Tetrahedron Letters,Vol.29,No.12,pp 1359-1362,1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Press plc

SYNTHESIS AND ROTATIONAL BARRIERS OF ARYL-SUBSTITUTED NAPHTHACENE SYSTEMS: FRAMEWORK FOR A RECEPTOR MODEL

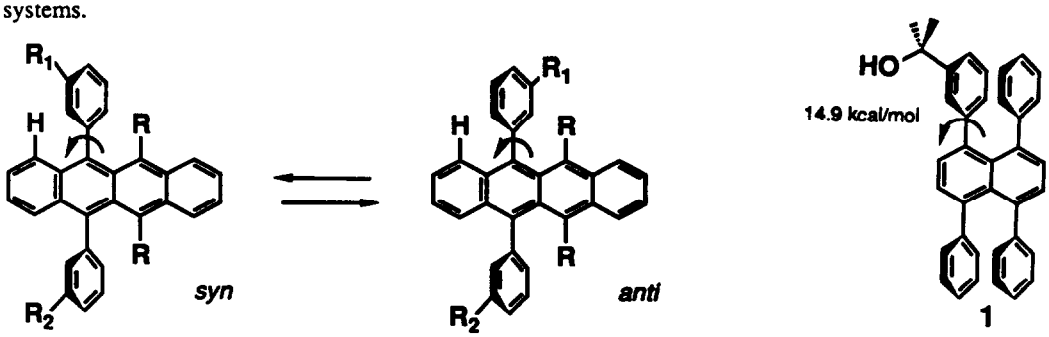
Jeffrey A. Dodge and A. Richard Chamberlin*

Department of Chemistry
University of California
Irvine, California 92717

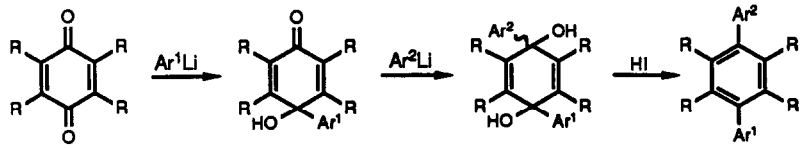
Summary: *Barriers to aryl rotation in* ortho *and* meta *aryl-substituted naphthacene systems have been determined.*

Extensive investigations of the relationship between structure and binding have shown that more highly preorganized hosts provide increased binding specificities toward the appropriate guest.[1] In fact, the availability of rigid synthetic molecular frameworks has led to several recent advances in the development of hosts capable of selective binding to cations[2] and anions,[3] as well as more complex substrates such as heterocycles[4] and aromatic amino acids.[5] Our interest in preparing a series of rigidly oriented (preorganized) amino acid receptors, using functionalized tetra-aryl naphthacene derived systems as a molecular framework, has led to an investigation of the barrier to rotation about the naphthacene-aryl bond in such systems (illustrated below).

Previous work[6] has shown that the barrier to rotation in a sterically crowded *meta*-substituted tetra-aryl naphthalene system, **1**, is only 14.9 kcal/mole, a surprisingly low value considering an apparently extensive non-bonded interaction between the two aryl rings. We were interested in determining if the additional non-bonded *peri* proton interaction present in related naphthacene ring systems would result in an increased rotational barrier, so that physical separation of *syn* and *anti* isomers would be possible. Inspection of CPK models in both **1** and in the related naphthacenes indicates that this 180 degree rotation is impossible without breaking bonds, so that models do not give a reliable prediction given the known barrier in **1**. Barriers to aryl rotation were therefore determined experimentally for some simple unsymmetrical aryl-substituted naphthacene systems.

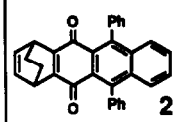
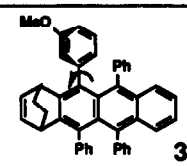
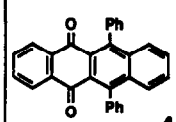
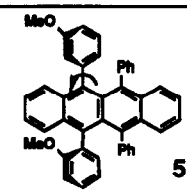
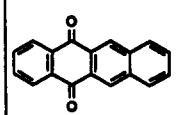
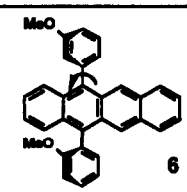
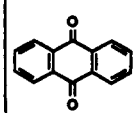
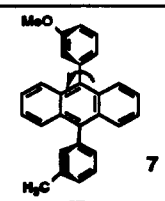


The general synthetic route to the required unsymmetrical arylated naphthacene derivatives consisted of addition of the appropriately substituted aryllithium (1.3 eq., THF, -78 °C) to a dilute solution of the quinone to give the corresponding mono-adduct. Subsequently, addition of a second functionalized aryllithium (> 2eq., THF, -78 °C) yielded the diol, which was reduced with aqueous HI[7] (THF, O °C) to give the aromatized product in good yield.



In each case, the aryllithium was prepared from the corresponding *ortho* or *meta* substituted aryl bromide by halogen-metal exchange with *n*-BuLi immediately prior to use. The starting quinones, 2 and 4 (Table), were prepared as follows: reaction of the Diels-Alder adduct of 1,4-benzoquinone and 1,3-cyclohexadiene[8] with 1,3-diphenylisobenzofuran (CH_2Cl_2, 0 °C) gave the oxo-bridged adduct which, without isolation, was converted into the quinone 2 by addition of BBr_3 (3 eq, CH_2Cl_2, -78 °C to reflux, air oxidation during work up, 42 %); the quinone 4 was prepared similarly, in 85 % yield, starting with 1,4-naphthoquinone and 1,3-diphenylisobenzofuran [9].

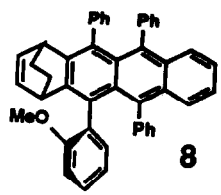
TABLE. BARRIERS TO ROTATION AND STARTING QUINONES FOR TETRA AND BIS ARYL AROMATICS.

quinone	Ar^1Li	Ar^2Li	Aromatized Product	$\Delta G_c^{\ddagger}$
 2	PhLi		 3	21.9 kcal/mol
 4			 5	22.0 kcal/mol
			 6	20.4 kcal/mol
			 7	20.5 kcal/mol

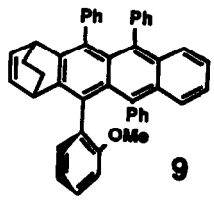
Neither of the tetra-aryl compounds (**3** and **5**) could be chromatographically separated into its *syn* and *anti* isomers, indicating the barrier to rotation was not dramatically increased compared with the known aryl naphthalenes.[6] .The rotation was slow enough on the ^{1}HNMR time scale, however, to allow for spectroscopic determination of the rotational barrier *via* coalescence studies. For example, the 300 MHz ^{1}HNMR of the tetra-aryl derivative **3** at ambient temperature ($CDCl_3$) exhibited two methoxy signals of equal intensity, one for the rotamer in which the methoxy group is *syn* to the saturated bridge, and one in which it is *anti*. Variable temperature ^{1}H-NMR (300 MHz, xylene-d_{10}) showed that these two signals coalesced at 115 °C, corresponding to a rotational barrier of 21.9 kcal/mol.[10] Likewise, the barrier in **5** was determined to be 22.0 kcal/mol (Table), based on the coalescence of the *syn* and *anti* methoxy signals. Thus, the additional *peri* hydrogen interaction in **3** and **5** raises the barrier by approximately 7 kcal/mole relative to the tetra-aryl naphthalene **1**.

In order to assess the effect of a *peri* phenyl group on aryl rotation, the analogues **6** and **7** (Table) were prepared, in which the non-bonded *peri* phenyl interaction has been replaced by a second non-bonded *peri* proton interaction. Through coalescence studies conducted as described above, the barriers to rotation were determined to be 20.4 and 20.5 kcal/mol, respectively, for **6** and **7**. *Surprisingly, these barriers are only approximately 1.5 kcal/mol lower in energy than in the phenyl substituted cases (3 and 5)*, meaning that a phenyl group actually plays only a very minor role in hindering aryl rotation in these molecules. The reason for such a small effect is not clear.

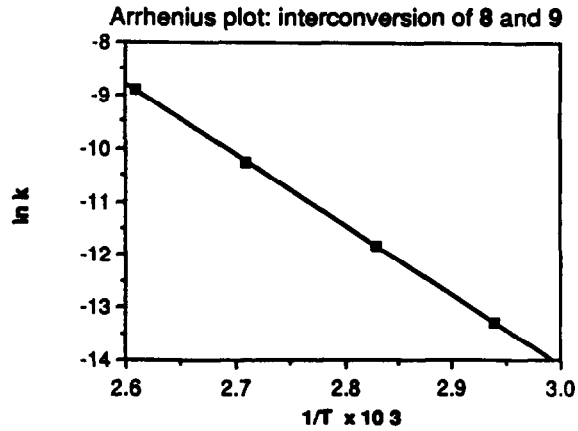
In the interest of finding a conformationally less mobile system more suited to our needs as a preorganized receptor model, the *ortho* methoxy substituted rotamers **8** and **9** were also prepared. The barrier here is expected to be higher than in the *meta* substituted derivatives because the *ortho* substituent suffers additional non-bonded interactions in the (approximately perpendicular) transition state. In fact, the barrier to rotation is high enough in this case to allow for separation of the two rotamers (7:1 ratio) by flash chromatography. To establish the energy barrier between the two isomers, the rate of conformational interconversion of each isomer into the other (equilibrium ratio of 1:1) was measured at four different temperatures. A plot of ln k vs. 1/T (Arrhenius plot below) gave a straight line with a slope of 1.32 x 10^{-3}, or an activation energy of 26.2 kcal/mol[11] for the interconversion of the two rotamers.



8



9



The results of this study, taken together with previous work,[6] show that additional *peri* hydrogen interactions increase aryl rotational barriers in these systems by *ca.* 5-6 kcal/mole (compare **1** with **6** and **7**). Strangely, however, replacing one of the *peri* hydrogens with a phenyl group increases the barrier by only 1.5 kcal/mole or so. An ortho methoxy substituent on the rotating aryl ring further increases the barrier, to the point that conformational isomers are separable by chromatography at room temperature. This information is currently aiding in the design of a series of tridentate neurotransmitter receptor models utilizing the tetraphenyl naphthacene skeleton as a molecular scaffolding.

Acknowledgement: We thank the NIH (NS-25401) for their generous support of this work.

References and Notes:

1. (a) Cram, D. J. ; Kaneda, T.; Helgeson, R. C.; Brown, S. B.; Knobler, C.B.; Maverick, E.; Trueblood, K. N. *J. Am. Chem. Soc.* **1985**, *107*, 3645. (b) Cram, D. J.; Lein, G. M. *ibid* 3657.

2. Cram, D. J.; Trueblood, K. N. *Top. Curr. Chem.* **1981**, *98*, 43.

3. (a)Katz, H.E. *J. Org. Chem.* **1985**, *50*, 5027. (b) Beauchamp, A. L.; Olivier, M.J.; Wuest, J.D.; Zacharie, B. *J. Am. Chem. Soc.* **1986**, *108*, 73.

4. (a)Kelly, T.R.; Maguire, M.P. *J. Am. Chem. Soc.* **1987**, *109*, 6549. (b) Rebek, J.; Nemeth, D. *J. Am. Chem. Soc.* **1986**, *108*, 5637. (c) Rebek, J.; Askew, B.; Islam, N.; Killoran, M.; Nemeth, D.; Wolak, R. *J. Am. Chem. Soc.* **1985**, *107*, 6736.

5. Rebek, J.; Nemeth, D. *J. Am. Chem. Soc.* **1985**, *107*, 6738.

6. Roberts, J.D.; Clough, R.L. *J. Org. Chem.* **1978**, *43*, 1328. The barrier is "surprisingly" low because molecular models indicate severe non-bonded interactions in the transition state (in which one aryl appendage is approximately perpendicular to the other). The authors propose substantial twisting of the naphthalene ring to account for this observation.

7. Rio, G. *Ann. Chem.* **1954**, *9*, 182.

8. Diels, O.; Alder, K.; Stein, G. *Chem. Ber.* **1929**, *62*, 2337.

9. All products gave satisfactory proton and carbon NMR, high resolution mass spectra, and infrared spectra.

10. Barriers to rotation were calculated using the formula $\Delta G^{\neq}_{C} = 4.57\ T_C[9.97 + \log(T_C/\Delta\sqrt{})]$ where $\Delta G^{\neq}_{C}$ is the barrier to rotation, T_C is the temperature of coalesence and $\Delta\sqrt{}$ is the difference in Hz between the two coalescing peaks at a specified temperature. Thus, for **3** T_C = 388 K, $\Delta\sqrt{}$ = 1.62 Hz at 70 °C; for **5** T_C = 403 K, $\Delta\sqrt{}$ = 4.2 Hz at room temperature; for **6** , T_C = 403 K, $\Delta\sqrt{}$ = 1.78 Hz at 70 °C; for **7**, T_C = 373 K, $\Delta\sqrt{}$= 3.32 Hz at room temperature.

11. The first order rate constants for rotamer interconversion were measured by heating solutions of the individual isomers in a constant temperature bath. Aliquots were periodically removed and the appearance of the rotameric form monitored by its proton NMR methoxy resonance. Integration of these signals for the two rotamers then gave the relative amount of each as a function of time, from which the rate constants were determined by standard methods.

(Received in USA 1 December 1987)