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Conformational Studies by Dynamic NMR. Part 56.[1] Enantiotopomerization and Conformational Analysis of Hindered Aryl Alkyl Ketones Investigated by Dynamic and Solid State NMR.†

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Abstract: The barriers ($\Delta G^{\ddagger}$) for the degenerate interconversion (enantiotopomerization) of a number of mesityl alkyl ketones have been measured by dynamic NMR in a chiral environment. These barriers were compared with those of more hindered ketones having the three methyl groups of the mesityl moiety replaced by three isopropyl groups. These prochiral probes allowed the barriers to be determinated in achiral solvents. The conformations were also assessed by high resolution solid state ^{13}C NMR and Molecular Mechanics calculations.

INTRODUCTION

Aryl alkyl ketones bearing substituents in the *ortho* (or *ortho*-like) positions have the plane of the aromatic ring twisted with respect to that of the carbonyl group. Substituents behaving as prochiral probes thus display diastereotopic geminal groups, yielding anisochronous NMR signals at temperatures where the rotation about the Ar-CO bond is slow in the NMR timescale. Accordingly, *ortho* substituents like CH_2-Bu^t display[3] diastereotopic methylene hydrogens and Me_2CH groups display diastereotopic methyl groups.[4]

On raising the temperature, the Ar-CO rotation becomes rapid enough to create a dynamic plane of symmetry which renders these groups enantiotopic. The appropriate NMR signals broaden as the temperature is increased and eventually coalesce in a reversible manner into a single signal. Computer simulations of the NMR line shape lead to rate constants and then to the free energy of activation for rotation. If the substituents are not prochiral (e.g. methyl, phenyl or *tert*-butyl groups) the corresponding signals do not become anisochronous at any rate of rotation and the process is NMR-invisible. However in a chiral environment even these enantiotopic substituents may yield anisochronous signals since they become diastereotopic when the Ar-CO rotation is slow.

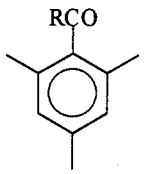
† Dedicated to Professor F. Montanari on the occasion of his 70th birthday.

This was first observed[5] for the pairs of *ortho* methyl groups in mesityl *tert*-butyl ketone at 25° in the presence of the chiral lanthanide[6] agent (*d*) Eu(hfbc)$_3$. Such a compound, and analogous ones, are not well suited, however, for studying dynamic processes occurring at very low temperatures, owing to the poor solubility and to the severe line broadening due to the paramagnetism of the lanthanide atoms. Therefore only barriers greater than 16 kcal mol^{-1} could be determined in this way, whereas those of less hindered ketones escaped detection. In the present work we investigated enantiotopomers exchanging by Ar-CO rotation in a number of variously hindered ketones (**1**) by making use of a diamagnetic chiral solvating agent[5b,7] which allowed us to perform experiments at temperatures as low as -140°C.

Analogous ketones (**2**), where the presence of prochiral probes (isopropyl groups) yielded anisochronous NMR signals in achiral solvents, were also prepared and their barriers measured and compared with the enantiotopomerization barriers for those of the series **1**.

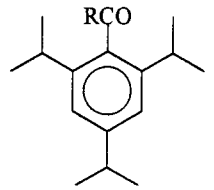
RESULTS AND DISCUSSION

The following derivatives were investigated:



1

R=H **1a**
Me **1b**
Et **1c**
Pr^i **1d**
Bu^t **1e**
Ph **1f**
CH_2Bu^t **1g**



2

R=H **2a**
Me **2b**
Et **2c**
Pr^i **2d**
Bu^t **2e**
R=Ph **2f**
CH_2Bu^t **2g**
CH_2Pr^i **2h**
CH_2Ph **2i**
$CHEt_2$ **2l**

As mentioned, derivatives of class **2** display anisochronous methyl signals for the *ortho* isopropyl moieties at appropriate temperatures whereas the methyl groups of the *para* isopropyl moiety are isochronous at all temperatures. Similarly the *ortho* methyl groups of derivatives of type **1** yield anisochronous ^{1}H signals in a chiral environment whereas the signal of the methyl group in the *para* position never splits. As a chiral agent we used S(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol (TFAE)[7]. As an example the relevant part of the ^{1}H spectrum of **1d** (R = Pr^i), in the presence of TFAE, is shown in Figure 1 as a function of temperature. At -100° the signal of the *ortho* methyl groups splits into a doublet (chemical shift difference $\Delta\delta$ = 0.39 ppm) in contrast to that of the *para* methyl group. At higher temperatures the two *ortho* methyl lines broaden, coalesce at -83° and eventually yield a single sharp line in a reversible manner. The computer line shape simulations at various temperatures (Figure 1) yield the rate constants for the degenerate interconversion of the enantiotopomers, hence the corresponding free energy of activation[8] (9.1 kcal mol^{-1} see Table 1).

Table 1. Free Energies of Activation ($\Delta G^{\ddagger}$ in kcal mol^{-1}) for the Enantiotopomerization Process of **1b-1g** Measured in the Presence of the Chiral Agent TFAE [7] and of **2b-2l** in Achiral Solvents (see Experimental).

Compound	$\Delta G^{\ddagger}$	Compound	$\Delta G^{\ddagger}$	Compound	$\Delta G^{\ddagger}$
1b	6.1	**2b**	12.2	**2h**	13.9
1c	7.2	**2c**	13.5	**2i**	13.7
1d	9.1	**2d**	14.9	**2l**	14.2
1e	19.2	**2e**	(24.1) [a]		
1f	10.6	**2f**	16.4		
1g	9.0_5	**2g**	14.8_5		

[a] Extrapolated value (see text).

Analogous behaviour was observed (in the presence of TFAE) for **1c,1e,1f** and **1g** whereas in the case of **1b** (R = Me) the line of the *ortho* methyl groups broadened so as to almost disappear at the coalescence temperature (-138°) but the solution (in CHF_2Cl) froze before displaying (even at 300 MHz) two separate signals. The difference of the corresponding chemical shifts could be nonetheless estimated from the analogous values observed for **1c,1d,1f,1g**. These differences were found to depend linearly on the temperature and the extrapolation to -138°C yielded values covering a relatively restricted range (0.4 - 0.65 ppm) for the four compounds. Thus, by assuming a chemical shift separation of 0.52 ± 0.13 ppm also for the *ortho* methyl signals of **1b** (i.e. 155 ± 40 Hz at 300 MHz) a $\Delta G^{\ddagger}$ value of 6.1 ± 0.25 kcal mol^{-1} was obtained.[9]

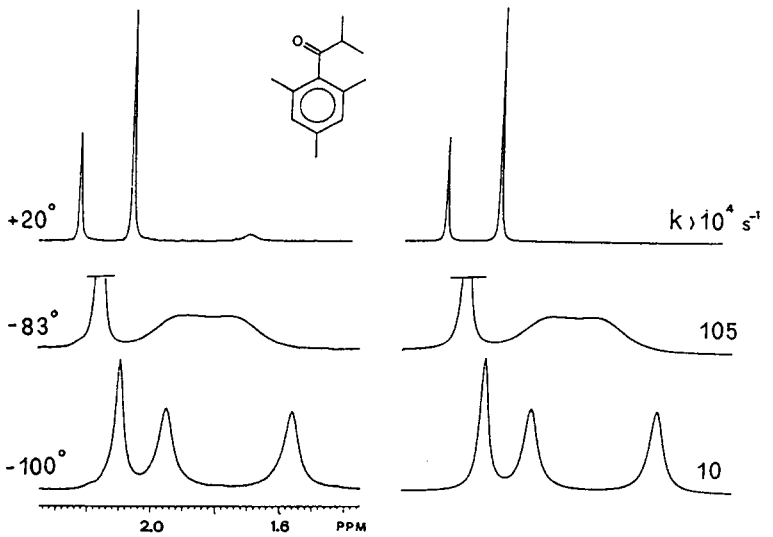


Fig 1. *Left*: Experimental ^{1}H 200MHz Signals (in CD_2Cl_2) of the *ortho* (upfield) and *para* (downfield) Methyl Groups of **1d** with a 50:1 Excess of TFAE.[7] At -100° the *ortho* Methyl Groups, which are Enantiotopic in Achiral Environments, Become Diastereotopic. *Right*: Line Shape Simulation Obtained with the Rate Constants Indicated.

In the case of **1a** (R = H) the barrier was too low to be detected but this is a consequence of **1a** adopting a near to coplanar, rather than an orthogonal, conformation.[10] A coplanar conformation should still have the *ortho* methyls anisochronous when rotation is slow but in **1a** this barrier is much lower than that of a similar aldehyde (2-methyl benzaldehyde) which exhibits two distinct NMR spectra at low temperature [11] due to the existence of two nearly planar [12] E, Z conformers. A Lanthanide Induced Shift (LIS) investigation indicates[13] indeed that in **1a** the Ar-CO dihedral angle should lie in the range 0 - 20° (corresponding to a nearly planar conformation) whereas an almost orthogonal conformation (range 60°- 90° for the same Ar-CO dihedral angle) was inferred for **1b** (R = Me) by the same technique. The latter prediction agrees well with the low temperature spectral behaviour observed here for **1b** (as well as for the analogous ketones of type **1**) in a chiral environment.

In the case of **1f** (R = Ph) our Molecular Mechanics calculations [14] indicate that the Ar-CO dihedral angle (Ar = 2,4,6-trimethylphenyl) is essentially orthogonal (computed value 95°) whereas the Ph-CO dihedral angle is almost planar (computed value -13°). As a consequence, if the Ph-CO rotation becomes slow in the NMR timescale, anisochronous signals for the *ortho* and *meta* carbon positions of the unsubstituted phenyl group should be observed. Indeed the ^{13}C spectrum (75.5 MHz) at -100° displays two signals for each pair of such carbons (Figure 2).

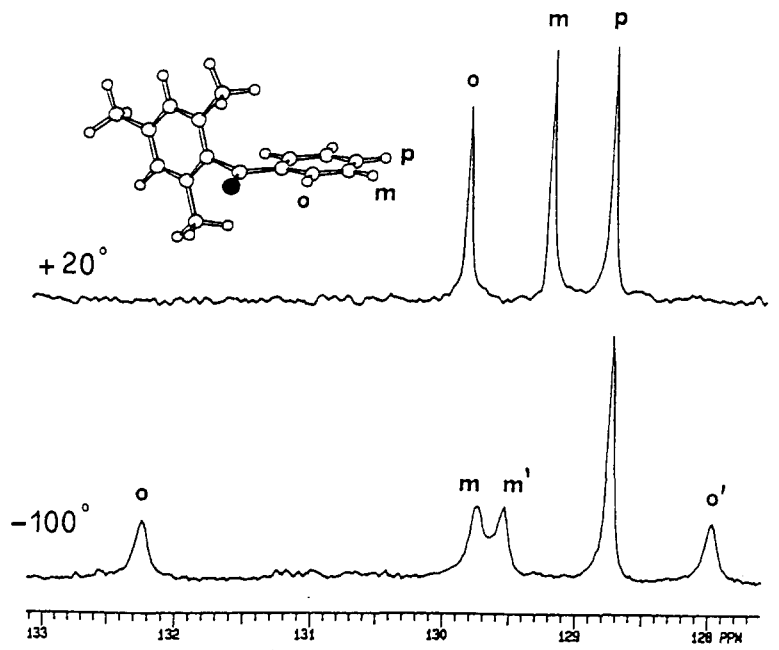


Fig 2. *Top*: Room Temperature ^{13}C Lines (75.5 MHz in CD_2Cl_2) of the *ortho*, *para* and *meta* Carbons of the Phenyl Group of **1f**. *Bottom*: the Same Spectral Region at -100° Displays a Large Splitting for the *ortho* and a Smaller one for the *meta* Carbons, due to the Restricted Ph-CO Rotation.

The free energy of activation (9.1 kcal mol^{-1}), obtained by line shape simulation, for the unsubstituted phenyl-CO rotation in **1f** is slightly smaller than that measured [4b] for the same rotation in **2f** (9.4 kcal mol^{-1}). Although the difference is almost within the experimental errors, it might still reflect the slightly higher hindrance exerted by the *ortho* isopropyl groups upon the Ph-CO rotation in **2f** with respect to that of the *ortho* methyl groups in **1f**.

The enantiotopomerization process in compounds of type **2** was investigated by monitoring the ^{13}C methyl signals of the *ortho* isopropyl groups (in **2e** we found more convenient to monitor the corresponding ^{1}H signals).

At appropriate low temperature two lines are observed, which coalesce into a single line on rising the temperature. The ΔG^{*} values (Table 1) were consistently found to be larger than those of the corresponding mesityl derivatives of type **1** and also higher than those of the corresponding 2,4,6-trineopentyl substituted phenyl alkyl ketones reported in ref. 3. This reflects the larger steric hindrance of the isopropyl group with respect to the Me and CH_2Bu^t groups. Nonetheless when R = H (**2a**) the barrier was still too low to be observable. This is in accordance with the calculations[10] that assign an orthogonal conformation to **2a** but indicate a very low (2.75 kcal mol^{-1}) barrier for the degenerate interconversion of the enantiotopomers. On the contrary when R = Bu^t (**2e**) the barrier is so large that even at the highest accessible temperature (+150°C) the rate is so low that the lines do not even begin to broaden and only the lower limit (i.e. $\Delta G^{*}>$ 22.5 kcal mol^{-1}) could be established for this barrier. We found however that a linear relationship (correlation coefficient = 0.98) holds between the free energies of activation for the five compounds of class **1** (ΔG^{*}_1) and those of the corresponding five compounds of class **2** (ΔG^{*}_2). The insertion in this equation (ΔG^{*}_2 = 6.66 + 0.91 ΔG^{*}_1) of the measured barrier of **1e** (19.2 kcal mol^{-1})[15] yields a ΔG^{*}_2 value for **2e** equal to 24.1 kcal mol^{-1}. This estimate actually exceeds the lower limit (22.5 kcal mol^{-1}) experimentally established and thus gives a reliable indication of a value not otherwise available.

Molecular Mechanics calculations (MMX)[14] predict that the compounds of class **2** have an Ar-CO dihedral angle of about 90° and a dihedral angle of 0° between the ring plane and the C-H bond of the methine isopropyl group in the *para* position (i.e. C3, C4, C13, H13 in Figure 3). Thus when the rotation about the C4-Pr^i bond becomes slow the ring carbons C3, C5 (as well as C2, C6) would display anisochronous ^{13}C signals. The rotational barrier for the C4-Pr^i bond is however too low to be observed in solution, but it may become detectable in the ^{13}C NMR spectra in the solid state (CP-MAS). In the solid state the C-C rotations involving isopropyl groups are known to be sufficiently slow even at room temperature.[16] Indeed the solid state NMR spectra of **2a** and **2b** display a pair of signals [17] for both C3, C5 and C2, C6. In addition, two lines are also visible for the methyl carbons of the *para* isopropyl group as well as for those of the *ortho* isopropyl groups. Whereas the latter methyl groups are diastereotopic also in solution (at low temperature) this is not the case for the methyl carbons of the *para* isopropyl moiety. Thus such a feature in the solid must have a different origin and is actually a consequence of the restricted C4-Pr^i rotation. As shown in Figure 3 for the case of **2b** (R = Me) one of these isopropyl methyl (C14) carbons is *syn* and the other (C15) *anti* to the oxygen (O8) of the carbonyl moiety which has its plane locked at about 90° with respect to the aromatic ring. The MM calculations[14] do agree with a X-ray diffraction structure which shows that the Ar-CO dihedral angle is 89°, with the six isopropyl methyl groups nearly symmetrically placed above and below the plane of the phenyl ring.[18]

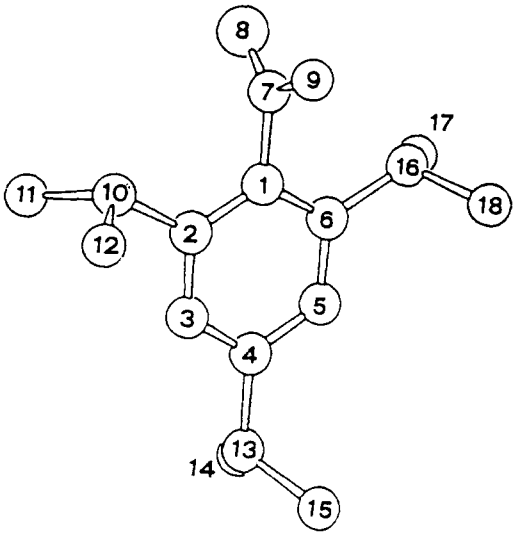


Fig 3. Structure of **2b** as Obtained from Molecular Mechanics Calculations.[14]

It should be pointed out that the arrangement found for the *para* isopropyl group should make not only the pairs of carbons C3, C5 and C2, C6 diastereotopic but also the isopropyl methine carbons bonded to the *ortho* positions (C10, C16) as well as the corresponding methyl groups, which should yield four lines in the solid state spectrum (i.e. one each for C11, C12, C17, C18). This however was not observed in the solid state spectra neither in **2a** nor in **2b**, most likely because of the accidental degeneracy due to these carbons lying too farther away from the source of asymmetry. This explanation is based upon the observed shift difference between C2,C6 which is smaller than that between C3, C5 as the latter carbons are closer to the C4-Pr^i bond.[19] Indeed this degeneracy could be removed in **2d** (R = Pr^i) whose CP-MAS spectrum is reported in Figure 4. The spectrum displays four lines (range 34-46 ppm) corresponding to the four isopropyl methine carbons [i.e. CHCO, CH(4), CH(2,6)] and seven lines (range 20-30 ppm) corresponding to the eight methyl carbons (only a single degeneracy has not been lifted, as revealed by a methyl line twice as intense as the other).

The observed spectral features require that the isopropyl group bonded to the carbonyl moiety is locked in a non symmetrical position in order to provide the asymmetric environment which lifts the degeneracy of the CH and Me carbon signals of the isopropyl moieties in the *ortho* positions.

Since the carbonyl plane is symmetrically situated with respect to the plane of the ring (the Ar-CO dihedral angle being about 90°) the H-C-C=O dihedral angle of the Me_2CH-CO moiety of **2d** must be thus significantly different from 180° in order to create the appropriate non equivalence visible in the spectrum of **2d**. This conclusion nicely agrees with the result of our MM calculations [14] predicting a values of 145° for

such an angle in **2d**. Therefore the solid state spectra indicate that, in the crystal, all the ketones of class **2** lose their dynamic plane of symmetry and become, consequently, chiral objects.

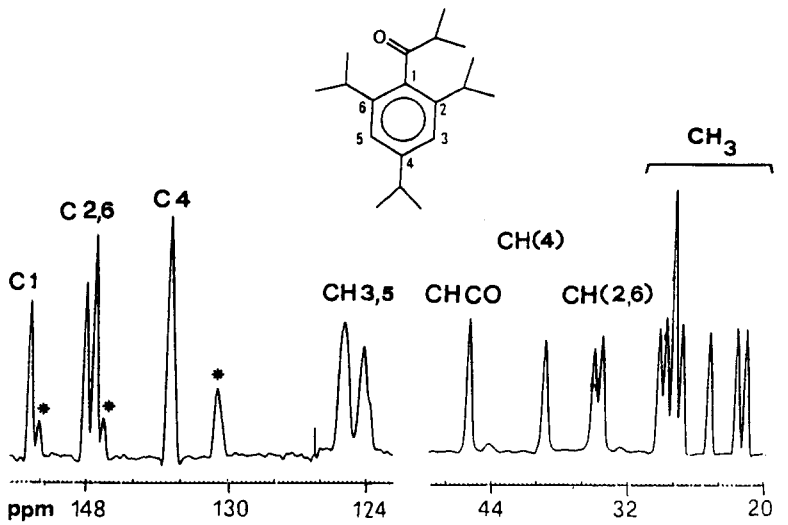


Fig 4. Aliphatic (*Right*) and Aromatic (*Left*) Region of the ^{13}C CP-MAS Spectrum (75.5 MHz) of **2d** in the Solid State. The Starred Lines are Spinning Side Bands.

EXPERIMENTAL

Material

Compounds **1a** and **1b** are commercially available whilst derivatives **1e**, **2e** and **2g** were synthesized by reacting (2,4,6)-trimethylphenyl or (2,4,6)-triisopropylphenyl lithium with the appropriate acyl chloride.[4c] The remaining ketones (**1c**,**1d** and **2b-2l**) were synthesized under Friedel-Craft conditions according to references 4a, 4b,5a. The compounds were identified as follows:

(2,4,6)-Trimethylphenyl ethyl ketone (**1c**). ^1H NMR ($CDCl_3$) δ 1.2 (t, 3 H, Me), 2.2 (s, 6 H, Me), 2.3 (s, 3 H, Me), 2.7 (q, 2 H, CH_2), 6.83 (s, 2 H, Ar). ^{13}C NMR ($CDCl_3$) δ 7.6 (Me), 19.0 (Me, Ar), 21.0 (Me, Ar), 37.9 (CH2), 128.4 (CH), 132.4 (C, Ar), 138.1 (C, Ar), 139.8 (C, Ar), 211.5 (CO).

(2,4,6)-Trimethylphenyl isopropyl ketone (**1d**). ^1H NMR ($CDCl_3$) δ 1.18 (d, 6 H, Me), 2.2 (s, 6 H, Me), 2.3 (s, 3 H, Me), 3.0 (m, 1 H, CH), 6.85 (s, 2 H, Ar). ^{13}C NMR ($CDCl_3$) δ 17.7 (Me), 19.5 (Me), 20.8 (Me), 42.1 (CH), 128.5 (CH, Ar), 133.0 (C, Ar), 138.1 (C, Ar), 138.9 (C, Ar).

(2,4,6)-Triisopropylphenyl methyl ketone (**2b**). ^1H NMR ($CDCl_3$) δ 1.25 (d, 12 H, Me), 1.26 (d, 6 H, Me), 2,5 (3 H, Me), 2.7 (m, 2 H, CH), 2.85 (m, 1 H, CH), 7.0 (s, 2 H, Ar). ^{13}C NMR ($CDCl_3$) δ 24.0 (Me), 24.4 (Me), 31.1 (Me), 34.0 (CH), 34.4 (CH), 121.4 (CH, Ar), 138.8 (C, A r), 143.5 (C, Ar), 149.8 (C,Ar), 210 (C,CO)

(2,4,6)-Triisopropylphenyl ethyl ketone (**2c**). ^1H NMR ($CDCl_3$) δ 1.95 (t, 3 H, Me), 1.22 (d, 6 H, Me), 1.25 (d, 12 H, Me), 2.62 (m, 2 H, CH), 2.72 (d, 2 H, CH_2), 2.88 (m, 1 H, CH), 7.0 (s, 2 H, Ar).

^{13}C NMR ($CDCl_3$) δ 7.5 (Me), 23.9 (Me), 24.3 (Me), 31.0 (CH), 34.2 (CH), 39.5 (CH_2), 121.2 (CH), 138.5 (C, Ar), 143.7 (C, Ar), 149.6 (C, Ar), 212.4 (C, CO)

(2,4,6)-Triisopropylphenyl isopropyl ketone (**2d**). ^1H NMR ($CDCl_3$) δ 1.2 (d, 12 H, Me), 1.25 (d, 12 H, Me), 2.6 (m, 2 H, CH), 2.9 (m, 2 H, CH), 7.0 (s, 2 H, Ar). ^{13}C NMR ($CDCl_3$) δ 18.6 (Me), 23.9 (Me), 26.1 (Me), 24.5 (Me), 26.1 (Me), 31.9 (CH), 34.8 (CH), 43.8 (CH), 121.9 (CH), 138.1 (C, Ar), 145.0 (C, Ar), 150.2 (C, Ar), 215.9 (C, CO).

(2,4,6)-Triisopropylphenyl tert-butyl ketone (**2e**) ^1H NMR ($CDCl_3$) δ 1.125 (d, 3 H, Me), 1.24 (s, 9 H, $C(CH_3)$), 1.26 (d, 3 H, Me), 1.32 (d, 3 H, Me), 2.6 (m, 2 H, CH), 2.87 (m, 1 H,Me), 6.98 (s, 2 H, Ar). ^{13}C NMR ($CDCl_3$) δ 23.1 (Me), 24.1 (Me), 25.8 (Me), 28.5 (Me), 31.9 (CH), 34.3 (CH), 45.0 (C), 121.3 (CH), 137.7 (C, Ar), 144.0 (C, Ar), 149.2 (C, Ar), 220.1 (CO).

(2,4,6)-Triisopropylphenyl neopentyl ketone (**2g**). ^1H NMR ($CDCl_3$) δ 1.12 (s, 9 H, $C(Me)_3$), 1.21 (d, 6 H, Me), 1.25 (d, 12 H, Me), 2.6 (s, 2 H, CH_2), 2.71 (m, 2 H, CH), 2.84 (m, 1 H,CH), 6.97 (s, 2 H, Ar). ^{13}C NMR ($CDCl_3$) δ 24.1 (Me), 24.6 (Me), 29.6 (Me, Bu^t), 30.8 (CH), 34.5 (CH), 58.6 (CH_2), 121.5 (CH), 139.0 (C, Ar), 143.9 (C, Ar) , 149.8 (C, Ar), 210.6 (CO).

(2,4,6)-Triisopropylphenyl isobutyl ketone (**2h**). ^1H NMR ($CDCl_3$) δ 1.03 (d, 6 H, Me), 1.24 (d, 12 H, Me), 1.26 (d, 6 H, Me), 2.35 (m, 1 H, CH), 2.6 (d, 2 H, CH_2), 2.65 (m, 2 H, CH),2.9 (m, 1 H, CH), 7.0 (s, 2 H, Ar). ^{13}C NMR ($CDCl_3$) δ 23.0 (Me), 23.7 (CH), 24.7 (Me), 31.1 (CH), 34.7 (CH), 55.7 (CH_2), 121.4 (CH), 128 (C, Ar) 144.0 (C, Ar), 149.9 (C, Ar), 211.0 (CO).

(2,4,6)-Triisopropylphenyl benzyl ketone (**2i**). ^1H NMR ($CDCl_3$) δ 1.1 (d, 6 H, Me), 1.15 (d, 12 H, Me), 2.6 (m, 2 H, CH), 2.8 (m, 1 H, CH), 3.95 (s, 2 H, CH_2), 6.95 (s, 2 H, Ar), 7.1-7.3 (m, 5 H, Ar). ^{13}C NMR ($CDCl_3$) δ 24.5 (Me), 24.6 (Me), 31.8 (CH), 34.9 (CH), 53.6 (CH_2), 212.9 (CH), 127.9 (CH), 129.4 (CH), 130.7 (CH), 134.3 (C, Ar), 138.4 (C, Ar), 144.5 (C, Ar), 150.6 (C, Ar), 209.1 (CO).

(2,4,6)-Triisopropylphenyl 3-pentyl ketone (**2l**). ^1H NMR ($CDCl_3$) δ 0.92 (m, 6 H, *Me*-CH_2), 1.18 (d, 12 H, Me), 1.21(d, 6 H, Me), 1.52 (m, 2 H, CH_2), 1.74 (m, 2 H, CH_2), 2.64 (m, 2 H, CH) 2.88 (m, 1 H, CH), 6.98 (s, 2 H, Ar). ^{13}C NMR ($CDCl_3$) δ 21.9 (Me), 24.1 (Me), 24.4 (Me), 31.0 (CH_2), 34.4 (CH), 56.9 (CH), 121.2 (CH), 140.2 (C, Ar), 145.3 (C, Ar), 149.9 (C, Ar), 213.8 (CO).

NMR spectra.

Solution spectra were recorded on spectrometers operating at 200 and 300 MHz for ^1H and the chemical shifts quoted above are referred to TMS (ppm) used as internal standard. The ΔG* values for compounds of class **1** were determined (in the presence of chiral TFAE) in CHF_2Cl (**1b**, **1c**, **1g**), in CD_2Cl_2 (**1d**, **1f**) and in C_2Cl_4 (**1e**). The values for compounds of class **2** were determined in CD_2Cl_2 (**2b**, **2c**) in DMSO (**2d-2f**) and in $CDCl_3$ (**2g-2l**). Different solvents were needed in order to reach the required temperature ranges which allowed the observation of the dynamic process by NMR. The low temperature spectra were obtained by cooling the sample with a stream of dry nitrogen passing through the variable temperature coils immersed in liquid nitrogen, whereas the high temperatures were obtained by heating directly the air flow used for spinning the sample. Low and high temperatures were calibrated [20] using the shift displacements with the temperature of methanol and ethylene glycol, respectively. The ^{13}C NMR solid state spectra were obtained using a spectrometer operating at 75.45 MHz. The samples were packed into a 7 mm rotor that was spun at the magic angle with a spinning speed of the order of 4 KHz. The 90° ^1H pulse

duration was 5 μs, which was also the value for the ^{13}C as set by the Hartmann Hahn conditions. [21] For the Cross Polarization (CP) the contact time was typically 2 ms, while the recycle delay was 5s.

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REFERENCES AND NOTES

1. Part 55. Anderson, J. E.; Casarini, D.; Lunazzi, L. *J. Org. Chem.* **1996**, in the press.
2. Erasmus student 1994 from the Department of Organic Chemistry , University of Nijmegen, The Netherlands.
3. Dahlberg, E.; Nilsson, B.; Olsson, K.; Martinson, P. *Acta. Chem. Scand.* **1975**, *B29*, 300.
4. (a) Ito, I.; Umeharo, Y.; Nakamura, K.; Yamado, Y.; Matsura, T.; Iamshiro, F. *J Org. Chem.* **1981**, *46*, 4359.
   (b) Bonini, B. F.; Grossi, L.; Lunazzi, L.; Macciantelli, D. *J. Org. Chem.* **1986**, *51*, 517.
   (c) Casarini, D.; Lunazzi, L.; Pasquali, F.; Gasparrini, F.; Villani, C. *J. Am. Chem. Soc.* **1992**, *114*, 6521.
5. (a) Holik, M.; Mannschreck, A. *Org. Magn. Resonance* **1979**, *12*, 28.
   (b) Kuspert, R.; Mannschreck, A. *Org. Magn. Resonance* **1982**, *19*, 6.
6. (*d*) $Eu(hfbc)_3$ stays for (+)-*tris*(3-heptafluorobutyryl-D-camphorate) Europium (III). For reviews on chiral agents in NMR see: Sullivan, G. R. *Top. Stereochemistry* **1978**, *10*, 287. Rinaldi, P. L. *Progress in NMR Spectroscopy* **1982**, *15*, 291. Parker, D. *Chem. Rev.* **1991**, *91*, 1441. Gasparrini, F.; Lunazzi, L. Misiti, D.; Villani, C. *Acc. Chem. Res.* **1995**, *28*, 163.
7. Pirkle, N. H. *J. Am. Chem. Soc.* **1966**, *88*, 1837.
8. The $\Delta G^{\ddagger}$ values were found independent of the temperature in the range examined, indicating a negligible value for $\Delta S^{\ddagger}$ as often observed in conformational processes.
9. The error is larger than that ($\pm$ 0.15 kcal mol^{-1}) estimated for the other derivatives, owing to the uncertainty (i.e. ±40 Hz at 300 MHz.) on the chemical shift separation of **1b**.
10. Molecular Mechanics calculations (MMPI) predict a coplanar conformation for **1a**, with a rotational barrier as low as 1.9 kcal mol^{-1}, and an orthogonal conformation for **2a**, with a barrier of 2.75 kcal mol^{-1} see: Andersson, S.; Carter, R.E.; Drakenberg, T. *Acta Chem. Scand.* **1984**, *B38*, 579.
11. (a) Drakenberg, T.; Jost, R.; Sommer, J. M. *J. Chem. Soc. Perkin Trans. 2* **1975**, 1882.

(b) Lunazzi, L.; Ticca, A.; Macciantelli, D.; Spunta, G. *J. Chem. Soc. Perkin Trans. 2* **1976**, 1121.

12. Benassi, R. J.; Iarossi, D.; Folli, U.; Schenetti, L.; Taddei, F. *J. Chem. Soc. Perkin Trans. 2* **1981**, 228.
13. Abraham, R. J.; Bergen, H. A.; Chadwick, D. J. *J. Chem. Soc. Perkin Trans. 2* **1983**, 1161.
14. Program PC Model, Serena Software, Bloomington, IN. The conformation predicted by these calculations for **1f** is analogous to that found by X-ray diffraction for **2f** (see ref. 4a).
15. It is noteworthy that the barrier of **1e** measured here using a diamagnetic chiral agent (TFAE) is equal to that of ref. 5a where the paramagnetic chiral agent $Eu(hbfc)_3$ was employed. Apparently the barrier is not affected by the environment.
16. (a) Groombridge, C. J.; Harris, R. K.; Packer, K. J.; Say, B. J.; Tanner, S. F. *J. Chem. Soc. Chem. Commun.* **1980**, 174.

    (b) Frey, M. H.; Opella, S. J. *J. Chem. Soc. Chem. Commun.* **1980**, 474.
17. This effect cannot be attributed to the existence of two molecules occupying different sites within the crystal in that the single carbons (i.e. C1, C4, and CO) always display a single line in the solid state.
18. Information kindly provided by Professor E. Foresti, University of Bologna.
19. The values are 2.1 vs. 0.6 ppm in **2a**, 1.9 vs. 1.8 in **2b** and 1.6 vs. 0.8 ppm in **2d**.
20. (a) Van Geet, A. L. *Anal. Chem.* **1968**, *40*, 2227.

    (b) Van Geet, A. L. *Anal. Chem.* **1970**, *42*, 679.
21. (a) Voekel, R. *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 1468.

    (b) Yannoni, C. S. *Acc. Chem. Res.* **1982**, *15*, 208.

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