Aryl ring dynamics in *bis*-succinimido- cyclophanes

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Dedicated to our friend Oswald Tee on the occasion of his retirement

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Abstract

The rotation or flipping barriers for the aryl rings of a series of *p*- and *m*-xylenes and related arenes mounted between the two nitrogen atoms of a rigid, *bis*-succinimido hexacyclic molecular 'rack' (eg **16**) have been measured using dynamic NMR (DNMR) methods and compared with relevant literature values.

Keywords: Succinimido-cyclophanes, rotation barriers, flipping barriers, aryl rings, dynamic nmr

Introduction

The ability to constrain two (or more) functional groups at predetermined and fixed distances and stereochemistries on a molecular frame is an expanding purpose in recent literature.[1] This objective can be expressed in two formats with the functionalities being 'permanent' (racks)[2] or demountable (workbenches)[3]. Our current capabilities in *bis*-succinimide rack synthesis,[4,5] have allowed us to apply these tools to the rather sparsely studied problem of the energetics of aryl-ring rotation within cyclophanes – but with an important difference. The observed rotations and flips described herein take place against a 'rigid' rack as distinct from other observations of [n]cyclophanes bearing flexible *ansa* bridges.

Background

Over a period of more than four decades, there have appeared reports on the energetics of the hindered internal flipping or rotation of benzene rings within a variety of *m*- and *p*-cyclophanes[6]. For simple [n]cyclophanes and their hetero-variants, as expected, the aryl-rings of *m*-

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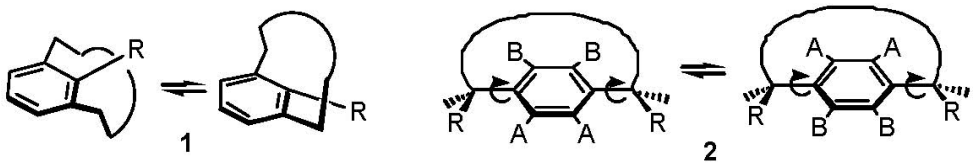
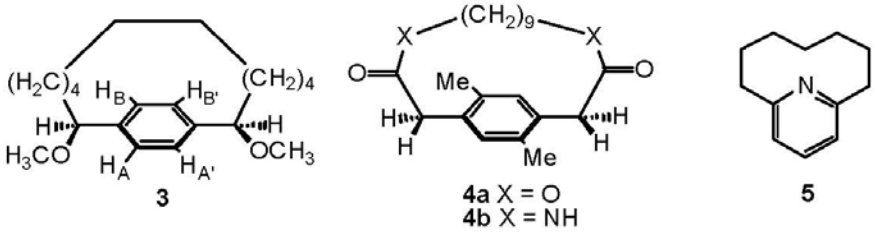
cyclophanes **1** can flip through smaller *ansa* bridges more easily than can those of *p*-cyclophanes **2**. As substituents other than hydrogen are placed on the aryl rings, so the *ansa* ring sizes need to be increased to accommodate the internal rotation. These dynamics are conventionally observed by DNMR methods and their energetics determined by variable temperature studies. In all such examples, some substituent 'marker' must be present so as to allow the observation of the dynamics of the aryl-ring and *ansa* bridge relative to each other and this may be positioned on the arenes or on the *ansa* bridges (or both). Also evident in some cases are conformational changes within the *ansa* bridges that may or may not complicate the aryl dynamics.[7]



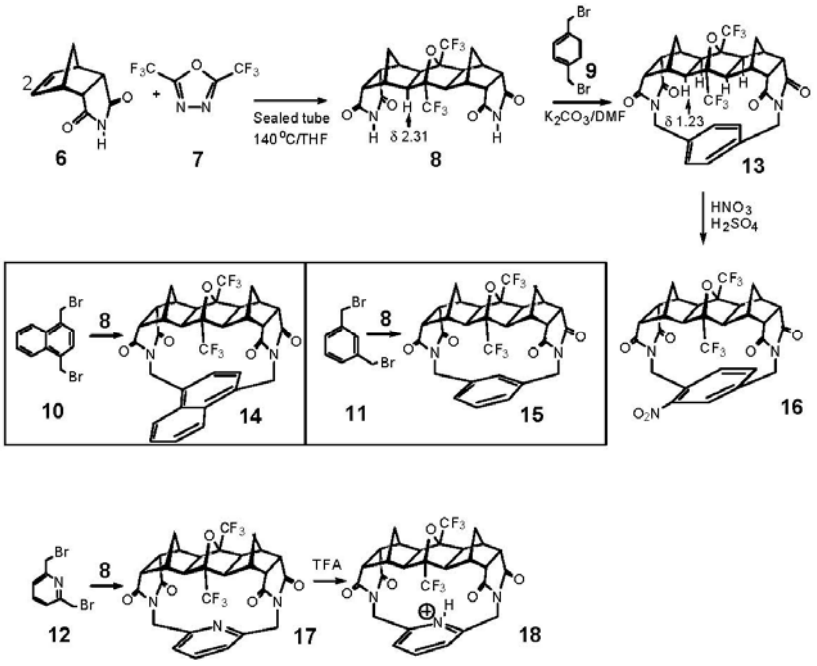
To indicate the size of the energy of rotation or flipping in these systems, the measured barrier for aryl flipping for [7]*m*-cyclophane is 11.5 kcal mol^{-1} [8] and about 17-19 kcal mol^{-1} for various [12]*p*-cyclophanes.[9] It is difficult to critically analyse the published data for these barriers as the wide diversity of aryl ring or *ansa* bridge substituted *m*- or *p*-[n]cyclophanes or [n]heteracyclophanes where [n] varies from [7] to [18] have been obtained in different solvents and where the coalescence temperature methods employed can be unreliable unless carefully executed.[10] However, the energies quoted above are typical. Recently, the spectacular observation of the effect of hydrostatic pressure on the barrier of [12]*p*-cyclophane **3** where the rate of rotation of the aryl ring *increased* with increasing pressure was published – an acceleration attributed to the negative activation volume of the rotation process.[11] In this example, the barrier was shown to be 21.2 kcal mol^{-1} at normal pressure and decreased to 20.6 kcal mol^{-1} at 392 Mpa in 1,1,2,2-tetrachloroethane-d_2 at 406.5 K.



Pertinent to the results of this submission, are comments regarding the flexibility of the *ansa* bridge versus chain length as well as the presence of differing hetero-atoms in this bridge. Thus, [15]*p*-dilactone **4a** displayed a lower rotation barrier relative to the analogous dilactam **4b** with greater *ansa* chain rigidity.[12] Also relevant is the comparison of the barriers for internal aryl flip for the [7]*m*-cyclophane (11.5 kcal mol^{-1}) and [7]*m*-pyridinophane **5** (9 kcal mol^{-1}).[13] The higher value for the benzene variant being attributed to the bulk of the 'extra' C-H in the former as compared to the lone pair on nitrogen in the latter.

Results and Discussion

The development of a simple route to the *bis*-succinimide **8**[4] followed by its internal dialkylation by *bis*-(halomethyl)arenes[5] has provided an efficient entry to a series of molecules **14**-**18** ideally suited to a study of internal aryl ring dynamics. Synthetic details outlining the condensation of **8** severally with dibromides **9**-**12** using potassium carbonate in DMF are shown in Scheme 1. The inherent 'rigidity' of the multi-bridged rack component of these cyclophanes is the defining characteristic of these systems. Unlike any other [n]-*ansa* bridges of *m*- and *p*-cyclophanes whose hindered rotations have been published, these rack-mounted systems require the arene to pass by the underside of the rack where the four shielded *endo*-hydrogen atoms (cf: ˜ 1.23 ppm in **13** and ˜ 2.31 ppm in **8**) can hinder this motion. These 'rigid' racks, unlike flexible polymethylene [n]-*ansa* loops (or their hetero variations), have very limited opportunity to undergo any conformational adjustments during the internal aryl ring passage and thus can be expected to present a larger barrier than flexible racks of the same [n]-size viz [13]. It is also important to recognise the distortions from normal sp^3 values that accompany the bonding angles around the benzylic carbon atoms as the aryl passage takes place and which no doubt contribute to the barriers discussed below.



Scheme 1. Synthesis of *m*- and *p*-cyclophanes

The symmetry (C_{2v}) of **13** precludes any observation of ring rotation by the DNMR method. However, the naphthalene analogue **14** being asymmetric about the long plane of the molecule, revealed a well-separated, diastereomeric pair of doublets for the benzylic protons (and also for the rack *endo*-protons). Thus the flipping of the 1,4-naphthyl fragment through the rack is slow on the NMR time-scale in $CDCl_3$ at room temperature. By heating this sample to 67 °C these

benzylic resonances were observed to coalesce and thus allow an internal flipping barrier of 16.5 kcal mol^{-1} to be calculated. A similar value was generated from the collapse of the *endo*-pair of doublets. An independent measurement of 16.6 kcal mol^{-1} for this barrier was obtained by observing the coalescence of the two ^{19}F lines of the trifloromethyl groups in **14** and should be compared with the ^{1}H-DNMR value. A similar situation was found for the nitro derivative **16** where the introduction of the second dissymmetric plane affords multiple AB pairs of resonances, the coalescences from which allowed four discreet barriers (av. 18.4 kcal mol^{-1}) to be calculated. Unfortunately, in this case, DMSO-d_6 was required to achieve the higher T_c so the barriers for **14** and **16** have been obtained in different solvents.[14] However they are certainly within the range of the rotations observed from other *p*-cyclophanes of similar *ansa* bridge size. Models (AM1)[15] indicate that only the unsubstituted half of the aryl rings may rotate through the *ansa* bridge in these examples. The data for these and other experiments are shown in Table 1. The size of the *ansa* bridges in all these compounds is [13] and we did not find any published [13]*p*-cyclophane examples though the homologue of **3** is mentioned as having been studied but with no barrier given.[11]

Table 1. Coalescence data for [rack]*p*-and *m*-cyclophanes

Compd.	Solvent	H observed	J (Hz)	Δυ (Hz)	T_c (^oC)	$\Delta G_c^{\ddagger}$ (kcal.mol^{-1})
14	$CDCl_3$	benzylic	13.6	82	67	16.4
	"	endo	5.9	273	90	16.8
	"	CF_3 (^{19}F)	0	15.7	49	16.6
15	$CDCl_3/CD_2Cl_2$ (1:3 mixture)	benzylic	(14)*	372	-116	6.9
16	DMSO	benzylic	13.5	63	104	18.5
	"	"	13.8	62	97	18.2
	"	endo	6.5	86	108	18.5
	"	"	6.5	72	102	18.3
17	$CDCl_3/CD_2Cl_2$ (1:3 mixture)	benzylic	(14)*	294	-78	8.7
18	$CDCl_3/CD_2Cl_2$ (1:3 mixture)	benzylic	14.8	393	21	13.2

* J estimated - note that variations of J from 0 - 20 Hz change ˜$G_c^{\ddagger}$ by less than 0.6%.

For the *m*-xylyl versions **15** and **17**, prepared as shown in Scheme 1, the internal flip barriers in $CD_2Cl_2/CDCl_3$ were much lower than their *p*-analogues as expected since only one H-atom is required to pass between the parallel pairs of the rack *endo*-hydrogens**.** From AMI modelling, it is clear that only the C-H fragment of the arene between the benzylic methylene groups can flip through the rack . The opposite three carbon segment has apparently no chance of passage at the temperatures accessible to the DNMR method. Interestingly, the pyridyl ring flip in **17** has a higher barrier than the analogous phenyl ring flip of **15**. Models (AMI) support only a slight

shortening (<0.1A) of the N…N distances between **17** and **15** so it is unlikely that an explanation based on geometry of 'strain' is significant. This result is opposite to the earlier mentioned example[13] and may serve to highlight the differences of a rigid rack vs. a flexible polymethylene chain as the *bis*-imido *ansa* bridge through which the flip motion must take place.However these differences are relatively small in comparison to the errors that are inherent in the experimental observations. More significant is the substantial increase in the barrier for the ring flip of the pyridinium salt (trifloroacetate) **18** when compared with the isoelectronic **15**. The only published example[16] for a similar pair of related compounds (neutral vs. ionic) exhibiting hindered internal dynamics that could be found did not involve the passage of **.**the pyridine/pyridinium moieties through the *ansa* bridge and so is not relevant to this study. There is clearly not enough room for the trifluoroacetate counter-anion to remain closely associated with the pyridinium charge during the flipping process. Thus,we propose that the disruption of the ionic association required for the flip to take place in $CDCl_3/CD_2Cl_2$ is reflected in the increased barrier for the pyridinium salt when compared with its neutral equivalent **15**. Since solvent plays a major role in ionic associations, a study of the barrier with differing solvents represents a worthwhile objective that we are pursuing.

Overall, the magnitudes of the barriers measured herein are consistent with published precedents confirming that *p*-aryl bridges are much more difficult to flip through the *ansa* bridges (of the same size) than *m*-variants. This report clearly establishes the utility of molecular racks such as **8** in internal rotation barrier studies in that they are easily prepared and are readily substituted with *m*- and *p*-aryl bridges. These in turn, may be further substituted or be higher aromatic ring systems eg naphthalene. The introduction a new dissymmetry element (such as replacement of one of the CF_3 groups with COOMe), may allow ring flips to now be observed even for the unsubstituted p-xylenyl case related to **13**. Such variations of unsymmetrical functionalities at the rack central, bridge heads subtend new opportunities to investigate atropisomer populations as a function of functional group and stimulate ideas for 'molecular machine' designs based on the driving of the ring flipping process. Finally, larger racks similar to **8**, but with greater N…N separations have now been prepared and we anticipate opportunities to 'load' more elaborate aryl bridges between their nitrogen atoms and to observe dynamics within these systems.

Experimental Section

General Procedures. ^1H, ^{13}C NMR spectra were recorded in $CDCl_3$, acetone-d_6 and DMSO-d_6 solution on Brüker AMX 300 or DPX400 NMR spectrometers. ^1H NMR spectra were referenced to TMS (0.00 ppm), and ^{13}C NMR spectra to $CDCl_3$ (77.0 ppm), and DMSO-d_6 (39.5 ppm). Mass spectra and accurate mass measurements were recorded on an AutoSpec spectrometer. Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. Merck Kieselgel 60 was used for column chromatgraphy under mediumressure. DMF was dried

over CaH_2. The exchange rates $k_c \left(= \pi/\sqrt{2} \times \sqrt{\Delta\vartheta^2 + 6J^2}\right)$ were calculated by observing the coalescence temperature (T_c) and the frequency separation Δ of relevant coupled (^{2}J Hz) proton pairs under conditions of slow exchange. These rates were then substituted into the standard form of the Eyring equation[16] to obtain the energy barriers (˜$G_c^{\ddagger}$) Errors in k_c evaluations using this method are high and the barrier data obtained can only serve as a comparative guide.

Preparation of rack (8). A mixture of bicyclo[2.2.1]hept –2-ene *endo, endo*-5,6-dicarboximide (1.00 g) and 1, 3, 4-oxadiazole (2.0 ml) in dry THF or DMF (2.0 ml) was heated in a sealed glass tube in a hot-air oven at 140 °C. After 48 hours the reaction was allowed to cool to room temperature and the solvent evaporated under reduced pressure. The resulting solid was suspended in dichloromethane, filtered and washed with dichloromethane before being crystallized from THF to afford **8** as colorless crystals (1.34 g, 86.8%).

Mp>350 °C (DMSO); ^{1}H NMR (300 MHz, DMSO-d_6) ˜ 1.47 (d, J = 10.3Hz, 2H), 2.12 (d, J = 10.3Hz, 2H), 2.31 (s, 4H), 2.90 (s, 4H), 3.20 (bd. m, 4H), 11.16 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) ˜ 37.1, 40.0, 48.6, 49.5, 87.6 (q, $^2J_{C\text{-}F}$ = 31.9 Hz), 123.9 (q, $^1J_{C\text{-}F}$ = 280.3 Hz), 178.2; exact MS calcd for $C_{22}H_{18}F_6N_2O_5$ M^+ 504.1120, found *m/z* 504.1121.

General procedure for the preparation of cyclophanes (13, 14, 15, 17)

A mixture of **8** (100.9 mg, 0.2 mmol), *bis*-(bromomethyl)arene (0.2 mmol), finely powdered anhydrous potassium carbonate (0.28 g, 2.0 mmol) and dry dimethyl formamide (7 ml) was stirred at room temperature for 10 min then at 65 °C for five days. The solvent was removed *in vacuo* and the residue was taken up in a mixture of water (40 ml) and $CHCl_3$ (50 ml). The aqueous phase was extracted with $CHCl_3$ (3x40 ml) and the combined organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated to give a residue which was purified by chromatography on silica gel column or by recrystallization.

Preparation of *p*-cyclophane (13). Compound **13** was prepared as described in general procedure from **8** and p-xylenyl dibromide. The residue was purified by recrystallization from a tetrahydrofuran/ petroleum ether mixture to give **13** in 83.1% yield as colorless crystals.

Mp: >350 °C; ^{1}H NMR (300 MHz, $CDCl_3$) ˜ 1.23 (s, 4H), 1.26 (d, J=12.3Hz, 2H), 2.22 (d, J=12.3Hz, 2H), 2.94-2.96 (m, 4H), 2.98 (s, 4H), 4.58 (s, 4H), 7.55 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) ˜ 38.2, 41.3, 42.0, 47.2, 48.9, 88.2 (q, $^2J_{C\text{-}F}$=31.6Hz), 123.7 (q, $^1J_{C\text{-}F}$=279.8 Hz), 130.0, 137.0, 175.8; exact MS calcd for $C_{30}H_{24}F_6N_2O_5$ M^+ 606.1589, found *m/z* 606.1591.

Preparation of *p*-cyclophane (14). Compound **14** was prepared as described in general procedure using **8** and 1,4-*bis*(bromomethyl) naphthalene. The residue was purified on silica gel column (ethyl acetate/petroleum ether = 1:2) to give **14** in 96.0% yield as colorless crystals.

Mp: >350 °C; ^{1}H NMR (300 MHz, $CDCl_3$) ˜ 0.71 (d, J=5.9Hz, 2H), 1.23 (d, J=11.3Hz, 2H), 1.56 (d, J=5.9Hz, 2H), 2.19 (d, J = 11.3Hz, 2H), 2.82 (m, 2H), 2.89 (m, 2H), 3.00 (m, 2H), 3.06 (m, 2H), 5.03 (d, J = 13.6Hz, 2H), 5.23 (d, J = 13.6Hz, 2H), 7.67 (dd, J= 6.6, 3.2Hz, 2H), 7.85 (s, 2H), 8.64 (dd, J = 6.6, 3.2Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) ˜ 37.8, 38.1, 41.2, 41.7, 47.0, 47.3, 48.7, 49.1, 88.1 (q, $^2J_{C\text{-}F}$=32.3Hz), 88.21 (q, $^2J_{C\text{-}F}$=32.8Hz), 123.4 (q, $^1J_{C\text{-}F}$= 280.9Hz), 123.7

(q, $^{1}J_{C-F}$=281.6Hz), 124.7, 126.5, 127.30, 131.0, 134.8, 175.7, 176.5; HRMS (EI) calc for $C_{34}H_{26}F_6N_2O_5$ M^+ 656.1746, found *m/z* 656.1738.

Preparation of *p*-cyclophane (15). Compound **15** was prepared as described in general procedure using **8** and m-xylenyl dibromide. The residue was purified by recrystallization from a tetrahydrofuran and petroleum ether mixture to give **15** in 96.0% yield as colorless crystals.

Mp: >350 °C; ^{1}H NMR (300 MHz, $CDCl_3$) ˜ 1.34 (d, J=11.0Hz, 2H), 1.68 (nm, 4H), 2.19 (d, J=11.0Hz, 2H), 2.99-3.01 (m, 4H), 3.08 (s, 4H), 4.57 (s, 4H), 7.07 (t, J=1.6Hz, 1H), 7.39 (t, J=7.7Hz, 1H), 7.63 (dd, J=7.7, 1.6Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) ˜ 37.4, 40.8, 42.9, 47.6, 50.7, 9.49 (q, $^{2}J_{C-F}$=32.0Hz), 123.6 (q, $^{1}J_{C-F}$=278.9Hz), 126.6, 128.5, 133.5, 134.9, 176.1; exact MS calcd for $C_{30}H_{24}F_6N_2O_5$ M^+ 606.1589, found *m/z* 606.1586.

Preparation of *p*-cyclophane (16). The cyclophane **13** (61 mg, 0.1 mmol) was added to a mixture of conc. sulfuric acid (1.4 ml) and conc. nitric acid (1.4 ml) and this mixture was heated on a hot water bath at 80 ^{o}C for 10 minutes. The nitro derivative **16** was isolated by pouring the mixed acid mixture with stirring onto crushed ice and then filtering the product. The crude product was washed well with cold water, dried in air and recrystallised from chloroform/methanol mixture to produce pure **16** as a buff-coloured powder.

Mp: > 350 ^{o}C; ^{1}H NMR (300 MHz, DMSO-d_6) ˜1.12 (d, J=6.5Hz, 1H), 1.20 (d, J=6.5Hz, 1H), 1.25-1.3 (m, 2H), 1.32 (d, J=6.5Hz, 2H), 2.22 (d, J=10.1Hz, 1H), 2.25 (d, J=10.1Hz, 1H), 2.95 (bd. s, 4H), 3.02 (bd. s, 4H), 4.55 (d, J=13.5Hz, 1H), 4.74 (d, J=13.5Hz, 1H), 4.76 (d, J=13.8Hz, 1H), 5.30 (d, J=13.8Hz, 1H), 7.84 (s, 2H), 8.04 (s, 1H).

Preparation of *p*-cyclophane (17). Compound **17** was prepared as described in general procedure using **8** and 2,6-*bis*(bromomethyl)pyridine. The residue was purified by recrystallization from a tetrahydrofuran and petroleum ether mixture to give **17** in 88.0% yield as colorless crystals.

Mp: >350 °C; ^{1}H NMR (300 MHz, $CDCl_3$) ˜ 0.59 (s, 4H), 1.35 (d, J=10.9Hz, 2H), 1.81 (s, 4H), 2.19 (d, J=10.9Hz, 2H), 3.00 (s, 8H), 4.64 (s, 4H), 7.64 (d, J=8.8Hz, 2H), 7.73 (t, J=8.8Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) ˜37.2, 40.7, 45.1, 47.7, 51.0, 87.4 (q, $^{2}J_{C-F}$=32.5 Hz), 123.7 (q, $^{1}J_{C-F}$=278.9 Hz), 127.7, 136.6, 1534.0, 176.3; exact MS calcd for $C_{29}H_{23}F_6N_3O_5$ M^+ 607.1542, found *m/z* 607.1550.

Preparation of *p*-cyclophane (18). Cation **18** was not isolated but observed by ^{1}H NMR spectroscopy by acidifying a $CD_2Cl_2/CDCl_3$ solution of **17** with excess trifloracetic acid.

^{1}H NMR (300 MHz, $CD_2Cl_2/CDCl_3$ 3:1, 35 ^{o}C) ˜ 1.30 (d, J=11.5Hz, 2H), 1.95 (bd. m, 4H), 2.20 (d, J= 11.5Hz, 2H), 3.09 (bd. m, 4H), 3.12 (bd. m, 4H), 4.39 (bd. 4H), 8.20 (d, J=8Hz, 2H), 8.39 (t, J=8Hz, 1H).

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