Conformational Studies by Dynamic NMR. 57.[1] Stereodynamics of *Syn*−*Anti* Interconversion of Disubstituted Acyl Durenes[†]

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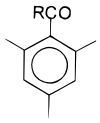
The orthogonal *syn* and *anti* isomers, originated by the restricted rotation about the Ar−C(O)Bu^t single bonds in 1,4-bis(2,2-dimethylpropanoyl)durene (**2e**), have been separated by preparative thin layer chromatography. In solution they reach an equilibrium where the *syn*−*anti* ratio depends 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^i, 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^t, indicating that in these cases we are dealing with conformational rather than with configurational isomers.

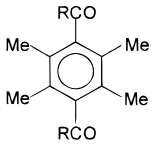
Introduction

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^i, Bu^t) can be measured in a chiral environment by dynamic NMR spectroscopy.[1]



1 R = Me, R = Et, R = Pr^i, R = Bu^t

Such an experiment has been made possible by the orthogonality of the Ar (Ar = 2,4,6-trimethylphenyl) and RCO planes[1,2] 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^t rotational barrier significantly higher. It is therefore conceivable that the symmetrically substituted 1,4-diacyl durene **2e**, (R = Bu^t) constitutes a pair of *syn*,*anti* isomers which might possibly be amenable to a physical separation.



2 R = H, **2a**; R = Me, **2b**; R = Et, **2c**; R = Pr^i, **2d**; R = Bu^t, **2e**

Indeed a case has been reported where analogous halogenated acyl derivatives (e.g. **2**, R = CCl_3) displayed, at room temperature, separated NMR signals for the orthogonal *syn* and *anti* isomers.[3] There, however, the interconversion barrier was still too 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^i, Et, Me, respectively).

Results and Discussion

Preparative thin layer chromatographic separation of **2e** afforded two isomeric compounds, each exhibiting a two line ^{1}H 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]

The two NMR signals (300 MHz in $CDCl_3$) of the least retained isomer were found at 1.214 ppm (*tert*-butyl) and 2.053 ppm (aryl bonded methyl groups), whereas the most retained isomer had the corresponding signals at 1.209 and 2.044 ppm, respectively (Table 1). Each isomer, on standing in a $CDCl_3$ solution, slowly develops the pair of NMR signals for the other isomer (Figure 1) until an equilibrium is reached whereby the upfield pair of signals become 36% and the downfield 64%, at 21 °C.

[†] This work is dedicated to the memory of Professor Carlo Zauli, 1931−1994.

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(4) The MMX force field (as implemented in the program PC Model, Serena Software, Bloomington, IN) has been employed.

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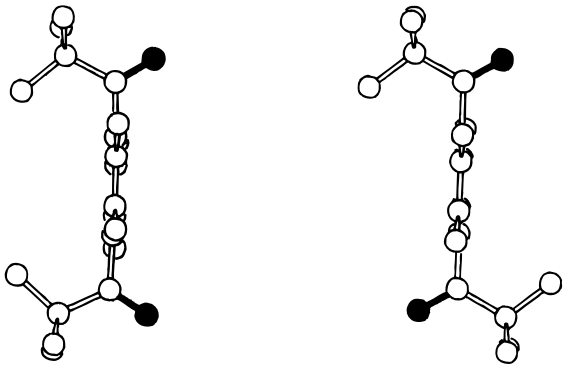
Scheme 1. MM-Computed Structures of the *Syn* and *Anti* Isomers of 2e: the Carbonyl Bonds Are Presented as Black for Convenience



syn *anti*

Table 1. Relative Proportion of the *Anti* and *Syn* Isomers of 2e in Solvents of Low and High Polarity. The ^{1}H Shifts (300 MHz) for the Two Isomers Are Also Reported

solvent	dielectric constant (ϵ)	percent of isomers	shift (ppm) of methyl-Ar	shift (ppm) of *tert*-butyl
$CDCl_3$	low (4.8)	anti: 64	2.053	1.214
		syn :36	2.044	1.209
CS_2	low (2.6)	anti: 68	1.983	1.158
		syn :32	1.972	1.133
C_2Cl_4	low (2.4)	anti: 60	2.055	1.209
		syn :40	2.043	1.201
acetone-d_6	high (25.0)	anti: 47	2.072	1.204
		syn :53	2.058	1.193
CD_3OD	high (32.6)	anti: 48	2.268	1.420
		syn :52	2.255	1.400
DMSO-d_6	high (46.5)	anti: 50	1.995	1.147
		syn :50	1.984	1.136

Similarly the ^{13}C spectrum of **2e** at the equilibrium displays, in $CDCl_3$, 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 ($k = 5.8 \times 10^{-5}$ s^{-1}, in $CDCl_3$ at 21 °C), hence a ΔG^* 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 Bu^{t}CO groups allows to achieve the interconversion).[5] 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^t (Ar = 2,4,6-trimethylphenyl).[1]

When each of the two isomers of **2e** is allowed to reach the equilibrium in acetone-d_6, rather than in $CDCl_3$, 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 (CS_2 and C_2Cl_4) where a ratio similar to that of $CDCl_3$ was observed (Table 1). Conversely in other polar solvents (CD_3OD and DMSO-d_6) the ratio became approximately 50:50 (Table 1).

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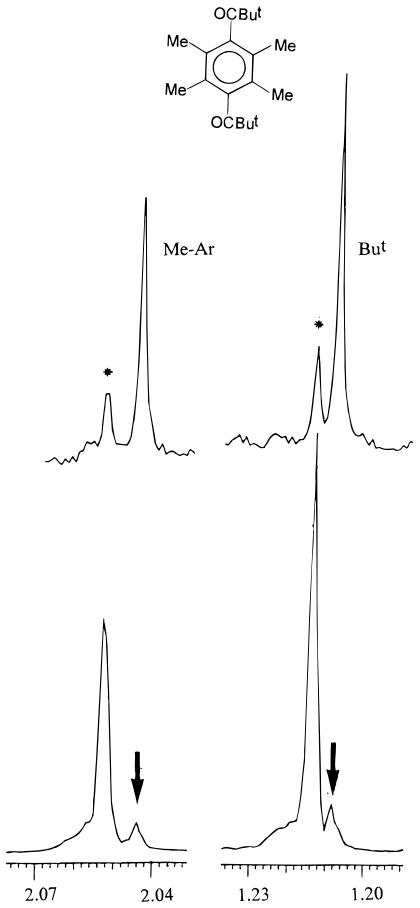

Figure 1. Top: ^{1}H signals (300 MHz) of the aryl-bonded methyl groups (left) and of the *tert*-butyl groups (right) of the most retained isomer (*syn*) of **2e** (2.044 and 1.209 ppm, respectively) taken about 20 min after being dissolved in $CDCl_3$. The weaker signals (starred) of the least retained isomer (*anti*) begin to appear at lower field. Bottom: ^{1}H signals (300 MHz) of the same groups of the least retained isomer (*anti*) of **2e** (2.053 and 1.214 ppm, respectively) taken about 20 min after being dissolved in $CDCl_3$. The weaker signals (arrowed) of the most retained isomer (*syn*) begin to appear at higher field.

Table 2. ^{13}C Chemical Shifts (ppm) of the *Anti* and *Syn* Isomers of 2e at the Equilibrium in $CDCl_3$ at 75.5 MHz

	Me(2,3,5,6)	Me(Bu^t)	C(Bu^t)	C(2,3,5,6)	C(1,4)	CO
anti (64%)	17.97	28.03	45.24	128.81	141.98	219.68
syn (36%)	17.79	27.79	42.78	128.76	141.54	218.48

The assignement of the *anti* structure to the most stable species *in non polar solvents* also agrees with the MM theoretical calculations[4] 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^i, 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^i) only at −55 °C the aryl-bonded methyl groups display a pair of ^{1}H signals (ratio ∼2:1 for the downfield and upfield lines, respectively) in nonpolar solvents such as CD_2Cl_2 and

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

compd	ΔG^*	*Anti*:*Syn*	temp (°C)	solvent
2b (R=Me)	10.9	67:33	−85	CHF_2Cl
2c (R=Et)	11.7	63:37	−65	CD_2Cl_2
2d (R=Pr^i)	13.4	68:32	−55	CD_2Cl_2
2e (R=Bu^t)	22.5	64:36	+21	$CDCl_3$
	22.5	47:53	+30	acetone-d_6

$CDCl_3$. In agreement with the observations made in the case of **2e** the conformers ratio of **2d** becomes about 1:1 in polar solvents (e.g. CD_3OD and acetone-d_6, at −55 °C). A further support is thus offered to the proposed assignment of the *anti* structure to the more stable conformer in nonpolar solvents. The barrier for the interconversion ($\Delta G^* = 13.4$ kcal mol^{-1}, Table 3) was determined by complete line shape analysis of the two ^{13}C signals of the isopropyl methyl groups, which exhibit a sufficiently large chemical shift difference (12.5 Hz at 300 MHz).

For the less hindered derivatives **2c** (R = Et)[6] and **2b** (R = Me),[7] the barriers (Table 3) were found even lower (11.7 and 10.9 kcal mol^{-1}, respectively): as an example the temperature dependence of the acetyl methyl ^1H signals of **2b** is reported in Figure 2, accompanied by the appropriate line shape simulation.

The differences between the ΔG^* values of **2e** (R = Bu^t) and **2d** (R = Pr^i) is much larger (i.e. 9.1 kcal mol^{-1}) than the difference between the values of **2d** and **2c** (i.e. 1.7 kcal mol^{-1}) as well as between that of **2c** and **2b** (i.e. 0.8 kcal mol^{-1}). This somehow reflects the much larger steric hindrance of the *tert*-butyl group with respect to the other alkyl groups. The same trend had been also found in acyl mesityl ketones (i.e. derivatives of type **1**): for R = Bu^t, Pr^i, Et, Me their ΔG^* values are, in fact, 19.2, 9.1, 7.2, 6.1, respectively.[1] The barriers observed here for compounds of type **2** are, as an average, 4.2 kcal mol^{-1} larger than those of the corresponding acyl mesityl ketones, **1**. 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 additional contribution to this enhancement should be also attributable to the reciprocal buttressing effect of the aryl-bonded methyl groups in derivatives **2**. For example, the pair of methyl groups in positions 2,6 would be pushed closer to the RCO moiety in position 1 by the presence of the second pair of methyl groups in positions 3,5 (the same would obviously occur for the methyl groups in positions 3,5 with respect to the acyl substituents in position 4). As a consequence the aryl-bonded methyl groups in derivatives of type **2** can exert a greater steric hindrance upon the RCO moieties, further enhancing the corresponding Ar−C(O)R rotational barriers. Such an interpretation seems, apparently, supported also by molecular mechanics calculations.[4] In the case of **2e**, for instance, the computed geometry suggests a Me(2)−C(2)−C(1) angle of 121° whereas in the *tert*-butyl mesityl ketone (**1**, R = Bu^t) the same angle is computed to be slightly wider (i.e. 123°). The buttressing effect might be indeed responsible for such a difference.

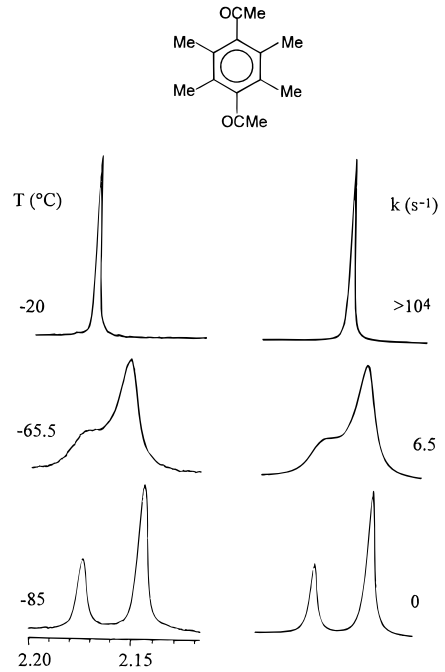

Figure 2. Experimental (left) ^1H signals (300 MHz in CHF_2Cl) of the methyl groups of the acetyl moieties of **2b** as function of temperature. On the right the computer simulation, obtained with the rate constants (k in s^{-1}) indicated, are also displayed.

Not even at −140 °C (in CHF_2Cl, at 300 MHz) was it possible to detect dynamic NMR features leading to observable conformers in the case of **2a** (R = H). This is because **2a**, contrary to **2b**−**e**, adopts a planar conformation, according to theoretical calculations and lanthanide induced shift (LIS) measurements carried out on a similar derivative (mesitylaldehyde).[9] Also, the computed Ar−C(O)H (Ar = 2,4,6-trimethylphenyl) rotational barrier is predicted[10] to be too low for NMR detection, contrary to the case of less hindered benzaldehydes.[11]

Conclusions

Durene 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.[1,2] The free energy of activation (ΔG^*) 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 stereolabile conformers into configurationally stable isomers. Although isolation of one of the two enantiomers arising from restricted motions in aryl ketones had been reported,[12,13] this represents a quite

(6) The low temperature ^1H 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 EtCO 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_2Cl_2 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 **2b** 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.

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unusual case of isolable *syn* and *anti* isomers, due to restricted rotation about the Ar−CO single bond.

Experimental Section

Materials. 1-(2,3,5,6-Tetramethyl-4-propionylphenyl)-propan-1-one (2c) was obtained with the same method reported for **2b**.[14] ^{1}H NMR ($CDCl_3$) δ 1.12 (t, 3 H, Me), 2.0 (s, 6 H, Me), 2.63 (q, 2 H, CH_2). ^{13}C NMR ($CDCl_3$) δ 7.2 (Me), 16.0 (Me, Ar), 38.3 (CH_2), 128.8 (CH, Ar), 143.3 (quat, Ar), 212.2 (quat, CO). Anal. Calcd for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00. Found: C, 78.05; H, 9.03.

1-(4-Isobutyryl-2,3,5,6-tetramethylphenyl)-2-methyl-propan-1-one (2d). ^{1}H NMR ($CDCl_3$) δ 1.18 (d, 6 H, Me), 2.1 (s, 6 H, Me), 2.9 (m, H, CH). ^{13}C NMR ($CDCl_3$) δ 16.6 (Me), 17.4 (Me), 42.5 (CH), 129.1 (CH, Ar), 142.1 (quat, Ar), 214.5 (quat, CO). Anal. Calcd for $C_{18}H_{26}O_2$: C, 78.78; H, 9.56. Found: C, 78.75; H, 9.53.

Compounds **2d** and **2e** were synthesized by reacting **2a**[15] with the appropriate Grignard or lithium alkyl derivatives, followed by oxidation[16] of the intermediate diol **3** to a diketone. The preparation is reported for the di-*tert*-butyl derivative **2e** and its intermediate **3**.

1-[4-(1-Hydroxy-2,2-dimethylpropyl)-2,3,5,6-tetramethylphenyl]-2,2-dimethylpropan-1-ol (3). To a solution of 0.5 g (2.6 mmol) of **2a** in 30 mL of dry Et_2O, kept at −20 °C under N_2, was added 3.0 mL (1.24 mmol) of *tert*-butyllithium (1.5M) in pentane (Acros). The temperature was allowed to reach 20 °C, and the mixture was subsequently refluxed. After 8 h a 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 Na_2SO_4, 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 CH_2Cl_2; 0.8 g (2.6 mmol) of **3** in 2.5 mL of dry CH_2Cl_2 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 Et_2O 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/Et_2O 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 ^{1}H and ^{13}C spectra are reported in Tables 1 and 2. Anal. Calcd for $C_{20}H_{30}O_2$: 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]

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