Factors affecting the threading of axle molecules through macrocycles: Binding constants for semirotaxane formation

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The threading of more or less linear axle molecules through macrocyclic molecules, a fundamental process relating to the formation of interlocked molecular structures, has been investigated through the study in acetone of the equilibrium constants for the formation of pseudorotaxanes by NMR methods. The 30 new axle molecules have in common a secondary ammonium group, present as the thiocyanate salt, and an anthracen-9-ylmethyl group, but are rendered unique by the second amine substituent. All rotaxanes involve the well known polyether macrocycle, benzo[24]crown-8. The constants for the binding of axles having linear groups ranging from 2 to 18 carbon atoms show little variation in binding constant but are divided into two groups by their equilibration rates. Those with less than five methylene groups react rapidly on the NMR timescale, whereas those having more than five methylene groups are slow. Branching inhibits binding, but the effect decreases as the branch is moved away from the amine. Phenyl groups weaken binding when close to the amine but strengthen binding when more remote. Some functional groups decrease pseudorotaxane stability (alcohol functions), whereas others increase binding (carboxylic acid groups).

The ultimate consequence of the very rapid growth in research on molecular structures in which molecules are interlocked mechanically is anticipated in the vision that “anything one can do with macroscopic strands, such as ropes, strings, or threads, should be doable with molecules” (1). Thus Stoddart and coworkers view long chains of linked macrocycles (2) in analogy to metal chains as a holy grail, and we predict (1, 3–6) molecular braids and cloth, woven from linear molecules, new forms of materials whose properties will doubtless provide some surprises. Early on, we pointed out the necessity to identify the underlying elementary processes that must be carried out repeatedly to build highly complex molecularly interlocked structures. If transition metal complex formation is involved in the formation of the interlocked structure, such processes may occur spontaneously; i.e., by self assembly. However, if a complicated interlocked carbon structure is to be produced, it will be necessary to incorporate traditional organic chemical reactions and, simultaneously, make use of certain elemental processes that are essential to produce the interlocked structure (7). Here we focus on the very basic process of threading a molecule through a second cyclic molecule. This paper reports a systematic study of structure/reactivity relationships as they relate to the elemental process to which we give the obvious label, threading.

Formation of mechanically interlocked structures, based largely on macrocyclic components, was first proposed by Frisch and Wassermann (7) and Van Gulick (8) independently in the early 1960s. The most primitive species are simple rotaxanes and catenanes. Rotaxanes, for example, are formed by threading an axle molecule through a cyclic molecule, followed by blocking the ends of the axle molecule by large groups to prevent its escape from the ring.

Catenanes are interlocking rings and may be viewed as the result of making a ring out of an axle molecule while that axle is threaded through a cyclic molecule (Fig. 1).

To learn about molecular threading, we focus on rotaxane formation. The seminal theoretical work predicted very low yields for the statistical threading of axle molecules through macrocyclic molecules of appropriate diameters (7). Classic early successful preparation of rotaxanes was achieved first by Wasserman (9) and then by Harrison and Harrison (10) by using statistical methods, and the yields were of the predicted low magnitude. High concentrations of one component or the other promote threading of the axle through the macrocycle. These pioneering studies provided the proof of concept, showing that rotaxanes can be formed, but the poor yields observed in these and other early studies limited the advancement of the field.

The birth of supramolecular chemistry (11, 12) in the late 1980s and the adoption of templating (5, 6) techniques pioneered, in turn, by the first studies on macrocyclic ligands (13), opened the way to synthesize rotaxanes in substantial yields. The critical principle is simple. A molecular/atomic anchor of some kind holds the precursor axle molecule in its threaded position while blocking groups are attached. Thereafter, the anchor group may or may not be removed. Early studies used templates featuring metal ion as anchors, as exemplified by the elegant rotaxanes of Gibson (14) and of Sauvage (15) and their coworkers (Fig. 2).

Reflecting on such long-range goals as the chemical synthesis of molecular cloth, it is clear that we must first learn to thread the needle, or shuttle, before we can learn to perform such intricate actions with interlocking molecules as molecular braiding or molecular weaving. Progress toward seemingly unachievable research goals often depends on defining and achieving reasonable goals. Accordingly, polyrotaxanes produced by the process of rotaxane formation provide a target of significance that can be confronted experimentally at this time.

Many examples of polymers with their backbones, or side chains, threaded through macrocycles have been reported (16–18); however, polymers actually involving rotaxane links are rarely prepared (19–28). Further, these polymers having rotaxane linkages were prepared by conventional polymerization techniques (29). Self-complementary rotaxane precursors comprised of molecules having both axle and macrocyclic moieties have been observed to form polypseudorotaxanes (30–32). Preparation of polyrotaxanes imposes a very strict requirement of nearly 100% formation of the pseudorotaxane intermediate, because reaction of any uncomplexed threading group with the growing polymer chain will terminate the growth of that chain. Hence high molecular weight polyrotaxanes of the topology described can be formed only if practically all of the threading group is bound up as the pseudorotaxane monomer.

Work in these laboratories used secondary ammonium groups in templates with the goal of forming rotaxanes in high yield (33). In principle, high-yield formation of a [3]rotaxane, in which a single axle molecule passes through two macrocyclic molecules, consti-

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Fig. 1. Rotaxanes and catenanes mechanically defined.

tutes a major step toward producing threading efficiencies great enough for polyrotaxane formation. These studies resulted in an 86% yield for a [3]rotaxane, suggesting >90% threading (34). Vögtle and coworkers (35) made use of an anion template strategy based on a macrocyclic amide and a phenolate threading group, resulting in an impressive rotaxane yield of 95%. Whereas encouraging results have been achieved, it is increasingly clear that the understanding of molecular threading requires quantification.

A review of the literature reveals a substantial number of determinations of the equilibrium constants associated with pseudorotaxane formation (see Table 2, which is published as supporting information on the PNAS web site, www.pnas.org), but there are only limited systematic investigations of the relationship of threading group structure to pseudorotaxane formation. For this study, we limit our attention to pseudorotaxane formation between amine-containing axle molecules and macrocycles containing ether linkages. Pseudorotaxane amide systems has been investigated (36, 37) and show that complementary hydrogen bonding between the amide macrocycle and the linear amide threading group is a requirement for high yield of the rotaxane and further established the pseudorotaxane as the intermediate of prime importance. Measurements of the effect of substitution at the phenyl ring of dibenzylamine on pseudorotaxane formation (38) revealed the inhibiting effect of electron-donating substituents, reducing the hydrogen bond donating ability of the threading groups. Steric effects due to 4-substitution of dibenzyl and biscycloalkylmethylammonium salts (39, 40) have been examined and show that even small changes in steric bulk can have deleterious effects on pseudorotaxane formation. Stoddart and coworkers (41) have shown a profound dependence of the equilibrium constant for pseudorotaxane formation on the solvent. For the same axle/macrocycle pair, they observed equilibrium constants ranging from unobservably small in deuterated DMSO to $27,000 \text{ M}^{-1}$ in CDCl_3 . Here we attempt to add answers to simple questions that provide a more complete evaluation of the effects of certain basic structural relationships on the abilities of axle molecules to thread through polyether macrocycles.

In this study, we report the binding constants that quantify the threading of 22 secondary alkylammonium salts through a common macrocycle, benzo[24]crown-8 (Fig. 3). Eight more axle molecules failed to give measurable constants under the methods available to us. The general structure of the axle molecule has a single blocking group so that when threading has been achieved, the particular kind of pseudorotaxane formed is unusual in that it would require

Fig. 2. An early and elegant catenane formed with a metal ion template (15).

addition of only one blocking group to become a rotaxane. For that reason, we describe these species as semirotaxanes.

We have investigated the effects of increasing the chain length of a linear alkyl group, the bulk in the vicinity of the ammonium-binding site, the distance between bulky groups and the ammonium group, the distance between aromatic groups and the ammonium group, and the effects of functional groups at the unblocked ends of axle molecules. Discussion of these results and their significance follows.

Methods and Materials

General. All reagents were purchased from Sigma-Aldrich or Lancaster Synthesis. Preparation of the macrocycle 6,7,9,10,12,13,15,16,18,19,21,22,24,25-tetradecahydro-5,8,11,14,17,20,23,26-octaoxa-benzocyclotetracosene (benzo[24]crown-8) has been described (42). NMR spectra were obtained in d_6 -DMSO purchased from Cambridge Isotope Laboratories (Cambridge, MA). Mass spectra were performed by the Mass Spectrometry Laboratory at the University of Kansas. IR spectra were obtained by using IR grade KBr (Acros) disks on a Perkin-Elmer 1600 Series FTIR. All synthesized compounds were characterized by ^1H or ^{13}C NMR on a Bruker (Billerica, MA) DRX400 MHz Spectrometer in d_6 -DMSO or CDCl_3 by using tetramethylsilane as internal standard. Thin-layer chromatography was performed on Merck aluminium-backed alumina 60 F₂₅₄ neutral (type E) plates and developed with iodine vapor.

Syntheses. Anthracen-9-ylmethyl-N-methylammonium thiocyanate (T). The synthesis of this axle molecule, as its thiocyanate salt, is included here, along with the corresponding characterization data

Fig. 3. The macrocycle (M) and family of axle molecules (T) used in this work

Table 1. Equilibrium constants for the binding of threading group (Sr) to benzo[24]crown-8 (M) (acetone, 25°C)

Threading group	$K^* \pm \sigma$ (M ⁻¹)	$V^\dagger$ (Å ³)
	I.S.	201.4
	149 ± 10	236.2
	17.06 ± 0.48	231.7
	43.46 ± 0.4	247.3
	12.86 ± 2.5	248.4
	x	251.0
	127 ± 17	247.9
	163 ± 8	268.6
	ICE	267.9
	177 ± 10	284.5
	16.9 ± 0.7	273.1
	x	289.1
	161 ± 3	302.1
	27 ± 3	294.1
	151 ± 2	317.5
	120 ± 4	331.7
	178 ± 7.5	483.5
	94 ± 1	264.3
	194 ± 4	281.1
	281.5 ± 0.5	296.3
	92 ± 8	225.1
	82 ± 7	241.2
	ICE	272.3
	99.8 ± 3	290.5
	ICE	252.4
	280 ± 9	272.8

Table 1. Continued

Threading group	$K^* \pm \sigma$ (M ⁻¹)	$V^\dagger$ (Å ³)
	223 ± 11	292.0
	221 ± 0.1	289.1

* $K_a = [Sr]/[M][Tg]$ (where Sr, M, and Tg are *semi*-rotaxane, macrocycle, and threading group, respectively); average of at least three titrations.

[†]Molecular volume was calculated in SYBYL (48) based on the van der Waals molecular surface.

x, threading not observed; I.S., not measured because of insolubility; ICE, not measured because of intermediate chemical exchange.

to illustrate the synthetic routes used for all 30 of these new compounds. Syntheses and characterization data for all of the threading groups are published as supporting information. Elemental analyses are reported for all of these compounds in the supporting information on the PNAS web site. Methylammonium chloride (0.655 g, 9.7 mmol), triethylamine (0.979 g, 9.7 mmol), and 9-anthraldehyde (2 g, 9.7 mmol) were stirred in MeOH (20 cm³) for 30 min, then sodium triacetoxyborohydride (4 g, 18.9 mmol) was added in one portion. Stirring was continued overnight. The solvent was removed at reduced pressure, after which water (50 cm³) was added, and the mixture was neutralized with saturated NaOH. The yellow suspension was mixed with diethylether, and the organic layer was separated and washed with water (2 × 30 cm³). After drying over anhydrous MgSO₄, the filtered solution was evaporated to give a viscous orange oil. Ethanolic HSCN solution was added until the mixture tested pH <2 by indicator paper. Over a 30-min period, orange blocks formed. The product was recrystallized from boiling ethanol/dimethylformamide to give orange blocks on cooling. Yield 0.759 g, 28%. FTIR (KBr) 3419(OH), 3057(w, ArH), 2962 (s, CH₂), 2690 (m, NCH₂), 2517, 2464, 2405 (s, ⁺NH₂), 2061(vs. SCN), 1634, 1612 (m, ⁺NH₂), 1555, 1526 (m, ArH), 1496, 1464 cm⁻¹; ¹H NMR (400 MHz (CD₃)₂SO) δ 8.81 (br s, 3H), 8.55 (d, *J* = 8.5 Hz, 2H), 7.73 (ddd, *J* = 7.1, 4.9, 1.3 Hz, 2H), 7.36 (t, *J* = 7.2 Hz, 2H), 5.25 (t, *J* = 6.0 Hz, 2H), 2.85 (t, *J* = 5.1 Hz, 3H); ¹³C NMR (100 MHz (CD₃)₂SO) δ 130.8 (Q), 130.5 (Q), 129.8, 129.1, 127.1, 125.5, 124.2, 123.1(Q), 43.5, 33.28(CH₃). HRMS (+FAB/MH⁺) Calcd for C₁₆H₁₆N, 222.1283. Found: 222.1274. Elemental analysis calculated for C₂₄H₂₂N₂S: C, 72.82; H, 5.75; N, 10.00. Found: C, 72.68; H, 5.62; N, 9.85.

Preparation of an ethanolic solution of hydrogen thiocyanic acid. Potassium thiocyanate (12.63 g, 0.13 mol) was stirred in ≈50 cm³ of ethanol, then 48% HBr (16.86 g, 0.1 mol) was added dropwise. The thick slurry was stirred for 1 hr, filtered to remove KBr, and that salt was washed with diethyl ether (40 cm³). The filtrate was made up to 100 cm³ to give a final concentration of HSCN of ≈1 mol dm⁻³. The solution was stable below 0°C for several weeks.

NMR Methods for Measuring Binding Constants. ¹H NMR spectra were measured on a Bruker DRX400 MHz Spectrometer by using presaturation pulse (43) techniques to suppress the proton signal of the undeuterated acetone used in these titrations. Deuterium lock was obtained with a sealed capillary of D₂O, which also contained sodium 2,2-dimethyl-2-silapentane-5-sulfonate as an internal standard. Acetone (Fisher Scientific Spectranalyzed grade) was further purified by stirring with anhydrous calcium sulfate (Drierite, Hammond, Fisher Scientific) for 12 h then filtering, followed by distillation and retaining the middle 50% fraction. In a typical experiment, a 0.5-ml 3 mM solution of the threading group was treated with an aliquot of between 2 and 20 μl of an acetone solution of the macrocycle (≈0.2 M), then an NMR spectrum was obtained at

25°C. This procedure was repeated with additional aliquots until the equilibrium reached saturation. In the case of fast chemical exchange kinetics, this equilibration was observed as minimal chemical shift changes of the anthracenyl methylene protons with further additions of macrocycle or, in the case of slow chemical exchange, integration of the anthracenyl methylene protons could no longer be reliably measured. Treatment of the spectra to obtain binding constants depended on the rate of the chemical exchange of the semirotaxane. Those systems showing fast chemical exchange on the NMR timescale were processed with the program EQNMR (44). If the system was slow on the NMR timescale, the equilibrium constant was determined by least-squares fitting of the data reflecting the dependence of the ratio of bound to unbound threading group (ϕ) on the added volume of macrocycle solution. The equation describing ϕ is shown below.

$$\phi = \frac{-\left[K\frac{T_{\text{lig}}}{V_i} - KV_t\frac{T_{\text{mac}}}{V_i} + 1\right] + \left(\left[K\frac{T_{\text{lig}}}{V_i} - KV_t\frac{T_{\text{mac}}}{V_i} + 1\right]^2 + \frac{4KV_tT_{\text{mac}}}{V_i}\right)^{\frac{1}{2}}}{2}$$

$$= \frac{\int H_a \text{ Complexed peak}}{\int H_a \text{ Uncomplexed peak}},$$

where K , T_{lig} , T_{mac} , V_t , V_i are semirotaxane formation constant, total mol of threading group, total mol of macrocycle, volume at titration point, and volume at start of titration, respectively. H_a refers to the NMR signal of the anthracenyl methylene protons of the threading group.

Considerable care was taken in making phase adjustments and baseline correction (quadratic function) to the spectrum before integration, as well as to prevent integration errors arising from insufficient recycle time. The effect of increasing recycle time on peak integration of the octyl derivative showed that ϕ is independent of recycle time if recycle time is greater than 5 sec. All spectra were obtained with a recycle time of 8.5 sec. Spectra exhibiting slow chemical exchange behavior but showing some line broadening and peak overlap of the bound and unbound threading group proton signals were converted to JCAMP (45) format, converted to simple X,Y data by a PERL script (see supporting information for a copy of the script), and then processed in ORIGIN (Ver. 6.0) as two overlapping lorentzian peaks. Otherwise, peak integrations were performed in the Bruker software XWIN-NMR.

Results and Discussion

Scope. This study focuses on the broad area of semirotaxane formation between macrocycles containing ether linkages and axle molecules having secondary ammonium ions as their binding sites. A substantial number of equilibrium studies have been reported for such systems, as summarized above and in Table 2. Electronic effects have been studied most extensively with a number of important observations also reported on steric effects. Here we report the synthesis, characterization, and evaluation of 30 new potential axle molecules as threading groups (Table 1) using the single crown ether, benzo[24]crown-8, as the receptor.

All were prepared (Scheme 1) by reductive alkylation of commercially available primary amines with 9-anthraldehyde, and all share the common feature that the amino group is attached by a methylene group to the 9 position of anthracene. The second substituent on the amine provides the site for structural variations by using different primary amines as starting materials. Synthesis

Scheme 1.

proceeds through formation of the intermediate Schiff base by condensation of each primary amine with 9-anthraldehyde.

Effective binding of the threading group to the macrocycle requires protonation of the secondary amine so they were prepared as their protonated amine salts. The choice of counter ion was determined by solubility requirements, because it was necessary to perform measurements on all of the compounds in the same media to facilitate comparisons. The thiocyanate salts were selected because the soft character of SCN makes its dialkyl ammonium salts more soluble in many organic solvents (46). The ammonium salts were prepared by reaction of the secondary amines with HSCN in ethanolic solutions. Of the salts examined, only those of SCN were sufficiently soluble in acetone for binding studies to be made; e.g., the chloride and bromide salts have very limited solubility in such solvents.

Binding Study. Most of the threading molecules were soluble in acetone, and in this solvent all binding constants and available concentrations fell in the range measurable by NMR. Unfortunately, threading groups such as anthracen-9-ylmethyl-pentyl-ammonium thiocyanate showed fast-intermediate exchange kinetics and could not be measured with accuracy (47), so are not reported here. The larger threading molecules exhibited slow chemical exchange and showed distinct peaks for the bound threading molecules. An example NMR spectrum for this behavior and the plot of ϕ vs. volume of macrocycle solution added are shown in Fig. 4.

Threading molecules with R groups containing chains shorter than five atoms showed fast chemical exchange, and the binding constants could be determined from chemical shifts of the anthracenyl methylene signal vs. concentration of the macrocycle (Fig. 5).

Table 1 presents the results of our measurements, and Fig. 6 displays the equilibrium constants for formation of semirotaxanes for all of the axle molecules having saturated alkyls as the distinguishing R groups on the secondary amine. The graph plots equilibrium constant against the molecular volume (48) of the axle molecule. Thoughtful selection of substituents has allowed us to examine a fascinating variety of structure/reactivity relationships.

First, the ragged roughly horizontal line that extends across the middle of Fig. 6 shows that the equilibrium constant for semirotaxane formation is distinctly insensitive to the length of the hydrocarbon chain for a wide range of chain lengths, extending from two to eighteen carbons. Notably absent is any hint of an odd/even alternation in stability or any trend in stability that is monotonic with respect to chain length. The small decrease in stability as the chain length increases from two to four, followed by a successive increase and decrease at, respectively, chain lengths of six and nine, exceeds the experimental error only by a small margin. Although it is conceivable that these brief trends reflect regions in conformational space where either the rate of binding or the rate of release is particularly affected, we have not investigated that possibility.

There is, however, a most striking dynamic effect of chain length. Secondary amines of this class that have distinguishing alkyl groups shorter than five carbons undergo rapid exchange, i.e., dissociation and reassociation, on the NMR (400 MHz) timescale at temperatures in the vicinity of room temperature. But when the chain length

Fig. 4. NMR determination of equilibrium constants for slow reactions (NMR timescale). C_M , ϕ , and Ha are the concentration of macrocycle, ratio of bound to unbound threading group and anthracenyl methylene proton resonance of the threading group, respectively.

is greater than five carbons, the semirotaxane undergoes only slow exchange on the same timescale under the same conditions. It must be emphasized that this is true despite the fact that the equilibrium constants all have similar values—regardless of chain length. Long

Fig. 5. NMR determination of equilibrium constants for rapid reactions (NMR timescale). C_M , C_{Tg} , and M are the concentrations of macrocycle, concentration of threading group, and macrocycle, respectively.

Fig. 6. Equilibrium constants for formation of semirotaxanes: saturated alkane derivatives (acetone, 25°C). $K = [Sr]/[M][Tg]$ (where Sr , M , and Tg are semirotaxane, macrocycle, and threading group, respectively). Molecular volume based on the van der Waals molecular surface (48). Triangles and squares represent fast and slow chemical exchange, respectively. Solid line connects linear alkyl derivatives, dashed line connects terminal gem-dimethyl derivatives, and dot-dashed line connects butyl derivatives.

chain secondary amines and short chain secondary amines form semirotaxanes of comparable stability, but the former react quite slowly, whereas the latter equilibrate very rapidly. These observations generalize corresponding results in a detailed kinetic study of the rates of release of axle molecules from rotaxanes whose axle and macrocycle are characterized by amide functions (48).

Further, 5-carbon alkyl chains invariably produce exchange rates that are intermediate and, therefore, indeterminate with the methods available to us. This may be seen by looking at entries for the substituents *n*-pentyl, 1-methyl pentyl, 5-hydroxy pentyl, and from ethyl glycinate in Table 1. As the table indicates by the absence of a value for the equilibrium constant, these all display intermediate exchange rates (see below). It is remarkable that the 5-atom chain in the derivative of ethyl glycinate shows a behavior typical of 5-carbon chains. The difference in behavior between 5-hydroxy pentyl and pentanoic acid derivatives also merits attention. Within the approximate nature of these observations, the alcohol function at the end of the pentyl group has little effect on the binding and release processes compared with a terminal methyl group. On the other hand, the carboxyl group as the terminal carbon in pentanoic acid effectively makes the threading behavior parallel that of a longer alkyl group; it exchanges slowly on the NMR timescale.

In contrast to chain length, branching of the hydrocarbon structure strongly influences semirotaxane stability. Incorporation of a methyl group at the carbon α to the ammonium group results in a dramatic reduction in the binding constant (compare the *n*-propyl and isopropyl derivatives and also the *sec*-butyl and *n*-butyl derivatives from Fig. 6). That the *tert*-butyl derivative shows no evidence of binding whatsoever indicates that this α branching effect is cumulative. The dashed line in Fig. 6 shows that the presence of branching further from the ammonium group is less deleterious by linking threading groups all of which incorporate a gem-dimethyl terminus. The isopropyl derivative with the dimethyl group closest to the ammonium-binding site shows the lowest binding constant. Positioning a single methylene between the dimethyl group and the ammonium-binding site in the 2-methylpropyl derivative results in a modest increase in the binding constant. Moving the dimethyl moiety away by adding another methylene unit (3-methylbutyl) gives a constant comparable with those of the linear alkyl ammonium derivatives. An equally powerful demonstration of this rela-

Fig. 7. Equilibrium constants for formation of semirotaxanes: other derivatives (acetone, 25°C). $K = [Sr]/[M][Tg]$ (where Sr, M, and Tg are semirotaxane, macrocycle, and threading group, respectively). Molecular volume based on the van der Waals molecular surface (48). Triangles and squares represent fast and slow chemical exchange, respectively. Solid line connects phenyl derivatives.

tionship is shown by the vertical line that links the butyl isomers: tert-butyl, sec-butyl, 2-methyl propyl, and *n*-butyl.

The cyclohexyl ring behaves somewhat differently. When bound directly to the amino group, weak binding of threading group to macrocycle is observed. In fact, the value of the equilibrium constant is identical within experimental error to that found for the threading group having an isopropyl group. This is easily rationalized on the basis that the isopropyl group represents the first three carbon atoms of the cyclohexyl ring. It is clear that the rest of the cyclohexyl moiety is important in the next derivative—attachment of cyclohexyl to the ammonium through a methylene bridge. Surprisingly, this more remote location of the bulky group fails to relieve the strain. In fact, the methylene cyclohexyl axle shows no evidence of threading the macrocycle at all. Recalling that the analogous 2-methyl propyl derivative binds moderately more strongly than isopropyl, it must be concluded that a steric effect arises from the bulk of the complete cyclohexyl ring. Stoddart and coworkers (39) observed weak binding of bis(methylene-cyclo-hexyl)ammonium ion to dibenzo[24]crown-8 but no binding with the corresponding derivative of cycloheptane, in 3:1 $CDCl_3/CD_3CN$. That medium generally produces larger equilibrium constants for pseudorotaxane formation than acetone.

Fig. 7 displays results with all of the new axle molecules that contain structural elements other than saturated hydrocarbons. Most closely related to those already described are the pure hydrocarbon substituents containing phenyl groups. Early on, Stoddart and coworkers (41) compared the stabilities of pseudorotaxanes formed by dibenzylamine and di-*n*-propylamine, finding the former to be about eight or nine times more stable, using dibenzo[24]crown-8 in acetonitrile. Interestingly, in our system

(acetone solvent, benzo[24]crown-8, and anthracenyl axle), the benzyl derivative is measurably more weakly bound than any of the saturated hydrocarbons. However, a most interesting effect is observed as the phenyl group is moved away from the amine function. As the sloping line in Fig. 7 shows, the semirotaxane of the 2-phenylethyl derivative is slightly more stable than that of the benzyl group, but the 3-phenylpropyl derivative is substantially more stable yet. Thus attaching phenyl groups at locations that are increasingly remote from the ammonium function provides a distinct stabilization of the threaded product. Intuitively, this is expected because unfavorable steric interaction between the 2 and 5 phenyl hydrogens and the macrocycle is expected to decrease stability of the semirotaxane. The large increase in stability going from the ethylphenyl to the propylphenyl derivative perhaps has less to do with further reduction of steric interaction and more to do with secondary favorable binding forces. Stoddart *et al.* proposed benzylic C—H—O hydrogen bonding and π - π stacking as secondary forces stabilizing dibenzylammonium pseudorotaxanes (41). The greater separation of the phenyl moiety from the binding site may increase the contribution of such stabilizing interactions.

The behavior of the alcohol derivatives puts to rest an early notion that a hydrogen-bonding proton at the point of entry of an axle molecule might help pseudorotaxane formation (15). From our limited data, these derivatives approximate the pattern of the linear alkyl derivatives but with smaller K values. To account for the diminished stability, we suggest that the presence of intramolecular hydrogen bonding between the hydroxyl oxygen and the ammonium protons may disfavor pseudorotaxane formation.

Interestingly, the carboxylic acid derivatives are among the strongest binding of these threading groups. Thus we see in this case a stabilization because of a remote group. It is well established that electron-withdrawing groups on aromatic rings in the axle moiety produce large stabilizations (38), but the remote character of our carboxyl groups requires a different explanation. This effect could be due to the presence of the relatively acidic carboxylic acid moiety increasing the degree of protonation at the ammonium nitrogen. Alternatively, this added stability may signal additional supramolecular interactions in these solutions. Formation of hydrogen-bound carboxylic acid dimers by the threaded axle molecules may produce, for example, a more stable pseudo [3]rotaxane. Such species have been observed recently in β -cyclodextrin-bound monocarboxylic acids in the solid state (49).

The results summarized here, from the present and earlier investigations, provide a growing foundation for the design of strongly threaded pseudorotaxanes. For example, for the hydrocarbon fragment of the threading member, a phenyl group at the 3-position of a *n*-propyl moiety is expected to maximize binding. Also, the addition of a carboxylic acid function at the 4-position of the phenyl group would further enhance pseudorotaxane formation. Such relationships should be considered in the design of polyrotaxanes.

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