Conformational Studies by Dynamic NMR. 57,† Stereodynamics of Syn–Anti Interconversion of Disubstituted Acyl Durenes

Daniele Casarini* and Lodovico Lunazzi
Department of Organic Chemistry "A. Mangini", University of Bologna, Risorgimento 4 Bologna 40136, Italy

Received March 5, 1996

The orthogonal syn and anti isomers, originated by the restricted rotation about the Ar–C(O)Bu
t single bonds in 1,4-bis(2,2-dimethylpropanoyl)durene (2e), have been separated by preparative thin layer chromatography. In solution they reach an equilibrium where the syn–anti ratio depends upon the polarity of the solvent. This allowed us to assign the anti structure, which has a null dipole moment, to the least retained isomer. The free energy of activation (ΔG* ) for the interconversion was found to be 22.5 kcal mol⁻¹, a value high enough for identifying these species as configurational isomers. When less hindered derivatives, also having two RCO (R = Pr, Et, Me) substituents in the positions 1,4 of the durene moiety, were examined, the syn and anti forms could be detected only at low temperature by means of NMR spectroscopy. The corresponding interconversion barriers (ΔG* = 13.4, 11.7, 10.9 kcal mol⁻¹, respectively) are, in fact, much lower than for R = Bu, indicating that in these cases we are dealing with conformational rather than with configurational isomers.

Introduction

Recently we have shown how the barrier to rotation about the Ar–C(O)R bond in derivatives of type 1 (R = Me, Et, Pr, Bu) can be measured in a chiral environment by dynamic NMR spectroscopy.1

Such an experiment has been made possible by the orthogonality of the Ar (Ar = 2,4,6-trimethylphenyl) and RCO planes1,2 which renders the otherwise enantiotopic o-methyl groups diastereotopic in the presence of a chiral environment at appropriate low temperatures. When R is a tert-butyl group a barrier (ΔG*) of 19.2 kcal mol⁻¹ was measured.1 In these nonplanar ketones it is expected that substitution of the methyl group in the para position of a derivative of type 1 with an electron-withdrawing substituent would enhance the Ar–C(O)R rotational barrier. Electron-withdrawing substituents should in fact destabilize the planar rotational transition state (where the phenyl–carbonyl conjugation delocalizes a positive charge upon the aromatic ring) without significantly affecting the orthogonal rotational ground state, where such a kind of conjugation cannot occur. As a consequence the introduction of an electron-withdrawing carbonyl group in the place of the electron-releasing methyl group in the para position of 1 (R = tert-butyl) should make the Ar–C(O)Bu rotational barrier significantly higher. It is therefore conceivable that the symmetrically substituted 1,4-diacyl durene 2e, (R = Bu) constitutes a pair of syn,anti isomers which might possibly be amenable to a physical separation.

Results and Discussion

Preparative thin layer chromatographic separation of 2e afforded two isomeric compounds, each exhibiting a two line ¹H NMR spectrum, with a 3:2 relative intensity, as expected for six and four equivalent methyl groups. These isomers have the structures displayed in Scheme 1, as obtained by molecular mechanics calculations.4

Indeed a case has been reported where analogous halogenated acyl derivatives (e.g. 2, R = CCl₃) displayed, at room temperature, separated NMR signals for the orthogonal syn and anti isomers.3 There, however, the interconversion barrier was still low (i.e. ΔG* = 18.8 kcal mol⁻¹)3 for allowing a physical separation to be attained, at least at room temperature.

Thus we have here undertaken the synthesis of derivatives of type 2 in order to isolate the pair of syn and anti isomers in the case of 2e, to assign the corresponding structures, to measure the interconversion barrier, and to determine the dependence of such a barrier on the steric hindrance by comparing the ΔG* value of 2e with those of 2d, 2c, 2b (R = Pr, Et, Me, respectively).

1 This work is dedicated to the memory of Professor Carlo Zauli, 1931–1994.
(4) The MMX force field (as implemented in the program PC Model, Serena Software, Bloomington, IN) has been employed.
Similarly the 13C spectrum of 2e at the equilibrium displays, in CDCl3, six lines for each isomer, those upfield corresponding to the least stable isomer (Table 2).

Analysis of the kinetic process afforded a first order rate constant for the transformation of the more into the less stable isomer (k = 5.8 × 10^-5 s^-1, in CDCl3 at 21 °C), hence a ∆G* value of 22.5 kcal mol^-1 (a transmission coefficient of 1/2 was used to account for the fact that rotation of either of the two BuCO groups allows to achieve the interconversion). Such a value confirms the prediction of a substantial increase of the rotational barrier in 2e with respect to the value (19.2 kcal mol^-1) measured for Ar-C(O)Bu (Ar = 2,4,6-trimethylphenyl).1

When each of the two isomers of 2e is allowed to reach the equilibrium in acetone-d6, rather than in CDCl3, the ratio of the two isomers is reversed: the most retained one (which also in acetone displays upfield NMR signals) becomes now 53% (the free energy of activation for the interconversion, on the contrary, remains essentially the same). This suggests that the most retained isomer should have the syn structure which, contrary to the anti, must exhibit a substantial dipole moment. Its stability, in fact, increases in acetone (a polar solvent) with respect to the case of a less polar solvent such as chloroform. This was further confirmed by investigations in two additional nonpolar solvents (CS2 and C2Cl4) where a ratio similar to that of CDCl3 was observed (Table 1). Conversely in other polar solvents (CD3OD and DMSO-d6) the ratio became approximately 50:50 (Table 1).

The assignment of the anti structure to the most stable species in non polar solvents also agrees with the MM theoretical calculations5 for an isolated molecule of 2e: the anti is predicted to have an energy 1.7 kcal mol^-1 lower than the syn (the computed dipole moments being, respectively, 0.0 and 4.5 Debye).

Less hindered compounds, like 2d, 2c, 2b (R = Pr', Et, Me, respectively), display separated NMR signals for the syn and anti species only at temperatures much lower than ambient (they could only be detected by low temperature NMR spectroscopy), in that the corresponding interconversion rates are much faster. Thus in these cases we are dealing with a pair of syn,anti conformational isomers rather than with a pair of configurational isomers. For instance in the case of 2d (R = Pr') only at -55 °C the aryl-bonded methyl groups display a pair of 1H signals (ratio ~ 2:1 for the downfield and upfield lines, respectively) in nonpolar solvents such as CD2Cl2 and
ment of the
Afurthersupportisthusofferedtotheproposedassign-
pretionseems,apparently,supportedalsobymolecular
sponding Ar
upon the RCO moieties, further enhancing the corre-
2

large chemical shift difference (12.5 Hz at 300 MHz).
As a consequence the aryl-bonded methyl groups in
3,5 with respect to the acyl substituents in position 4).
This seems too large an enhancement to be solely
explained by the electron-withdrawing properties of the
second RCO moiety in position 4.8 An additionalcontri-
bution is reversed in
ketones had been reported,12,13 this represents a quite
enantiomers arising from restricted motions in aryl
allystableisomers. Althoughisolationofoneofthetwo
transformthestereolabileconformersintoconfiguration-
antly in nonpolar solvents (e.g. CD\textsubscript{3}OD and acetone-
Pri, Et, Me their

Figure 2. Experimental (left) \textsuperscript{1}H signals (300 MHz in CHF\textsubscript{2}Cl) of the methyl groups of the acetyl moieties of 2b as function of temperature. On the right the computer simulation, obtained with the rate constants (k in s\textsuperscript{-1}) indicated, are also displayed.

Table 3. Interconversion Barrier (\(\Delta G^*\) in kcal mol\textsuperscript{-1}) and Anti/Syn Ratio at the Equilibrium for Compounds 2b–e at Appropriate Temperatures

<table>
<thead>
<tr>
<th>Compd</th>
<th>(\Delta G^*)</th>
<th>Anti/Syn</th>
<th>Temp (°C)</th>
<th>Solvent</th>
</tr>
</thead>
<tbody>
<tr>
<td>2b (R=Me)</td>
<td>10.9</td>
<td>67:33</td>
<td>85</td>
<td>CHF\textsubscript{2}Cl</td>
</tr>
<tr>
<td>2c (R=Et)</td>
<td>11.7</td>
<td>63:37</td>
<td>65</td>
<td>CD\textsubscript{3}Cl</td>
</tr>
<tr>
<td>2d (R=Pr\textsuperscript{t})</td>
<td>13.4</td>
<td>68:32</td>
<td>55</td>
<td>CD\textsubscript{3}Cl</td>
</tr>
<tr>
<td>2e (R=Bu\textsuperscript{t})</td>
<td>22.5</td>
<td>64:36</td>
<td>+21</td>
<td>CDCl\textsubscript{3}</td>
</tr>
<tr>
<td>2f</td>
<td>22.5</td>
<td>47:53</td>
<td>+30</td>
<td>acetone-d\textsubscript{6}</td>
</tr>
</tbody>
</table>

(6) The low temperature \textsuperscript{1}H spectrum of 2c does not display, even at 300 MHz, separate signals for the syn and anti conformers: only an unresolved shoulder was observed for the triplet of the methyl group of the ETO moiety. This accidental coincidence outlines how the chemical shift of the aryl-bonded methyl groups cannot be used for conformational assignment. A meaningful line shape analysis could only be obtained by monitoring the \(^{13}C\) lines of the CO moiety which, in CD\textsubscript{3}Cl, at –65 °C, display a relatively large separation (33 Hz at 75.5 MHz).

(7) The position of the lines due to the aryl-bonded methyl groups is reversed in 2e with respect to 2d, 2e in that the signal of the more stable (anti) conformer appears upfield (by 0.005 ppm) rather than downfield. This confirms once more how the relative chemical shifts of these groups do not follow a pattern which can be related to the structure in a simple manner.

Conclusions

Durane derivatives containing a pair of RCO groups in positions 1,4 display syn,anti conformers due to restricted rotation about the Ar–C(O)R single bonds, the corresponding dihedral angles being essentially orthogonal.\textsuperscript{1,2} The free energy of activation (\(\Delta G^*\)) for the interconversion increases with the increasing bulkiness of the alkyl groups (R) of the acyl moiety, eventually reaching, for R = tert-butyl, a value high enough as to transform the sterediabale conformers into configurationally stable isomers. Although isolation of one of the two enantiomers arising from restricted motions in aryl ketones had been reported,\textsuperscript{12,13} this represents a quite

syn–anti Interconversion of Disubstituted Acyl Durenes

GC-MS showed a 306 m/e peak and the complete disappearance of the starting material. The mixture was cooled to room temperature and 10 mL of distilled water was added. The organic layer was separated, washed (4 × 20 mL), and dried over Na₂SO₄, and the solvent was removed by distillation at reduced pressure. The crude product (0.8 g) was directly used in the next reaction.

1-(4-(2,2-Dimethylpropanoyl)-2,3,5,6-tetramethylphenyl)-2,2-dimethylpropan-1-one (2e). In a three-necked flask was suspended 1.3 g (10 mmol) of pyridinium chlorochromate in 15 mL of dry CH₂Cl₂; 0.8 g (2.6 mmol) of 3 in 2.5 mL of dry CH₂Cl₂ was added in one portion, and the mixture vigorously stirred at room temperature. After stirring for 2 h the reaction was completed and a GC-MS showed only a 302 m/e peak. A 25 mL volume of Et₂O was then added, and a black gum precipitate was observed. The mixture was filtered off, and the solvent removed at reduced pressure. The crude product (0.5 g) was purified by chromatography using as a solvent n-hexane/Et₂O 97:3. From the column was obtained 220 mg of a syn/anti isomer mixture (∼60/40) and a fraction of 70 mg of a white, crystalline solid of pure anti isomer. Thin layer chromatography of the mixture allowed to isolate both the syn and the anti isomers. The corresponding 1H and 13C spectra are reported in Tables 1 and 2. Anal. Calcd for C₂₀H₃₀O₂: C, 79.42; H, 10.00. Found: C, 79.37; H, 9.9.

NMR Measurements. The spectra at variable temperature were obtained at 300 MHz, the temperatures having been calibrated by means of the shift of methanol. The errors are believed not to exceed ±2 °C. The line shape analyses were carried out by means of a PC program based upon the Bloch equations.⁵

Acknowledgment. Financial support from the Ministry of the University and Scientific Research (MURST) and from the National Research Council (CNR), Rome, is acknowledged. This work was carried out in the frame of the “Progetto di Finanziamento Triennale, Ateneo di Bologna”.

JO9604503

(13) Pinkus, A. G.; Riggs, I., Jr.; Broughton, S. M. J. Am. Chem. Soc. 1968, 90, 5043. The enantiomer isolated here was, however, quite short lived having a lifetime of 6.2 min at 20.5 °C.