, 5.6 mmol, Aldrich) in one portion. The reaction mixture was stirred for 30 min and then quenched with methanol (6 mL). The reaction mixture was stirred for a further 30 min, and then the volatiles were evaporated in vacuo. The residue was diluted with water (50 mL) and basified with saturated $Na_2CO_3$ to give a pale brown precipitate. The precipitate was collected by filtration and dried, giving a brown solid which was purified by flash column chromatography on a 2-in. × 12-in. column eluting with 5:1 ethyl acetate/petroleum ether to give **33** (198 mg, 0.578 mmol, 95%) as a red solid: $^1H$ NMR ($CDCl_3$) $\delta$ 4.00 (4 H, s), 5.31 (4 H, s), 6.78 (2 H, dd, $J$ = 7.2 , 1.2 Hz), 7.03 (2 H, t, $J$ = 7.2 Hz), 7.03 (2 H, s), 7.11 (2 H, dd, $J$ = 7.2 , 1.2 Hz), 7.91 (2 H, s); MS $m/z$ (relative intensity) 342 (14, $M^+$), 341 (12), 129 (15), 97 (29), 84 (91), 69 (100); IR (KBr) $\nu$ 3431, 3339 (br), 2924, 2854, 1736, 1623, 1504 $cm^{-1}$. Recrystallization from $Et_2O$ give **33** as a brick red solid, mp > 300 °C.

**4,8-Diaminodibenz[*b,i*]acridone (34).** A stirred suspension of bis(3,5-diamino-2-naphthyl) ketone (**33**, 208 mg, 0.607 mmol) and stannic chloride (1.77 g, 5.05 mmol) in concentrated HCl (30 mL) was refluxed for 3 h. After being cooled to room temperature, the reaction mixture was basified with saturated $Na_2CO_3$. The resulting solid was collected by filtration to give **34** (185 mg, 0.569 mmol, 94%) as a dark purple solid, which was ordinarily used without further purification: $^1H$ NMR ($CD_3OD$) $\delta$ 6.92 (2 H, dd, $J$ = 7.8 , 0.6 Hz), 7.20 (2 H, t, $J$ = 7.8 Hz), 7.48 (2 H, dd, $J$ =7.8, 0.6 Hz), 7.90 (2 H, s), 8.89 (2 H, s); MS $m/z$ (relative intensity) 325 (14, $M^+$), 55 (100); IR (KBr) $\nu$ 3374 (br), 3051, 1623, 1560, 1497 $cm^{-1}$. An analytical sample was obtained as a black powder, mp > 300 °C, after recrystallization from 1:1 methanol/$CHCl_3$. Anal. Calcd for $C_{21}H_{15}N_3O \cdot {}^1/_2H_2O$: C, 75.43; H, 4.83; N, 12.57. Found: C, 75.57; H, 4.89; N, 12.05.

**4,8-Diaminodibenz[*b,i*]acridan (35).** A suspension of 4,8-diaminodibenz[*b,i*]acridone (**34**, 32 mg, 0.098 mmol) in dry THF (10 mL) was sonicated for 20 min at room temperature to give a dark pink homogeneous solution. To this solution was added $BH_3$ (2.3 mL of a 1.0 M solution in THF, 2.3 mmol, Aldrich) in one portion at room temperature with stirring. The reaction mixture was stirred for a further 1 h under nitrogen and quenched by slow addition of water (1.5 mL) (***CAUTION***!). The solvent was then removed *in vacuo*. The resulting residue was taken up in water (ca 6 mL) and basified with saturated aqueous $Na_2CO_3$ to give a pale green precipitate. The precipitate was collected by filtration to give **35** (29 mg, 0.093 mmol, 95%) as a green solid, which was used without further purification: $^1H$ NMR ($CD_3OD$) $\delta$ 4.19 (2 H, s), 6.73 (2 H, dd, $J$ = 7.8 , 0.9 Hz), 6.93 (2 H, t, $J$ = 7.8 Hz), 7.08 (2 H, s), 7.14 (2 H, apparent d, $J$ = 7.8 Hz), 7.49 (2 H, s); MS $m/z$ (relative intensity) 312 (23, $(M + 1)^+$), 311 (100, $M^+$), 318 (66), 295 (24), 155 (38), 141 (327); IR (KBr) $\nu$ 3360 (br), 2924, 2487, 1631, 1490 $cm^{-1}$.

**4,8-Bis[((*n*-butylamino)carbonyl)amino]dibenz[*b,i*]acridan (2).** To a stirred solution of 4,8-diaminodibenz[*b,i*]acridan (**35**, 29 mg, 0.093 mmol) in dry THF (20 mL) was added *n*-butyl isocyanate (0.50 mL, 4.4 mmol) in one portion at room temperature, and the reaction mixture was heated at reflux for 18 h under nitrogen. The solvent was evaporated, and the resulting residue was taken up in $CH_2Cl_2$. The insoluble precipitate was collected by filtration to give **2** (31 mg, 0.061 mmol, 66%) as a black solid: $^1H$ NMR (DMSO-$d_6$), see supplementary material $\delta$ 0.93 (6 H, t, $J$ = 7.1 Hz), 1.37 (4 H, m), 1.48 (4 H, m), 3.15 (4 H, q, $J$ = 6.1 Hz), 4.32 (2 H, s), 6.41 (2 H, t, $J$ = 6.1 Hz), 7.13 (2 H, t, $J$ = 7.8 Hz), 7.33 (2 H, s), 7.45 (2 H, d, $J$ = 7.8 Hz),7.51 (2 H, d, $J$ = 7.8 Hz), 7.69 (2 H, s), 8.19 (2 H, s), 9.56 (1 H, s); IR (KBr) $\nu$ 3318 (br), 2954, 2931, 2868, 1631, 1553, 1483, 1455 $cm^{-1}$; exact mass calcd for $C_{31}H_{35}N_5O_2$ $[M]^+$ 509.2791, found 509.2821.

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**Supplementary Material Available:** $^1H$ NMR spectrum of **2** (1 page). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.