Conformational Studies by Dynamic NMR. 85.[1] Stereomutation of Conformational Atropisomers of *o-tert*-Butylphenyl Alkyl Ketones

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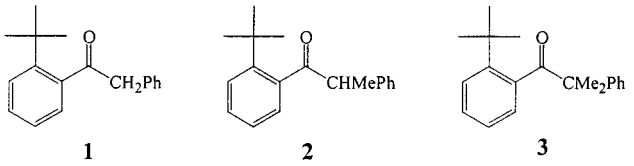
Unhindered aryl ketones have the plane of the carbonyl moiety essentially coplanar with that of the aryl ring, owing to the conjugation occurring between the C═O and the Ar moieties. The barrier for the rotation process about the Ar−CO bond (π-barrier) can be measured by dynamic NMR since at low temperature the ortho positions become diastereotopic, yielding anisochronous ^{1}H and ^{13}C signals.[2,3] Conversely, hindered aromatic ketones (for instance, those bearing ortho or ortho-like substituents) have the plane of the carbonyl group significantly twisted with respect to that of the aromatic ring, as shown by the X-ray diffraction structures determined in the crystalline state.[4−6] In these cases, the rotation barriers (steric barriers) can be measured by dynamic NMR only if prochiral probes are also available,[7−12] or if pairs of diastereoisomers are present at the equilibrium.[13−15] In favorable circumstances the barriers become NMR detectable when the hindered ketone adopts a propeller-like chiral conformation,[16] or if the enantiotopic groups in the molecule can be made diastereotopic by the presence of an appropriate chiral agent.[17] An exception to the near orthogonality of hindered aryl ketones is apparently offered by 2,4,6-trihydroxyphenyl acetophenone, where the hydrogen bonding seems to maintain the MeCO and the aryl ring almost coplanar.[18]

Chart 1



1 **2** **3**

When dealing with non-coplanar phenyl ketones, the rotation barriers are sufficiently high for NMR detection only when substituents are present in both the ortho positions.[7,9−11] So far, therefore, restricted rotation has never been measured by NMR in phenyl ketones containing solely one ortho substituent,[19] the only exception being the peculiar situation encountered in the racemic conformer of a phenyl bearing two *i*-PrCO groups in an ortho relationship.[12a]

The latter finding thus suggests that it should be possible to render NMR visible the Ar−CO bond rotation if a sufficiently large group is purposely introduced in one of the two ortho positions of a phenyl ketone. As a consequence, we synthesized and investigated the following aryl alkyl ketones (**1**−**3**, as in Chart 1**)** where a *tert*-butyl substituent is expected to severely hinder the Ar−CO rotation process.

Molecular mechanics (MM) calculations[20] predict that the planes of the carbonyl and aryl groups of **1** are orthogonal (dihedral angle $\vartheta = 90°$), so that the molecule comprises two stereolabile atropisomers (conformational enantiomers), indicated as **1** (P) and **1** (M) in Scheme 1. The rotation about the Ar−CO bond interconverts these antipodes (enantiomerization), and such a process might occur, in principle, through two possible transition states. The one (TS-2) where the benzyl group crosses the *tert*-butyl substituent ($\vartheta = 180°$) entails a theoretical barrier (16 kcal mol^{-1}) much higher than that (8 kcal mol^{-1}) due to the transition state (TS-1), where the carbonyl moiety crosses the *tert*-butyl substituent ($\vartheta = 0°$).[21] The latter pathway is therefore expected to be the route followed by **1** to achieve the interconversion of the two enantiomers. As a consequence, the motion about the Ar−CO bond would not be a complete 2π-rotation pathway: a π-rotation (from $\vartheta = 90°$ to $\vartheta = -90°$) is in fact sufficient to accomplish this process.

Even allowing for the approximations involved in the MM approach, the lower of the two enantiomerization

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(19) Contrary to aryl ketones, aryl aldehydes bearing a single substituent in the ortho (or ortho-like) position maintain a quasi-coplanar conformation, thus exhibiting pairs of rotamers of different stability. See: Drakenberg, T.; Jost, R.; Sommer, J. M. *J. Chem. Soc., Perkin Trans. 2* **1975**, 1682. Lunazzi, L.; Ticca, A.; Macciantelli, D.; Spunta, G. *J. Chem. Soc., Perkin Trans 2.* **1976**, 1121. Drakenberg, T.; Sandström, J.; Seita, J. *Org. Magn. Reson.* **1978**, *11*, 246. See also ref 12a.

(20) MMX force field, as implemented in the PC Model 88.0 computer program, Serena Software, Bloomington, IN.

(21) Calculations[20] indicate that the rotation barrier of the *tert*-butyl group is as low as 0.5 kcal mol^{-1}.

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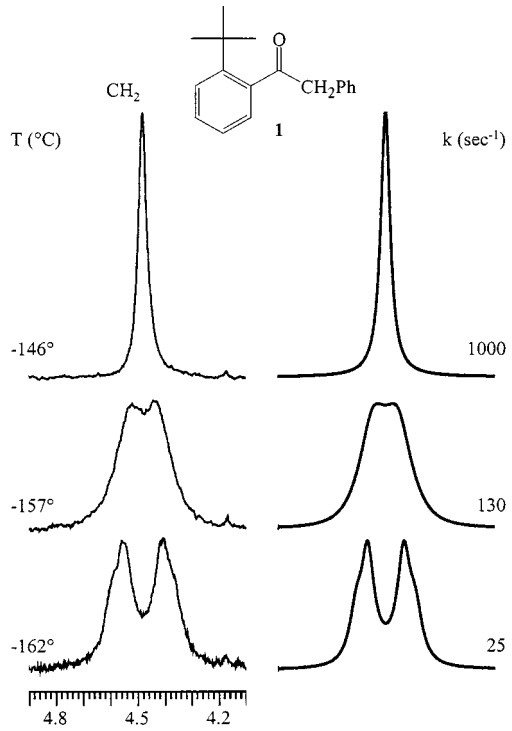
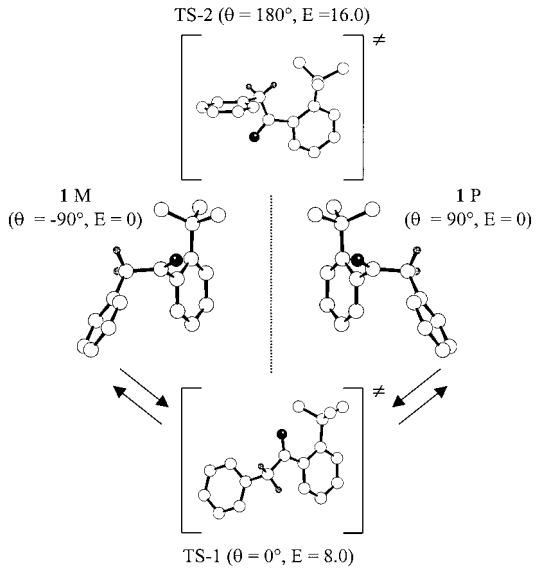


Figure 1. Left: experimental ^{1}H signal (400 MHz) of the methylene hydrogens of **1** as a function of temperature. Right: computer simulations obtained with the rate constants indicated.

Scheme 1



barriers predicted for **1** should be amenable to an experimental observation by NMR spectroscopy. The spectrum of **1**, taken at 400 MHz, actually shows how the single line of the methylene hydrogens broadens considerably below −140 °C, eventually exhibiting (at −162 °C) the typical pattern ($\Delta\nu$ = 70 Hz, J = −17 Hz) of an AB system (Figure 1). This is because the slow Ar−CO bond rotation makes diastereotopic the two otherwise enantiotopic methylene hydrogens. Line shape simulation (Figure 1) provided the rate constants, hence, the $\Delta G^{\ddagger}$ value (5.5 ± 0.15 kcal mol^{-1}), for the corresponding enantiomerization process.

In derivative **3**, the dynamic process was more conveniently followed by monitoring the ^{13}C NMR signal of the

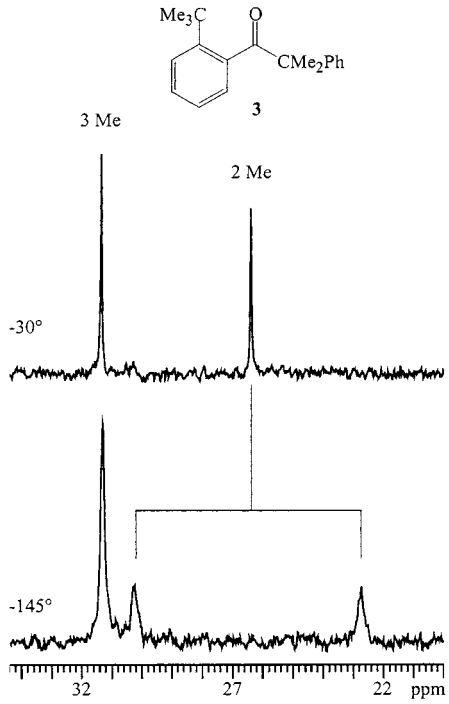


Figure 2. ^{13}C spectra (75.5 MHz) of the methyl region of **3** at −30 and −145 °C. At the latter temperature, the signal of the three *tert*-butyl methyl groups remains a singlet whereas that of the two methyl groups splits into a pair of lines.

Table 1. Experimental $\Delta G^{\ddagger}$ Values,[a] MM-Computed Relative Energies (E),[a] and Dihedral Angles (θ)[b] for the Ground (GS) and Lower Rotation Transition State (TS-1) of 1−3

compd	**1**	**2**(RM)	**2**(RP)	**3**
θ (deg)	90	−75	65	75
		−73[c]	53[c]	
$\Delta G^{\ddagger}$ (expt)	5.5	not measurable		6.7
E (GS)	0	0	0.4	0
		0	0.55[c]	
E (TS-1)	8.1	8.2		9.9

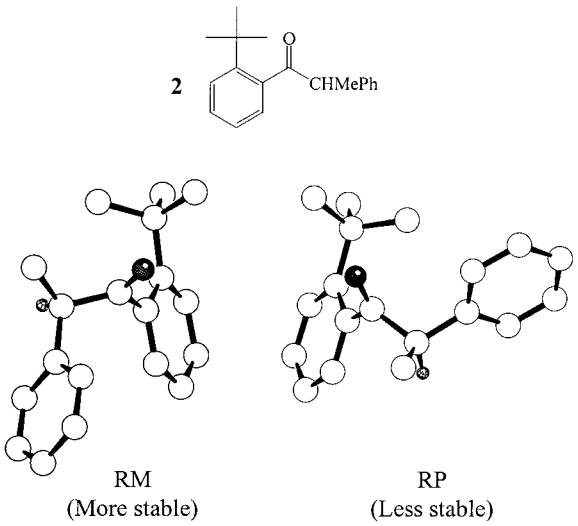
[a] In kcal mol^{-1}. [b] Dihedral angles between the C=O and aryl ring planes in the ground state. [c] Results from ab initio computation.[22]

two enantiotopic methyl groups. At −145 °C, these methyls become diastereotopic, so that the corresponding signal splits into a pair of equally intense lines, displaying a chemical shift difference as large as 7.5 ppm (Figure 2). The related enantiomerization barrier (6.7 ± 0.2 kcal mol^{-1}) was found to be higher than that of **1**, due to the increased steric effect: a result also predicted by MM calculations, as reported in Table 1.

Derivative **2** bears a configurationally stable chiral center, so that two stereolabile diastereoisomers of different stability (Chart 2) are expected to be observable when the rotation about the stereogenic Ar−CO axis is blocked, each diastereoisomer comprising two enantiomeric forms (i.e., the pair RM, SP and the pair RP, SM).

Since derivative **2** has steric requirements intermediate between those of **1** and **3**, the barrier for the interconversion of **2** RM into **2** RP cannot be lower than that of **1**: indeed, MM computations predict this barrier to be essentially equal to that for the enantiomerization of **1** (Table 1). Although the Ar−CO rotation of **2** should be consequently frozen at about the same temperature, yet the ^{13}C spectrum displays signals due to a single species, even at −160 °C. Unless all the ^{13}C lines of the

Chart 2



two diastereoisomers happen to be accidentally coincident, we must conclude that only one of the two diastereoisomers is appreciably populated. Actually an accidental coincidence is not very plausible since, for instance, the lines of the five quaternary carbons of **2** have a width of only 2 or 3 Hz at −160 °C. Had two diastereoisomers been present in comparable amount, it is unlikely that not even one of these sharp lines would display the expected splitting.

It has also to be considered that the poor solubility at such low temperatures makes, in practice, invisible the ^{13}C spectrum of a minor species having a population lower than 10−15%. The MM calculations estimate that diastereoisomer **2** RM is 0.4 kcal mol^{-1} more stable than **2** RP (Table 1), thus entailing a 85:15 ratio at −160 °C. Likewise, ab initio calculations[22] predict an energy difference of 0.55 kcal mol^{-1}, which corresponds to a RM population of 92% at that temperature. If we consider the differences likely to come about between the situation computed for the isolated molecule and the experimental situation occurring in solution, it is quite plausible that the actual population of the major diastereoisomer is definitely larger than 90%. This would account for the NMR detection of only one of the two diastereoisomers, to which the RM structure should be therefore assigned.

Experimental Section

General Procedures and Material. Mass spectra (MS) were performed by electron impact with a beam energy of 70 eV: relative intensities are given in parentheses. Column chromatography was carried out on silica gel (63−200, 60 Å) by gradual elution with light petroleum (40−70 °C)/diethyl ether mixtures (from 0 up to 100% diethyl ether). Preparative TLC chromatography was performed on 1 mm thick aluminum oxide plates. 2-*tert*-Butylbenzaldehyde was prepared according to a known procedure.[23]

1-(2-*tert*-Butylphenyl)-2-phenylethanol. A solution of 2-*tert*-butylbenzaldehyde (8.0 g, 50 mmol) in dry diethyl ether (25 mL) was added dropwise to a stirred solution of benzylmagnesium chloride, obtained by treatment of benzyl chloride (6.85 g, 50 mmol) with magnesium turnings (1.35 g, 50 mmol) in dry diethyl ether (150 mL). The resulting mixture was stirred for 3 h and cautiously hydrolyzed with an aqueous 10% ammonium chloride solution. The organic phase was separated and the aqueous layer extracted twice with diethyl ether. The combined organic phases were dried, the solvent removed under vacuum, and the residue chromatographed to give the title compound (9.5 g, 75%): oil; IR ν_{max} (neat, cm^{-1}) 3434 (OH); MS *m*/*z* 164 (M$^+$ − 90, 100), 91 (36), 57 (50); ^1H NMR (200 MHz) δ 1.27 (9 H, s, *t*-Bu), 2.04 (1 H, bs, O*H*), 2.86 (2 H, d, J = 6.3 Hz, CH_2), 5.38 (1 H, t, J = 6.3 Hz, C*H*), 6.99−7.17 (7 H, m, Ar-*H*), 7.20 (1 H, dd, J_1 = 7.4 Hz, J_2 = 1.9 Hz, Ar-*H*), 7.54 (1 H, dd, J_1 = 7.4 Hz, J_2 = 1.9 Hz, Ar-*H*); ^{13}C NMR (50 MHz) δ 32.06, 35.26 (q), 45.45 (CH$_2$), 71.07 (CH), 125.43, 126.34, 127.25, 128.20, 128.33, 129.28, 138.86 (q), 142.95 (q), 146.10 (q) (2 aromatic CH overlapped). Anal. Calcd for $C_{18}H_{22}O$: C, 84.99; H, 8.72. Found: C, 85.30; H, 8.70.

1-(2-*tert*-Butylphenyl)-2-phenylethanone (1). Following the literature,[24] concentrated sulfuric acid (2.4 mL) was cautiously added, at 0 °C, to a solution of CrO_3 (2.86 g, 29 mmol) in water (20 mL). The resulting mixture was added dropwise to a stirred solution of the above alcohol (5.6 g, 22 mmol) in acetone (10 mL). The reaction course was monitored by TLC; after a few hours, an approximately 1:1 ketone/alcohol ratio was obtained that did not change by prolonging the reaction time. After 12 h, the mixture was diluted with water and extracted with diethyl ether. The organic phase was dried, the solvent removed under vacuum, and the residue chromatographed to give, together with some unreacted starting alcohol (45%), the title ketone (2.8 g, 50%): oil; IR ν_{max} (neat, cm^{-1}) 1703 (CO); MS *m*/*z* 252 (M$^+$, 1), 237 (3), 161 (100), 91 (45); ^1H NMR (200 MHz) δ 1.35 (9 H, s, *t*-Bu), 4.14 (2 H, s, CH_2), 7.11 (1 H, dd, J_1 = 7.1 Hz, J_2 = 2.0 Hz, Ar-*H*), 7.15 (1 H, dd, J_1 = 6.5 Hz, J_2 = 1.2 Hz, Ar-*H*), 7.20−7.38 (6 H, m, Ar-*H*), 7.47 (1 H, bd, J = 7.1 Hz, Ar-*H*); ^{13}C NMR (50 MHz) δ 32.46, 36.60 (q), 51.88 (CH$_2$), 125.84, 126.92, 127.60, 127.87, 129.09, 129.81, 130.46, 134.45 (q), 142.10 (q), 147.62 (q), 207.24 (q). Anal. Calcd for $C_{18}H_{20}O$: C, 85.67; H, 7.99. Found: C, 85.82; H, 7.96.

Methylation of 1-(2-*tert*-Butylphenyl)-2-phenylethanone. According to the literature,[25] in a three-necked round-bottomed flask sodium hydride (60% dispersion in mineral oil, 0.64 g, 16 mmol) was suspended under stirring at 10 °C in anhydrous DMF (20 mL) under nitrogen. Methyl iodide (2.8 g, 20 mmol) was added, followed by dropwise addition of a solution of the above ketone (3.68 g, 15 mmol) in anhydrous DMF (10 mL). After 5 h, the mixture was carefully hydrolyzed with water and extracted with diethyl ether. The organic phase was dried and the solvent removed to give an oily residue that was purified twice by column chromatography and finally by preparative TLC to yield *1-(2-tert*-butylphenyl)-2,2-dimethyl-2-phenylethanone **3** (1.03, 25%) [oil; IR ν_{max} (neat, cm^{-1}) 1690 (CO); MS *m*/*z* 280 (M$^+$, <1), 265 (3), 161 (100), 91 (44); ^1H NMR (200 MHz) δ 1.42 (9 H, s, *t*-Bu), 1.62 (6 H, s, CMe$_2$), 6.43 (1 H, dd, J_1 = 7.7 Hz, J_2 = 1.4 Hz, Ar-*H*), 6.86 (1 H, bt, J = 7.5 Hz, Ar-*H*), 7.16−7.60 (7 H, m, Ar-*H*); ^{13}C NMR (50 MHz) δ 28.18, 33.07, 36.63 (q), 52.32 (q), 125.18, 126.68, 127.48, 128.50, 129.33, 129.53, 140.16 (q), 145.41 (q), 148.53 (q), 213.26 (q) (two aromatic CH overlapped). Anal. Calcd for $C_{20}H_{24}O$: C, 85.67; H, 8.63. Found: C, 85.89; H, 8.59], 1-(2-*tert*-butylphenyl)-2-methyl-2-phenylethanone **2** (0.66, 17%) [oil; IR ν_{max} (neat, cm^{-1}) 1697 (CO); MS *m*/*z* 251 (M$^+$ − 15, 3), 161 (100), 91 (55); ^1H NMR (200 MHz) δ 1.32 (9 H, s, *t*-Bu), 1.62 (3 H, d, J = 7.0 Hz, CH*Me*), 4.30 (1 H, q, J = 7.0 Hz, C*H*Me), 6.62 (1 H, dd, J_1 = 7.8 Hz, J_2 = 1.4 Hz, Ar-*H*), 6.96 (1 H, ddd, J_1 = J_2 = 7.2 Hz, J_3 = 1.0 Hz, Ar-*H*), 7.19−7.35 (6 H, m, Ar-*H*), 7.45 (1 H, dd, J_1 = 8.2 Hz, J_2 = 1.0 Hz, Ar-*H*); ^{13}C NMR (50 MHz) δ 19.90, 32.71, 36.56 (q), 55.04, 125.43, 127.82, 128.01, 128.99, 129.37, 129.60, 140.99 (q), 141.74 (q), 147.73 (q), 210.74 (q) (two aromatic CH overlapped). Anal. Calcd for $C_{19}H_{22}O$: C, 85.67; H, 8.32. Found: C, 85.92; H, 8.30], and the starting ketone (0.56 g, 15%). Some fractions of the first column contained minor amounts of 1-(*tert*-butyl)-2-[1-methoxy-2-phenylethenyl]benzene [^1H NMR (300 MHz) δ 1.44 (9 H, s, *t*-Bu), 3.40 (3 H, s, MeO), 5.50 (1 H, s, C=CH), 7.10−7.40 (6 H, m, Ar-*H*), 7.49−7.59 (1 H, m, Ar-*H*), 7.63−7.73 (2 H, m, Ar-*H*)] and 1-(*tert*-butyl)-2-[1-methoxy-2-phenyl-1-propenyl]benzene [^1H NMR (300 MHz) δ 1.44 (9 H, s, *t*-Bu), 1.73 (3 H, s, C=CMe), 3.19 (3 H, s, OMe),

(22) Calculations carried out at the RHF 6-31G* level using the Jaguar 3.5−42 version, as implemented in the computer package Titan, Wavefunction Inc., Irvine, CA.

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7.15−7.27 (3 H, m, Ar-*H*), 7.29−7.41 (3 H, m, Ar-*H*), 7.46−7.59 (3 H, m, Ar-*H*)].

NMR Measurements. ^{1}H and ^{13}C NMR spectra were recorded in deuteriochloroform using tetramethylsilane or deuteriochloroform, respectively, as internal standards. The assignment of the ^{13}C signals was carried out by DEPT sequences. The samples for the low-temperature measurements were prepared by connecting to a vacuum line the NMR tubes containing the desired compounds dissolved in some C_6D_6 (for locking purpose) and condensing therein the gaseous solvents CHF_2Cl and $CHFCl_2$ (in a 4:1 proportion) by means of liquid nitrogen. The tubes were subsequently sealed *in vacuo* and introduced into the precooled probes of the 300 or 400 MHz spectrometers. The temperatures were calibrated by substituting the sample with a precision Cu/Ni thermocouple before the measurements. Total line shape simulations were achieved by using a PC version of the DNMR-6 program.[26] Since at the low temperatures required to observe the exchange process the intrinsic line width of the compounds was significantly temperature dependent, the corresponding dependence of the solvent signal was measured. The appropriate ratio with the line width of the compound was then taken into account. We also checked that errors as large as 50% on this value affected the activation energy by less than 0.05 kcal mol^{-1} in the temperature range investigated.[27]

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Supporting Information Available: MMX computed[20] *Z*-matrixes for compounds **1**−**3** and ab initio computed[22] *Z*-matrixes for compounds **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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