Pergamon

*Tetrahedron Letters*, Vol. 35, No. 30, pp. 5359-5362, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01083-8

# Synthesis And Rotational Properties Of A Series Of Polyaromatic Clefts

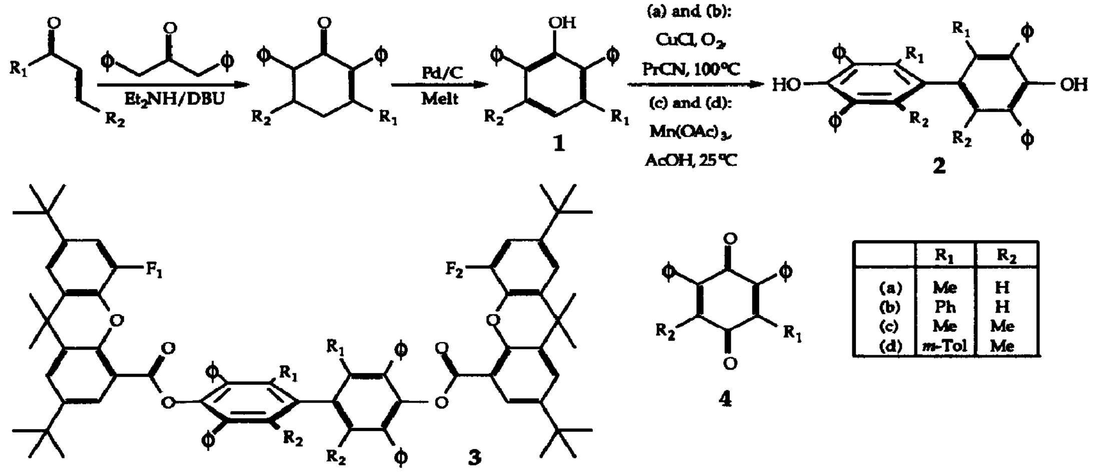
Amalia Galán[a], Andrew J. Sutherland[a], Pablo Ballester[b] and Julius Rebek, Jr.[a]*

[a]Department of Chemistry, Massachusetts Institute of Technology,
Cambridge, Massachusetts 02139, USA.

[b]Departament de Quimica, Universitat de les Illes Balears,
07071 Palma de Mallorca, Spain

***Abstract:*** A series of molecular clefts containing convergent functional groups has been developed. The rotational processes occurring within these molecules have been investigated by dynamic NMR experiments and these results are compared with those obtained from molecular modelling.

Our continued interest in molecular recognition phenomena has led us to prepare **3** containing various convergent functional groups. These molecules contain rigid, rotationally restricted spacer units **2a-d**. Their sterically congested nature results in unusual dynamic properties, which we report here.



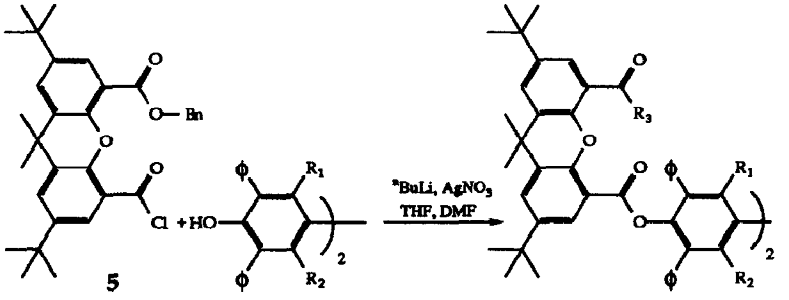
| | $R_1$ | $R_2$ |
|---|---|---|
| (a) | Me | H |
| (b) | Ph | H |
| (c) | Me | Me |
| (d) | *m*-Tol | Me |

***Scheme 1***

***Synthesis:***

Biphenols **2a** and **2b** were prepared using the methodology of Kim and Hay[1] involving copper mediated oxidative homocouplings of phenols **1a** and **1b**. Reaction of phenols **1c** and **1d** under analogous conditions resulted solely in formation of quinones **4c** and **4d**. Manganese(III) acetate in acetic acid has recently been reported to achieve hindered oxidative couplings[2] and biphenols **2c** and **2d** were synthesized successfully using this reagent.

Biphenols **2a-d** were coupled to the mono-benzyl ester of xanthene dicarboxylic acid (readily synthesized from 2,7-di-*tert*-butyl-9,9-dimethyl-4,5-xanthenedicarboxylic acid[3]). Standard procedures (e.g. DCC, DCI) for this transformation failed, but fully deprotonating the biphenols with *n*-butyl lithium and reacting the resultant dianions with xanthene acid chloride **5** in the presence of silver nitrate and DMF succeeded. Subsequent debenzylation of the products proceeded smoothly in all cases by hydrogenolysis using palladium/charcoal as a catalyst. Diamide **8c** was formed by treating the acid chloride of diacid **8b** with gaseous ammonia in dichloromethane.



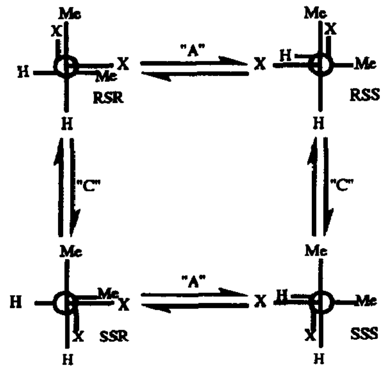
**5** **2 (a-d)** **6 - 9**

| Cleft | $R_1$ | $R_2$ | $R_3$ |
|---|---|---|---|
| 6 (a) | Me | H | OBn |
| (b) | Me | H | OH |
| 7 (a) | Ph | H | OBn |
| (b) | Ph | H | OH |
| 8 (a) | Me | Me | OBn |
| (b) | Me | Me | OH |
| (c) | Me | Me | $NH_2$ |
| 9 (a) | *m*-Tol | Me | OBn |
| (b) | *m*-Tol | Me | OH |

*Scheme 2*

***Structural Investigations:***

Structure **6** has three elements of axial chirality and thus eight possible atropisomers. A schematic representation of these atropisomers and the rotational processes by which they can interconvert is shown in Figure 1. Molecule **6a** is comprised of three pairs of enantiomers (RRR, SSS-pair I), (RSR, SRS-pair II) and (RRS=SRR, SSR=RSS-pair III). The $^1$H NMR spectrum



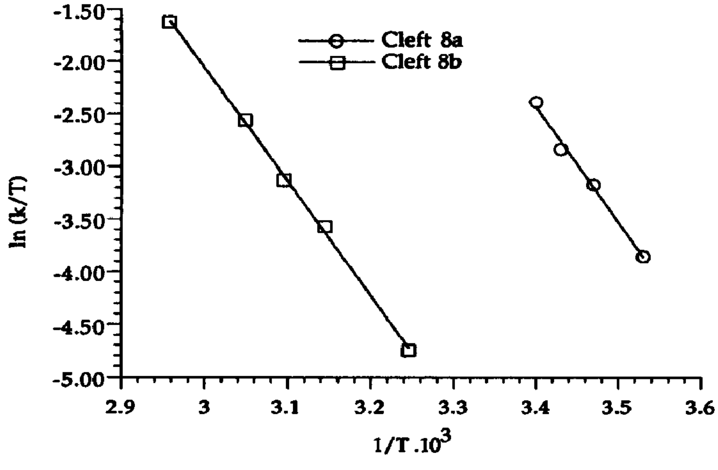
RRR and SSS are enantiomers
RSR and SRS are enantiomers
RRS SRR } and { SSR RSS are enantiomers

"A" = rotation of the front xanthene sidearm.
"C" = rotation of the rear xanthene sidearm.

*Figure 1: Schematic representation of cleft 6a showing interconversion of one set of enantiomers by rotation of the xanthene sidearms*

of **6a** measured at 500 MHz in chloroform at -15°C has four biphenyl methyl resonances (pair I-one methyl signal; pair II-one methyl signal; pair III-two methyl signals). At room temperature these signals fully coalesce indicating a rapid interconversion of the various atropisomers. This coalescence can occur only if there is fast rotation of the xanthene sidearms about the ester function. A variable temperature study[4] of the biphenyl methyl signals (assuming an equally populated two-site exchange) indicated that the barrier to rotation is about 15 kcal/mol at the coalescence temperature. Such a low rotational barrier of the xanthene side arms was unexpected. It had been anticipated that the size of the four *ortho* phenyl rings attached to the biphenyl spacer should have prevented rotation of both the central biaryl bond[5] (butressing effects) and the xanthene sidearms (clash of F1 with the phenyl rings). Molecular modelling[6] of a sterically similar cleft (where the benzyl ester is replaced by a methyl ester for computational ease) indicated that the barrier to rotation of the xanthene sidearms is approximately 16 kcal/mol. It was considered possible that the rotation was around the central biaryl bond despite the calculated barrier for this process being 34 kcal/mol.

To clarify the situation, the more sterically congested cleft **8** was investigated. Cleft **8** possesses a single element of axial chirality and is formed as a racemate. The four methyl groups on the central spacer unit give rise to two distinct singlets. $^{1}$H NMR coalescence studies, measured in chloroform and bromoform, of these signals for clefts **8a** and **8b** gave barriers to rotation of about 15 kcal/mol and 17 kcal/mol respectively. Band shape analysis[7] of the $^{1}$H NMR spectra of clefts **8a** and **8b** was also carried out to obtain more accurate values for the rotational barriers. The spectra were run in chloroform from 283 to 294K for cleft **8a** and in bromoform from 308 to 338K for cleft **8b**.[8] The resultant Eyring plots[9] and the calculated values of $\Delta H^{\ddagger}$, $\Delta S^{\ddagger}$, $\Delta G^{\ddagger}$ are shown in Figure 2. These values are in excellent accord with those obtained from the simple coalescence studies. Unfortunately excessive broadening of the signals in the respective $^{1}$H NMR spectra of clefts **7** and **9**, precluded similar studies.



For Cleft **8a**

$\Delta H^{\ddagger}$ = 22 kcal/mol

$\Delta S^{\ddagger}$ = 22 e.u.

$\Delta G^{\ddagger}_{300}$ = 15 kcal/mol

For Cleft **8b**

$\Delta H^{\ddagger}$ = 21 kcal/mol

$\Delta S^{\ddagger}$ = 13 e.u.

$\Delta G^{\ddagger}_{353}$ = 17 kcal/mol

***Figure 2: Eyring Plots of Clefts 8a and 8b***

Molecular modelling of cleft **6b** gave a calculated value of 17.5 kcal/mol for rotation of the xanthene sidearms which was in good agreement with the values obtained in the $^1$H NMR experiments. The rotational barrier about the central biaryl bond for a similarly tetra substituted biaryl is 39 kcal/mol[10] and the calculated barrier for the same rotation in **8b** was 46 kcal/mol. It can be concluded that the coalescence of the two signals in the $^1$H NMR spectra resulted solely from rotation of the xanthene sidearms.

### *Conclusion:*

We have successfully demonstrated that biphenols **2a-d** behave as rigid, rotationally hindered spacers. These properties will be applied to the construction of clefts with complete control of molecular conformation over long distances.

### *Acknowledgment:*

We would like to thank Neil Branda and Yoko Kato for their invaluable experimental assistance, Prof. I. O. Sutherland (University of Liverpool, U.K.) for performing the molecular modelling and the National Institutes of Health for funding.

### *References and Notes:*

1. Kim, W. G.; Hay, A. S. *Makromol. Chem., Macromol. Symp.* **1992**, *54/55*, 331-336.
   Hay, A. S.; Clark, R. F. *Macromolecules* **1970**, *3*, 533-535.
2. Nishino, H.; Itoh, N.; Nagashima, M.; Kurosawa, K. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 620-622.
3. Nowick, J. S.; Ballester, P.; Ebmeyer, F.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1990**, *112*, 8902-8906.
4. Gutowsky, H.S.; Holm, C.H. *J. Chem. Phys.* **1956**, *25*, 1228.
   Equation used to calculate $\Delta G_c^‡$: $\Delta G_c^‡ = 4.575 \times 10^{-3} \times T[9.972 + \log(T/\delta v)]$.
5. Mislow, K.; Glass, M. A. W.; Hopps, H. B.; Simon, E.; Wahl, G. H., Jr. *J. Am. Chem. Soc.* **1964**, *86*, 1710-1733.
6. Molecular modelling was carried out on a Personal Iris Workstation using the CHARMm force field.
7. See: Sandström, J. *Dynamic NMR Spectroscopy;* Academic: London, 1982.
8. An equally populated two site exchange was assumed in each case. After digitalization, the data was analysed using DNMR5 (Stephenson, D. S.; Binsch, G. *Quantum Chemistry Program Exchange* **1978**, *11*, 365).
9. Eyring, H. *Chem. Revs.* **1935**, *17*, 65.
   See: Gladstone, S.; Laidler, K. J.; Eyring, H. *The Theory Of Rate Processes;* McGraw-Hill: New York, 1941.
10. Mislow, K.; Gordon, A. J. *J. Am. Chem. Soc.* **1963**, *85*, 3521.

(*Received in USA* 12 *April* 1994; *revised* 1 *June* 1994; *accepted* 2 *June* 1994)