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Aryl−Csp^3 Bond Rotation Barriers of 2-Aryl Perhydropyrrolo[3,4-*c*]pyrrole-1,3-diones

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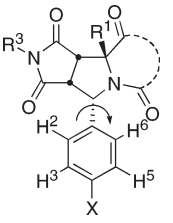

The static and dynamic features of 2-aryl perhydropyrrolo[3,4-*c*]pyrrole-1,3-diones bearing *N*-acyl substituents have been assessed with the aid of crystal structures and VT NMR spectra. Rotation barriers for the aryl−Csp^3 bonds in these molecules show surprising variation. Amide-substituted derivatives and fused piperazinediones (six-membered fusion) exhibit very substantial barriers of 14−15 kcal/mol. Fused benzodiazepinediones (seven-membered fusion) have lower but still significant barriers (10 kcal/mol), while fused hydantoins (five-membered fusion) have barriers that are too low to measure by VT NMR (≤10 kcal/mol). A rationale for the origin of the barriers is presented.

Introduction

Fluorous methods for solution phase parallel synthesis have recently been combined with microwave chemistry and multicomponent reactions to make a wide variety of small molecule libraries.[1] An especially productive vein of library synthesis has been tapped by condensing aldehyde **1** and fluorous amino ester **2** to generate an azomethine imine 1,3-dipole, which reacts in situ with dipolarophiles like maleimides **3**.[2] The resulting substituted perhydropyrrolo[3,4-*c*]pyrrole-1,3-diones **4** (Figure 1) can be further diversified by straightforward postcondesation reactions to produce, among other structures, fused hydantoins **5**, piperazinediones **6**, and benzodiazepinediones **7**. The presence (in the intermediates) or absence (in the final products) of the fluorous tag enables rapid separations by fluorous solid phase extractions,[3] thereby facilitating library production.

Over the course of making several libraries, we noticed that products derived from para-substituted aryl aldehydes, (for example, $R^2 = C_6H_4$-*p*-OMe or C_6H_4-*p*-Cl) sometimes exhibited unusual features in their ^{1}H NMR spectra. In several series of compounds, broadened resonances or even well-resolved pairs of resonances were observed for apparently equivalent aromatic protons. Compounds exhibiting these features shared the general structure **8** shown in Figure 2. Apparently, such compounds have restricted rotation about the indicated C−C bond between the perhydropyrrolo ring and the aryl ring.

These features surprised us because standard Ar−Csp^3 bonds have very low rotation barriers.[4] For example, the

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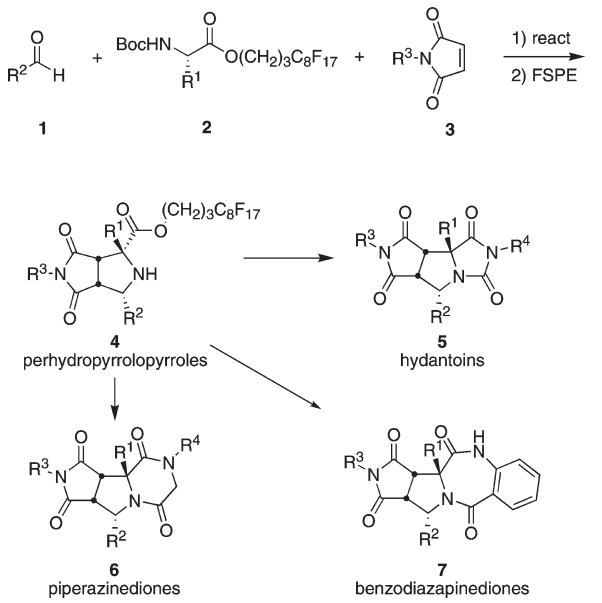

FIGURE 1. Fluorous-tagged pyrrolopyrroles **4** are readily made by dipolar cycloaddition and conveniently functionalized by postcondensation reactions to interesting heterocycles.

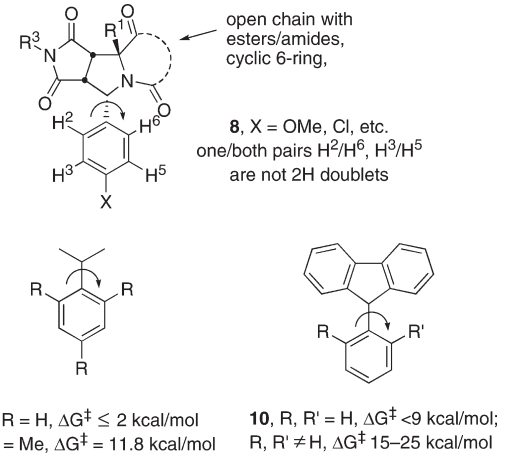

FIGURE 2. Postulated Csp^3-Ar bond rotation process and simple benchmark structures.

rotation barrier of the $Ph-CH(Me)_2$ bond of isopropylbenzene **9a** (R = H) is only about 2 kcal/mol.[5a,5b] There are many examples of compounds with much higher rotation barriers about an $Ar-Csp^3$ bond, but such compounds usually have bulky ortho-substituents on the aromatic ring,[6] or bulky substituents on a tertiary benzylic carbon,[7] or both. For example, the barrier to rotation in 1-isopropyl-2,4,6-trimethylbenzene **9b** (R = Me) increases to 11.8 kcal/mol.[5c] Rotation barriers in the 9-arylfluorene series **10** have been

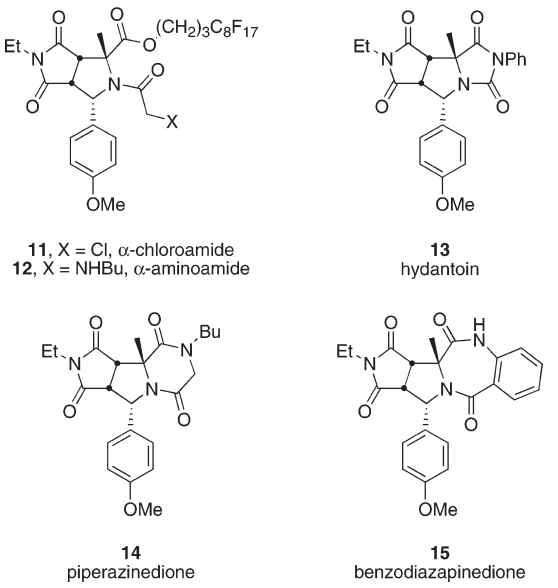

FIGURE 3. Representative structures **11**–**15** selected for further study.

well studied,[8,9] and barriers range from 15 to 25 kcal/mol depending on the number and nature of ortho substituents R and R′. But the rotation barrier of the parent 9-phenylfluorene **10** (R = R′ = H) is <9 kcal/mol.[8]

To better understand the behavior of members of the libraries shown in Figure 1, we undertook a series of studies of the five compounds shown in Figure 3. These compounds were chosen as a representative slice of the many different structures available. In addition to the two bicyclic compounds **11** and **12**, there are tricycles with additional five- (hydantoin **13**), six- (piperazinedione **14**), and seven-membered rings (benzodiazepinedione **15**). The compounds have the same genesis (cycloaddition between *N*-ethyl maleimide, *p*-anisaldehyde, and alanine perfluorooctylpropyl ester), and therefore share common substitution patterns. Variable-temperature (VT) NMR studies were conducted on four compounds to help understand the structural features that dictate the dynamics of $Ar-Csp^3$ rotation barriers. We also secured X-ray crystal structures of two compounds to provide a static snapshot of the conformations. Here we report the results of these studies.

Results and Discussion

Static pictures of two of the compounds are provided by the X-ray crystal structures shown in Figure 4. The bicyclic structures are represented by α-chloroacetamide **11** (the precursor to **12**). The amide bond has the *Z*-geometry with the carbonyl oxygen cis to the larger group, as usual.[10] One of the C–C bonds of the propylene spacer of the ester substituent adopts a gauche orientation, and this allows the fluorous chain to wrap beside the aromatic ring and pack with other chains in nearby molecules in the crystal.

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(9) (a) Oki, M. *Topics in Stereochemistry*; Allinger, N. L., Eliel, E. L., Wiley, S., Eds.; Wiley: New York, 1984; Vol. 14, pp 9–19. (b) Oki, M. *The Chemistry of Rotational Isomers*; Springer-Verlag: New York, 1993; especially pp 62–73.

(10) Stewart, W. E.; Siddall, T. H. III. *Chem. Rev.* **1970**, *70*, 517–551.

The aromatic ring substituent is tucked under the bicyclic ring with a C=C bond nearly eclipsed with the C−H bond of the benzylic ring carbon (H−C−C−C angle = 20°). For the aryl−ring bond to rotate, the ortho-hydrogens must pass by the imide carbonyl group on the left side and the amide carbon substituent (CH_2Cl) on the right.

The tricyclic structures are represented by piperazinedione **14.** The aromatic ring in the crystal of tricycle **14** adopts a similar geometry to **11** with respect to the adjacent ring (H−C−C−C angle = 29°). For the aryl−ring bond of **14** to rotate, the ortho-hydrogens must again pass by the imide carbonyl group on the left side and now must pass by one of the piperazinedione carbonyl substituents on the right side.

The four compounds selected for VT NMR study are **12**−**15**, shown in Figure 3. The compounds were selected because they have similar perhydropyrrolo[3,4-*c*]pyrrole ring substituents and because the aryl resonances in the rt NMR spectra exhibited very different features. The syntheses of all these compounds have been previously described.[2d,2e] The fluorous-tagged amide **12** is the immediate precursor to piperazinedione **14**, and these have similar substitution patterns to **13** and **15**.

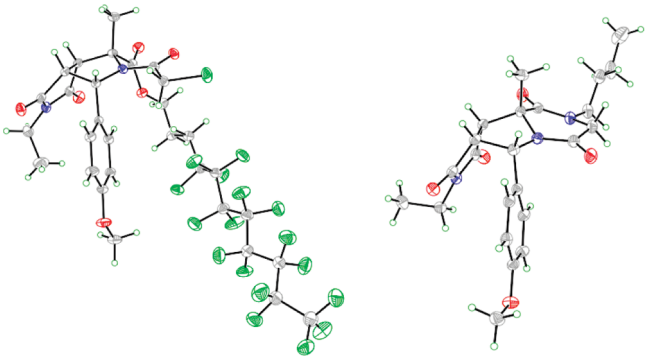

FIGURE 4. Views of the ORTEP plots of **11** (left) and **14** (right) looking into the side of the aromatic ring.

Expansions of the aromatic regions of the rt NMR spectra of **12**−**15** are shown in Figure 5. At room temperature, the four aromatic protons of amide **12** appear as two broad one-proton resonances (H^2, then H^6) downfield of a third broad, two-proton resonance (H^4 and H^5 together). Piperazinedione **14** exhibits four broad one-proton resonances: H^2, H^3, H^5, then H^6. At the other extreme, hydantoin **13** exhibits two sharp, mutually coupled, two-proton doublets, as usually seen for such systems (AA′BB′; H^2/H^6, H^3/H^5). Benzodiazepinedione **15** also exhibits mutually coupled,

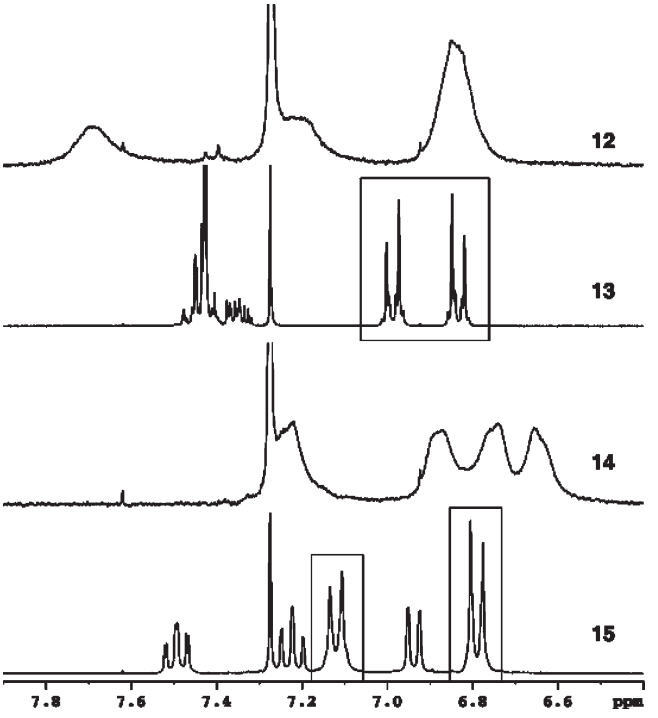

FIGURE 5. Expansions of a portion of the aromatic region of the rt NMR spectra of **12**−**15** in $CDCl_3$. Rectangles highlight the relevant resonances for **13** and **15**. The peak at 7.27 ppm is residual $CHCl_3$.

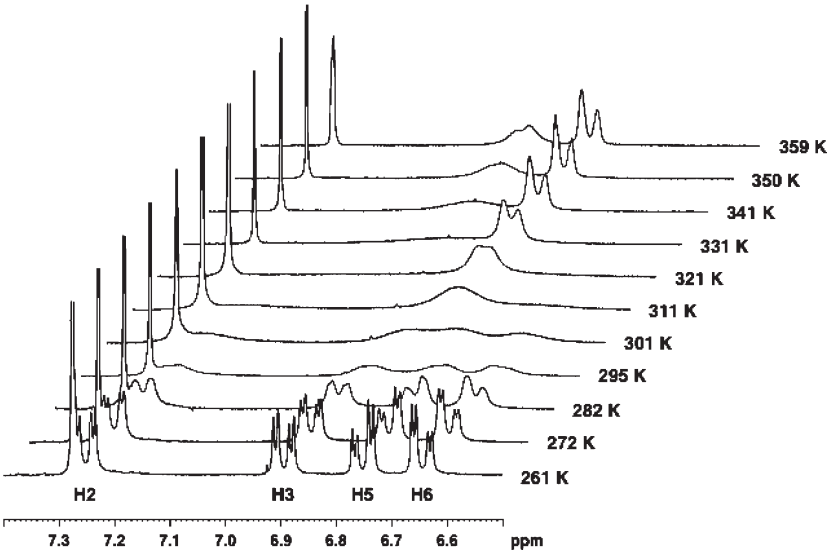

FIGURE 6. Stacked plot of the VT NMR spectra of **14** in $CDCl_3$. The two outer doublets of doublets at 261 K coalesce to the broader (left) doublet at 359 K, while the two inner doublets of doublets coalesce to the sharper (right) doublet. The peak at 7.27 ppm is residual $CHCl_3$.

two-proton doublets, but the doublets are somewhat broader (especially the downfield one, H^2/H^6) than those of **13**. They are also broader than the resonances for the other aromatic protons in **15**. (Three of the four resonances of the benzodiazapine ring protons of **15** are visible in the expansion in Figure 5.)

VT spectra were recorded in the standard way. As an example, piperazinedione **14** was dissolved in $CDCl_3$ along with a small amount of tetramethylsilane for use as a chemical shift and line width standard. ^1H NMR spectra were recorded at temperature intervals in the range of 261−359 K. The aromatic portions of these spectra are shown in Figure 6, while Figure 7 shows views of the aryl ring from two sides with the protons relevant for the analysis.

The four broad resonances in the 295 K spectrum of **14** decoalesce by 261 K into two pairs of doublets at 7.25 ppm (H^2)/6.65 ppm (H^6) and 6.90 ppm (H^3)/6.75 ppm (H^5) that share small meta couplings ($J = 2$ Hz). Each member of a pair is also linked to a member of the other pair by a large ortho coupling ($J = 7$ Hz). An nOe experiment at 270 K showed a very strong cross peak from the ring CH adjacent to N in the central ring to a single aromatic resonance.

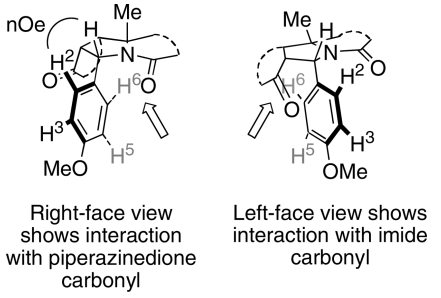

FIGURE 7. Cutaway views of piperazinedione **14** looking into the right face and the left face of the aromatic ring. Rotation of the CH−Ar bond exchanges H^2 with H^6 and H^3 with H^5.

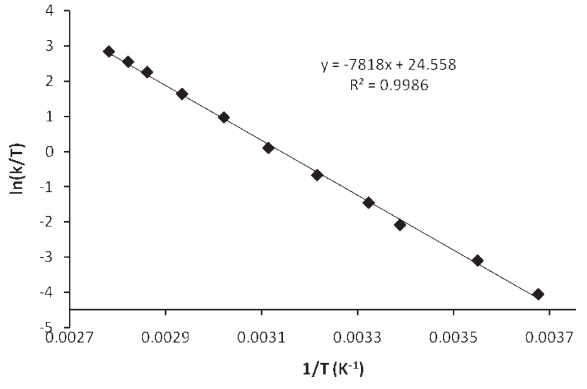

FIGURE 8. Erying plot of the VT NMR data for **14** recorded in $CDCl_3$.

This must be H^2 (see Figure 7). The other assignments follow rigorously from standard decoupling experiments at 270 K.

On heating the sample **14** to 360 K, the more closely spaced pair of resonances (H^3/H^5) had clearly coalesced to a doublet at 6.80 ppm, while the more widely spaced resonances (H^2/H^6) had coalesced into a broader but recognizable doublet at 6.91 ppm.

Using the line-shape analysis routine of Topspin 2.1 to analyze the aromatic peaks of **14**, we determined the rotational rate constant k_{rot} at each temperature T. The standard Eyring plot of these data is shown in Figure 8. The rate constant for the CH−Ar bond of **14** at 298 K is 70 s^{-1}, and $\Delta G^{\ddagger}_{298} = 15.1$ kcal/mol.

The amide **12** behaved very similarly to its derived product **14**, despite lacking the piperazinedione ring (Table 1). VT spectra and the Erying plot of the data for **12** are contained in the Supporting Information. The rate constant for the CH−Ar bond of **12** at 298 K is 115 s^{-1}, and $\Delta G^{\ddagger}_{298} =$ 14.7 kcal/mol.

In contrast, the five-membered ring hydantoin **13** and the benzodiazepinedione **15** behaved differently from these samples. The key resonances were already coalesced (**13**) or nearly so (**15**) at rt, so high-temperature spectra were not recorded. In a preliminary set of low-temperature spectra recorded in $CDCl_3$, the resonances for **13** did not decoalesce at all at 260 K, while those for **15** showed partial decoalescence. We next recorded a second set of spectra in tetrahydrofuran-d_8 down to about 200 K.

The resonances for the benzodiazepinedione **15** decoalesced in this set of spectra, which is shown along with the Erying plot of the data in the Supporting Information. The rate constant for the CH−Ar bond of **15** at 298 K is about 75 000 s^{-1}, so its bond rotates about a factor of 10^3 faster than those of **12** and **14** at ambient temperature. Its $\Delta G^{\ddagger}_{298}$ drops correspondingly to 10.6 kcal/mol.

In the VT NMR spectra of hydantoin **13**, there was no indication of decoalescence as low as 200 K. The resonances remained largely unchanged from the rt spectrum; the slight broadening and small changes in chemical shifts that were observed (see the Supporting Information) can be accounted for by temperature effects.

The appearance of peaks of chemically exchanging protons in an NMR spectrum depends on both the rate of the process and the difference in chemical shift between the protons at the slow exchange limit. We made many other hydantoins related to **13** and all exhibited very similar NMR spectra at 298 K (two sharp resonances typical of AA′BB′ systems). It is inconceivable that all these compounds have accidentally equivalent or nearly equivalent pairs of resonances at the slow exchange limit. So the different behavior in the VT spectra of hydantoin **13** must originate primarily because its CH−Ar bond is rotating

TABLE 1. Bond Rotation Rates and Activation Parameters from Variable-Temperature NMR Experiments

entry	substrate	temp range (K)	sol[a]	k_{rot}(298 K) (s^{-1})	$\Delta H^{\ddagger}$ (cal/(mol K))	$\Delta S^{\ddagger}$ (cal/(mol K))	$\Delta G^{\ddagger}_{298}$ (kcal/mol)
1	**12**	330−260	C	1.15×10^2	11.8	−9.8	14.7
2	**13**	298−200[b]	T	$\geq 10^5$			≤10
3	**14**	360−270	C	7.00×10^1	15.5	1.6	15.1
4	**15**	293−203	T	7.54×10^4	8.2	−8.1	10.6

[a]C = $CDCl_3$; T = THF. [b]No significant change was observed on cooling

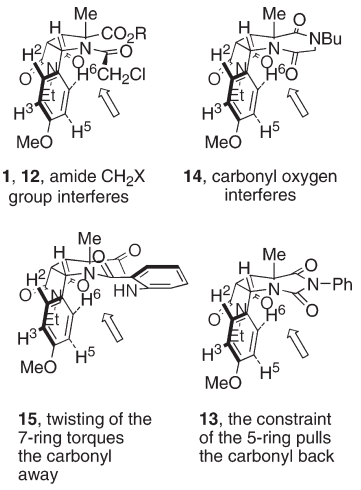

FIGURE 9. Views illustrating how the pyrrolopyrrole *N*-acyl substituent may be positioned for more or less hindrance.

much faster than that of the other three compounds. The $\Delta G^{\ddagger}_{298}$ for this process in **13** must be considerably less than 10 kcal/mol.

Conclusions

Unusual features in the NMR spectra of members of a series of libraries derived from cycloadduct **4** (Figure 1) have been clarified with the aid of crystal structures and VT NMR spectra of representative compounds. The dynamic exchange features seen in the NMR spectra of these molecules are interpreted as originating from restricted rotation about the C−Ar bond from the aromatic substituent to C2 of the perhydropyrrolopyrrole ring.

At 14−15 kcal/mol, this barrier is surprisingly high for the amide (**11**/**12**) and piperazinedione (**14**) classes of molecules. Analysis of the X-ray structures suggests that the rigidity of the rings and their substituents retard the C−Ar rotation even though the ortho-substituents on the rotating bond are only hydrogens. Replacing one of these hydrogens with a larger group would likely increase the barrier significantly, possibly resulting in stable atropisomers. The rotation barriers for the amide and piperazinedone molecules are among the highest seen for CH−Ar bonds where the aromatic ring lacks ortho-substituents.[9]

At 10 kcal/mol, the corresponding barrier for the seven-membered benzodiazapinedione series (**15**) is still significant, yet is considerably lower than the barriers for **12** and **14**. We speculate that the fusion of the seven-membered ring to the pyrrole enforces twisting at the junction of the two rings, so that the acyl group on the pyrrole nitrogen is reoriented into a position that does not interfere as much with passing of the ortho-hydrogen on rotation, see Figure 9.

In contrast to these three series, the spectra of the hydantoin series (**13**) is consistent with a relatively freely rotating bond, $\Delta G^{\ddagger}_{298} \leq 10$ kcal/mol. This again suggests that the carbonyl group on the pyrrole nitrogen is an especially important source of steric hindrance to the C−Ar bond rotation. Compared to the acyclic and larger ring systems, the carbonyl group of the 5-membered hydantoin must be pulled back significantly, allowing the ortho-hydrogens to pass easily during C−Ar bond rotation. Though it is perhaps not surprising that the five-membered ring series has a lower barrier than the other series,[11] the magnitude of the difference is remarkable.

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Supporting Information Available: Copies of VT NMR spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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