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Conformational Studies by Dynamic NMR. 70.[1] Stereomutations of Homochiral Dicarvone in Solution and in the Solid State

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Dynamic NMR experiments have shown that the title compound exists in two helical, *P* and *M*, forms (atropisomers) having a 99.5:0.5 ratio at −40 °C in methylene chloride. The experimental interconversion barrier (13.3 kcal mol^{-1}) is close to that theoretically computed by a molecular mechanics (MM) method (14.7 kcal mol^{-1}). A second stereomutation process has also been discovered, with a conformer having antiparallel exocyclic isopropenyl groups interconverting into a second conformer having these groups in a parallel disposition, their relative proportion being 95.5:4.5 at −135 °C. The corresponding MM computed barrier (7.9 kcal mol^{-1}) matched satisfactorily that determined experimentally (8.4 kcal mol^{-1}). Solid-state (CP-MAS) NMR at low temperatures showed that the latter motion occurs also in the crystal, the corresponding barrier being however significantly higher (14.8 kcal mol^{-1}) due to the effects of the crystal lattice.

Introduction

In asymmetric synthesis, the presence of a *C*2 symmetry axis within a chiral auxiliary serves the important function of reducing the number of possible competing diastereomeric transition states.[2]

With the aim of devising new and effective chiral auxiliaries, it might prove possible to assemble two identical simple monomeric units containing configurationally stable stereocenters (for example, a monoterpene) to produce a more complex molecular structure where the primary chirality, due to the original stereocenters of the monomers, is enhanced by a secondary chirality provided by the three-dimensional geometry of the entire molecule. The synergistic effect, brought about by the native chirality of the monomers and by the chiral geometry of the whole system, may play an important role in the transmission of the chiral information in asymmetric synthesis.

Results and Discussion

In this perspective the dimer of carvone, i.e., dicarvone (**1**), which bears four asymmetric carbon atoms, has been synthesized [3] in the form of the homochiral 1*R*,6*R*,11*R*,16*R* enantiomer (Scheme 1). In addition to the four configurationally stable chiral centers, this molecule also comprises a stereolabile chirality axis coincident with the C1−C11 bond (Schemes 1 and 2). As a consequence, the two possible helical forms, *P* and *M* (as defined in ref 3), should, in principle, be observable. The X-ray diffraction structure of **1** showed, however, that solely the 1*R*,6*R*,11*R*,16*R*,*P* atropisomer (**1a**) is present in the crystalline state.[3] Our molecular mechanics calculations (MMX force field[4]) indicate that **1a** is indeed more stable than the atropisomer 1*R*,6*R*,11*R*,16*R*,*M* (**1b**), the computed energy difference (Scheme 1) being 1.5 kcal mol^{-1}. Such a relatively high value for this difference suggests that the less abundant **1b** atropisomer can be present at the equilibrium only in an extremely low proportion.

The computed structure of **1a** is essentially the same as that experimentally determined by X-ray: in particular the C2−C1−C11−C12 dihedral angle measured in the solid (52°) is close to the calculated one (42°). On the other hand, the computed structure of the *R*,*R*,*R*,*R*,*M* atropisomer **1b** predicts a much larger value (−160°) for this angle. Consequently, whereas in **1a** the two carbonyl moieties are in a gauche relationship, in **1b** they are essentially anti to each other, as displayed in the simplified Newman projection along the C1−C11 chirality axis (Scheme 2). Such a shape entails a dipole moment for **1b** larger than that of **1a**, the computed values being in fact 3.6 and 3.0 D, respectively.

The energies of the structures generated by stepwise rotations of the two molecular halves about the C1−C11 bond were computed to describe the pathway which interconverts the atropisomer **1a** into **1b**. Such a stereomutation requires the passage across a transition state having a C2−C1−C11−C12 dihedral angle of −77°, with an energy 15.7 kcal mol^{-1} higher than that of the ground state **1a**. A second transition state was also encountered along this torsion pathway, the dihedral angle of which

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[1] For part 69 see: Anderson, J. E.; Casarini, D.; Lunazzi, L.; Mazzanti, A. *Eur. J. Org. Chem.*, **2000**, in press.

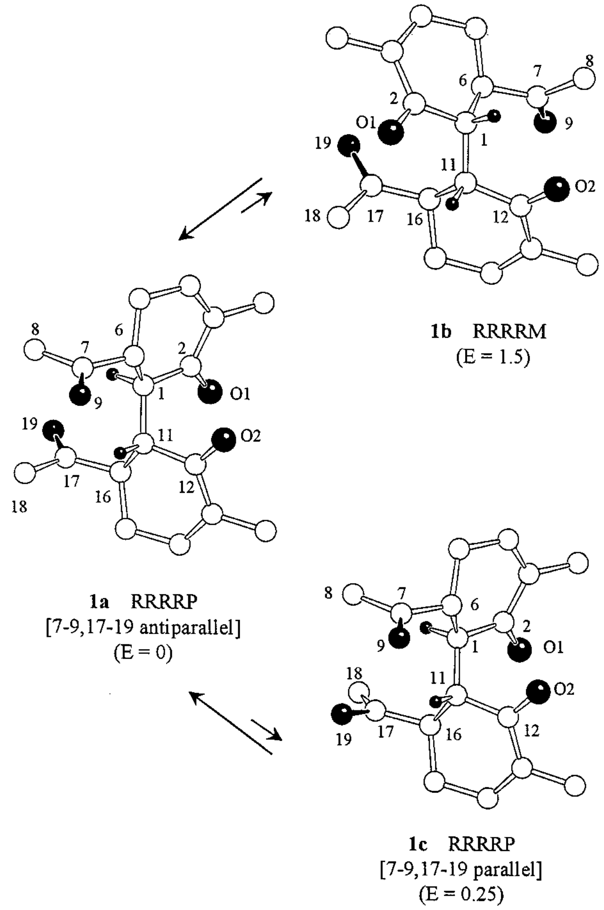
[2] Whitesell, J. K. *Chem. Rev.* **1989**, *89*, 1581.

[3] Mazzega, M.; Fabris, F.; Cossu, S.; De Lucchi, O; Lucchini, V.; Valle, G. *Tetrahedron* **1999**, *55*, 4427.

[4] Computer package PC Model, Serena software, Bloomington, IN.

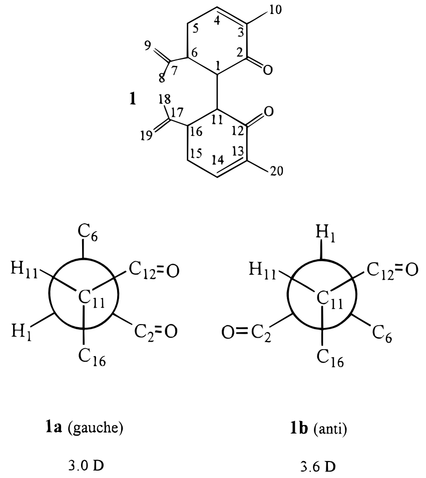
10.1021/jo9913964 CCC: $19.00

Scheme 1. MMX Computed Structures of the Three Experimentally Detected Forms of Dicarvone (1)[a]



[a] The calculated relative energies (E) are in kcal mol^{-1}.

Scheme 2. Schematic Newman Projection, along the C11−C1 Axis, of the *P*- and *M*-Helical Atropisomers (1a and 1b, Respectively) of Dicarvone, Showing the Gauche and Anti Relationship of the Two Carbonyl Moieties[a]



[a] The computed dipole moments are in debyes.

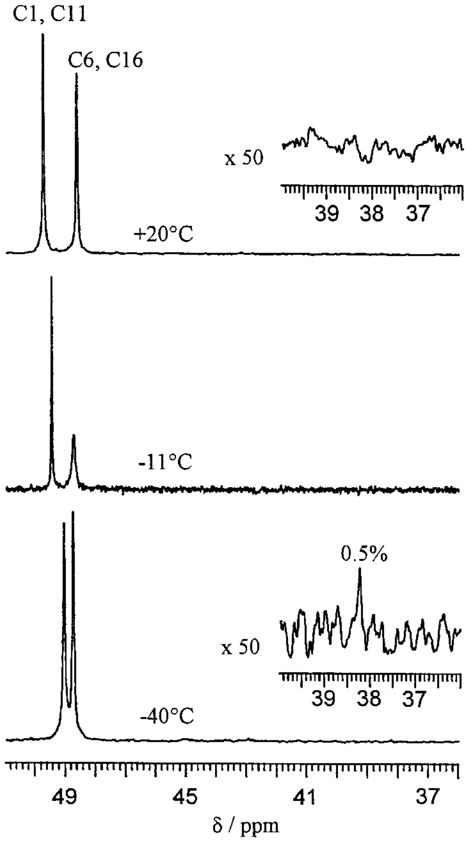


Figure 1. The two C1,C11 and C6,C16 lines of dicarvone (**1**) at three different temperatures in CD$_2$Cl$_2$ (75.46 MHz). The downfield line does not change its width, whereas the one upfield broadens at −11 °C and sharpens again at −40 °C. The 50-fold vertically enhanced trace at −40 °C reveals the presence of the C6,C16 line due to the minor atropisomer **1b** (0.5%), which is absent in the equally enhanced trace at +20 °C.

is −240°, with an energy 14.7 kcal mol^{-1} higher than that of **1a**: the latter value thus represents the barrier that has to be overcome to interconvert **1a** into **1b**. Even allowing for the approximations of the MM method, such a value lies within the range accessible to dynamic NMR experiments,[5] so that it might be possible to detect two individual spectra for the *P* and *M* atropisomers at an appropriate low temperature.

In the ^{1}H spectrum of **1** the H1,H11 signal, which appears as a moderately sharp doublet ($\delta = 2.55$ ppm) at ambient temperature, broadens considerably at lower temperature and sharpens again on further cooling. Likewise the C6,C16 signal in the corresponding ^{13}C spectrum (75.46 MHz) is a relatively sharp line (half-height width 3.4 Hz) at +20 °C, which broadens on cooling (reaching a maximum width of 10.2 Hz at −11 °C) and restores to its original width at −40 °C (Figure 1). Such a behavior is typical of an exchange process between an intense signal and an apparently "invisible" companion.[6,7] This interpretation is further supported by the variation observed in the position of this ^{13}C line: its chemical shift, which is 48.63$_5$ ppm at +20 °C, moves downfield (to 48.75 ppm) at −40 °C. Although this displacement could be simply due to the effect of varying the temperature, it might also indicate that the line

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(5) Sandström, J. *Dynamic NMR Spectroscopy*; Academic Press: London, 1982.

(6) (a) Anet, F. A. L.; Basus, V. J. *J. Magn. Reson.* **1978**, *32*, 339. (b) Okazawa, N.; Sorensen, T. S. *Can. J. Chem.* **1978**, *56*, 2737.

(7) (a) Grindley, T. B. *Tetrahedron Lett.* **1982**, *23*, 1757. (b) Lunazzi, L.; Placucci, G.; Chatgilialoglu, C.; Macciantelli, D. *J. Chem. Soc., Perkin Trans. 2* **1984**, 819. (c) Lunazzi, L.; Placucci, G.; Macciantelli, D. *Tetrahedron* **1991**, *47*, 6427. (d) Pawar, D. M.; Noe, E. A. *J. Org. Chem.* **1998**, *63*, 2850.

observed at +20 °C is the weighted average of two signals of very different intensities. If this is the case, the invisible partner must lie at a much higher field, to account for the observed 0.11$_5$ ppm displacement. The rationale for this feature can be found in the almost anti arrangement adopted by the carbonyl groups in the minor atropisomer **1b**. In such a situation carbon C6 lies directly above the C12=O moiety, and the carbon C16 lies symmetrically below the C2=O moiety. By virtue of such positions, they experience, in **1b**, the shielding effect of the carbonyl π-electrons (hence the large upfield shift),[7b,c,8] an effect which is not operative in **1a**, due to its gauche geometry (Scheme 2).

The theory of the exchange between two very biased species at equilibrium predicts that, at the temperature of maximum broadening, the major form interconverts into the minor form with a rate constant (k, s^{-1}) defined by the equation $k = 2\pi\omega^*$, where ω^* represents the maximum broadening (Hz) experienced by the major line.[6] In the present case, ω^* is 6.8 Hz (i.e., 10.2−3.4 Hz) at −11 °C, from which the corresponding rate constant (43 s^{-1}) leads to a free energy of activation $\Delta G^‡ = 13.3 \pm 0.2$ kcal mol^{-1} (the error includes the uncertainties in the various measurements). This value corresponds to the barrier for the interconversion of the atropisomer *P* into *M* (i.e., **1a** into **1b**) in solution and is satisfactorily close to the one calculated for the isolated molecule of dicarvone (14.7 kcal mol^{-1}). Such a similarity supports the assignment of the observed stereomutation to the process which interchanges the two helical forms of **1**.

Having established in an indirect manner the presence of the minor form of dicarvone, a search was undertaken for a direct identification of the signal due to atropisomer **1b**. A small line (0.5% ± 0.1%) lying upfield, as predicted, to that of the major partner was actually detected at −40 °C (signal at 38.23 ppm in Figure 1). A number of independent proofs support this attribution.

(i) On warming to higher temperatures (see the +20 °C spectrum of Figure 1), this signal disappears, to appear again at −40 °C, in a reversible manner.

(ii) According to the theory,[6] the maximum broadening of the major line is given by the equation $\omega^* = p\Delta\nu$, where p is the population of the minor form and $\Delta\nu$ is the separation of the two exchanging signals (here 795 Hz at 75.46 MHz). From this relationship the population is calculated to be 0.85%, a value in excellent agreement with that (0.89%) expected[9] at the temperature of maximum broadening (−11 °C) on the basis of the population (0.5%) measured at −40 °C.

(iii) From the shifts of the minor and major lines (38.22 and 48.75 ppm, respectively, at −40 °C) and from the ratio (98.5:1.5) expected[9] at +20 °C, the weighted average was calculated to be 48.65$_5$ ppm, a value which matches satisfactorily the measured one (48.63$_5$ ppm).

Having now obtained the shifts of the two exchanging lines, it was also possible to simulate the line shape of the major signal at a few different temperatures: the more accurate rate constants obtained in this way confirmed the $\Delta G^‡$ value of 13.3 ± 0.2 kcal mol^{-1}.

As previously mentioned, the less abundant atropisomer **1b** had been calculated to have a larger dipole moment than **1a**, and its proportion should consequently increase in a solvent largely more polar than methylene chloride. The ^{13}C spectrum of **1** was thus recorded in CD_3OD, where two lines, with the same separation as in CD_2Cl_2, were observed at −40 °C for C6 and C16 carbons: both these lines are in fact shifted downfield by the very same amount (1.16 ppm) relative to their positions in CD_2Cl_2. As the proportion of the minor signal is still quite low, the measurement of its relative intensity (0.7% ± 0.1% at −40 °C) does not allow a decision, beyond the experimental errors, on whether the ratio of the two atropisomers has actually changed. However, unambiguous evidence that the amount of **1b** has indeed increased in the more polar methanol solution comes from the observation that the maximum broadening of the major line (observed at −15 °C in CD_3OD) is definitely greater, now being 7.8 rather than 6.8 Hz.[10] From this value the amount of **1b** is derived to be 7.8/795 = 0.98%, corresponding to a 15% increase with respect to the population of **1b** in CD_2Cl_2 (0.85%) at the same temperature. The related rate constant (49 s^{-1} at −15 °C) provides, within the errors, essentially the same free energy of activation ($\Delta G^‡ = 13.0 \pm 0.2$ kcal mol^{-1}), indicating that the polarity of the solvent does affect the populations of the atropisomers but not the barrier for their stereomutation.

To ascertain, in a way independent of the MM calculations, whether the major atropisomer present in solution is the one having the *M*-helicity or the same *P*-helicity observed in the single crystal, an ad hoc experiment was performed. Since at −40 °C the exchange between the *P* and *M* forms does not occur anymore, the more intense spectrum at that temperature must correspond, consequently, to only one of the two atropisomers, rather than to their average: for this reason its spectral lines are slightly sharper than at ambient temperature, where a residual exchange process is still taking place. As shown in Figure 2, the ^{13}C satellites of the H1,H11 doublet[11] at −40 °C reveal an additional splitting ($J_{H1,H11} = 1.2$ Hz) which is not present in the main signal, since the H1,-H11 degeneracy has been removed in the satellite spectrum, one of these hydrogens being bonded to the isotope ^{13}C and the other to the isotope ^{12}C.

In the atropisomer *P* the dihedral angle H1−C1−C11−H11 is $\theta = -84°$ (X-ray) or $\theta = -93°$ (MM calculations), whereas in the atropisomer *M* the computation predicted θ to be +61°. According to one of the generalized Karplus[12] equations,[13] the coupling should be either 1.4 Hz (if $\theta \approx -90°$, as in the *P* atropisomer) or 2.8 Hz (if $\theta \approx +60°$, as in the *M* atropisomer). The experimental values of 1.2 Hz clearly indicate that the more abundant atropisomer has the same *P*-helicity in solution as in the crystal.

When the temperature is further lowered below −50 °C, a number of the ^{13}C signals of the major atropisomer **1a** broaden and eventually split at −135 °C (see the

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[8] (a) Chadwick, D. J.; Meakins, D.; Richards, E. E. *Tetrahedron Lett.* **1974**, 3183. (b) Roques, P. B.; Combrisson, S.; Wehrli, F. *Tetrahedron Lett.* **1975**, 1047. (c) Casarini, D.; Lunazzi, L.; Macciantelli, D. *J. Chem. Soc., Perkin Trans. 2* **1985**, 1839.

[9] The Boltzmann equation $\ln(N_1/N_2) = -\Delta G°/RT$ has been used to predict the increased population of the minor form N_1 at equilibrium when the temperature increases, on the assumption of the invariance of $\Delta G°$.

[10] The error in the measurement of the frequencies (±0.1 Hz) is much lower than that in the intensities. For instance the width of the sharp line C1,C11 of Figure 1 (in CD_2Cl_2 at −11 °C) is 3.4 Hz, a value exactly equal to that measured in CD_3OD at the same temperature.

[11] The proton−carbon coupling $J_{C1,H1} = J_{C11,H11}$ is 121 Hz, and the proton−proton coupling $J_{H1,H6} = J_{H11,H16}$ is 12.4 Hz.

[12] Karplus, M. *J. Chem. Phys.* **1959**, *30*, 11.

[13] This equation takes the form $J = 7.76 \cos^2 \theta - 1.1 \cos \theta + 1.40$; see: Haasnoot, C. A. G.; Leeuw, F. A. A. M.; Altona, C. *Tetrahedron* **1980**, *36*, 2783.

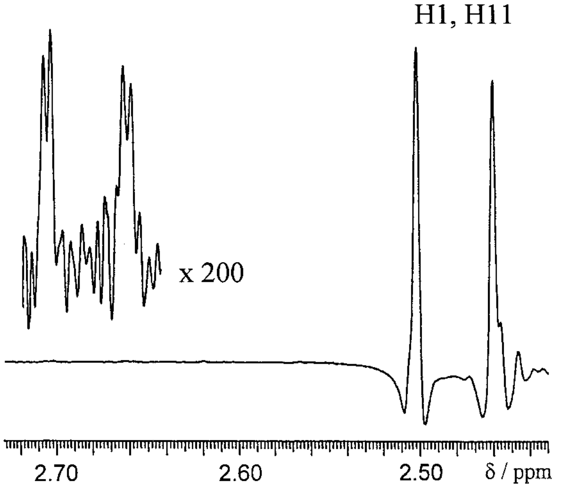

Figure 2. Doublet signal of H1,H11 at −40 °C in CD_2Cl_2 (300 MHz). The inset (vertically amplified 200 times) reports on the same horizontal scale the downfield half of the corresponding ^{13}C satellites showing the additional doublet ($J = 1.2$ Hz) due to the coupling of H1 with H11. The intensity of the satellite lines is ∼0.55% of the main doublet, i.e., half of the 1.1% proportion of the ^{13}C isotope.

Experimental Section) into pairs of lines with a 95.5:4.5 intensity ratio. A second dynamic process is obviously taking place, and a computer line shape analysis (Figure 3) provided the appropriate rate constants and hence the value for the corresponding free energy of activation ($\Delta G^{\ddagger} = 8.4 \pm 0.2$ kcal mol^{-1}). To obtain a satisfactory simulation of the traces of Figure 3, we had to take explicitly into account the increasing proportion of the minor conformer at higher temperatures.[9,14]

Since in the −135 °C spectrum the largest separation between the pairs of ^{13}C signals belonging to the two conformers (8.61 ppm) is that observed for the methyl group of the exocyclic isopropenyl moiety (i.e., C8,C18 as in Figure 3), it is conceivable that this stereomutation is the consequence of a motion involving the two isopropenyl substituents on the six-membered rings. The X-ray structure shows that the C7−C9 double bond is in an antiparallel relationship with the analogous C17−C19 double bond. The experimental dihedral angles C1−C6−C7−C9 and C11−C16−C17−C19 are, in fact, 110° and 106°, respectively: [3] these values correspond to those of the MM computed structure, where both are 109°. The calculations, however, predict that the conformer with the double bonds parallel to each other also corresponds to an energy minimum, which is less stable than **1a** by 0.25 kcal mol^{-1} (see conformer **1c** of Scheme 1, where these two angles are 109° and −59°, respectively). In the major form **1a** the methyl carbon C8 lies above the C17−C19 double bond (and likewise the methyl carbon C18 lies below the C7−C9 double bond), thus experiencing the shielding effect of the ethenyl π-electrons. Accordingly, the corresponding signal lies at much higher field in the major (**1a**) than in the minor (**1c**) conformer, as is experimentally observed (see the −135 °C spectrum of Figure 3). This approach is essentially the same as that used to explain the shifts of C6,C16 in **1a** and **1b,** but the resulting trend turns out to be opposite (the minor signal here is at lower, rather than higher, field) owing to the different geometrical relationship of the carbons involved. This establishes a gratifying consistency of the assignments performed in both cases.

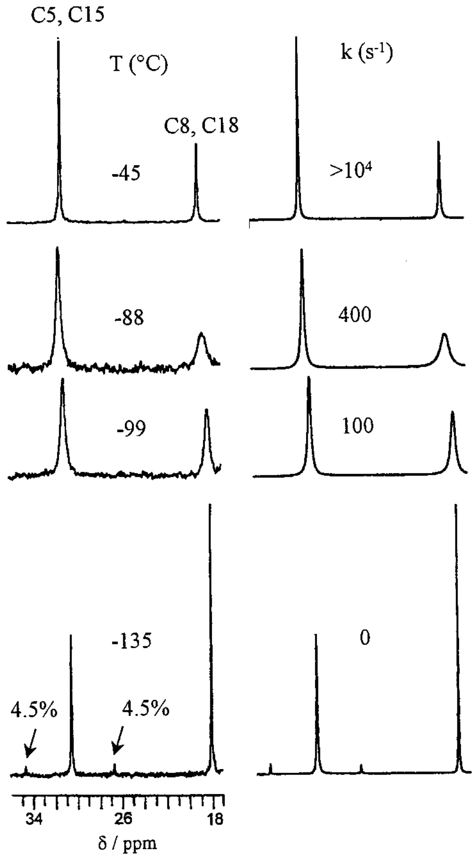

Figure 3. Left: Experimental ^{13}C lines of C5,C15 and C8,C18 of dicarvone (**1**) (in a 2:1 mixture of CHF_2Cl and CD_2Cl_2 at 75.46 MHz) as function of temperature, showing, at −135 °C, the corresponding signals of the minor (4.5%) conformer **1c** (see the text and Scheme 1). Right: Computer simulation obtained with the rate constants (k, s^{-1}) indicated.

The computed stereomutation pathway was obtained by driving one of the two exocyclic isopropenyl moieties about its pivotal bond (e.g., C16−C17), allowing all the other parameters to relax accordingly. Two transition states were encountered, one having an energy value 8.9 kcal mol^{-1} higher than that of the ground state, the other a value of 7.9 kcal mol^{-1}:[15] the latter thus represents the theoretical barrier, which agrees well with that measured in solution (8.4 kcal mol^{-1}). Such a result supports the assignment of the second stereomutation to the process exchanging the exocyclic isopropenyl moieties from an antiparallel (**1a**) to a parallel (**1c**) conformational arrangement.

Although the two halves of the *P* atropisomer (observed at −40 °C) of dicarvone are not related by a plane or center of symmetry, still the chemical shifts of the hydrogen and carbon atoms in one half are isochronous with the corresponding ones in the other half (i.e., H1 = H11, C1 = C11, and so on till C10 = C20). This is because the environment experienced by the various atoms within each half-molecule are identical, except for their handedness, and NMR spectroscopy cannot discriminate between two such situations, much in the same way as it

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[14] The proportions were found to be 8% at −99 °C and 9.5% at −88 °C.

[15] The corresponding dihedral angles are 101° and 50° for the first transition state, and 95° and 200° for the second transition state.

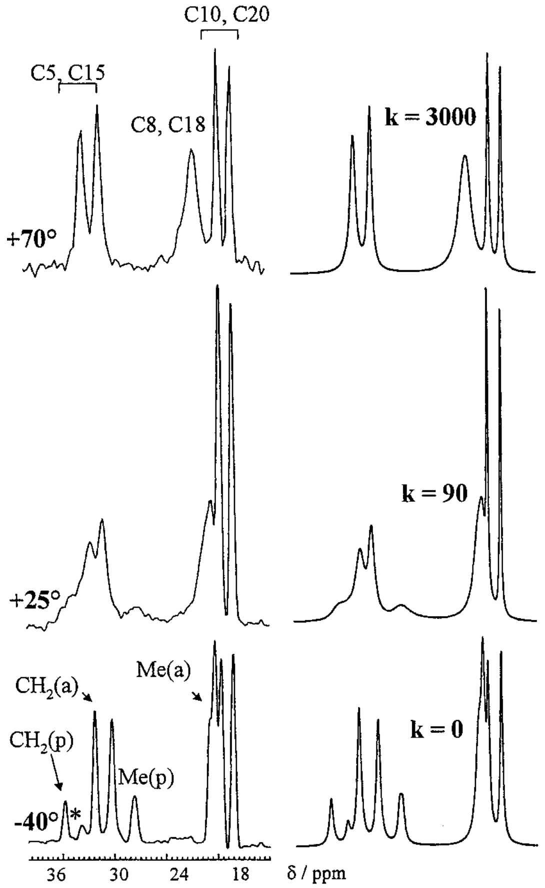

Figure 4. Left: High-field region of the ^{13}C NMR spectrum of **1** in the solid state (CP-MAS at 75.46 MHz) at three sample temperatures. Right: Computer simulations obtained using the rate constants (k, s^{-1}) indicated. Of the two methylene lines, due to the C5,C15 carbons, the one at lower field broadens and finally splits, at −40 °C, into a pair of signals labeled $CH_2(p)$ and $CH_2(a)$. The same exchange process is also visible for the nearly coincident pair of methyl lines C8,C18, which also split into the signals labeled Me(p) and Me(a). The upfield methylene line of the pair C5,C15 does not show any line broadening or splitting because its minor partner has an accidentally coincident shift, the same coincidence also occurring for the pairs of methyl lines C10,C20.

cannot identify a pair of enantiomers in achiral solutions. In principle, this should not be the case in the solid state, where the crystal lattice provides a reference frame which makes diastereotopic the pairs of the corresponding atoms in the two halves.[16,17] Indeed many of the ^{13}C signals, which were isochronous in solution, display two lines in the solid-state CP-MAS spectrum of **1**.[18] In Figure 4 (top trace, at +70 °C) it is shown, for instance, how the methylene carbons C5 and C15 and the methyl carbons C10 and C20 yield a 1:1 doublet, rather than the single lines displayed in solution; other signals, such as C8 and C18, have a separation of their doublet smaller than the line width, thus appearing as one single signal at +70 °C.

At temperatures lower than +70 °C some of the solid-state signals broaden and eventually split (lower trace at −40 °C in Figure 4) into additional pairs of lines having different intensities (about 23:77). This process is reversible since on warming the sample again the same patterns observed at higher temperatures are reproduced. A differential scanning calorimetry performed in the range of −70 to +108 °C (mp) did not show any phase transition in the crystalline state, thus indicating that the additional low-intensity spectrum must be that of a minor conformer which exchanges reversibly with the major one. The shifts of the minor lines are quite close to those that were assigned to the "parallel" conformer **1c** observed in solution at −135 °C (Figure 3). For instance in Figure 4 the methylene carbon line labeled $CH_2(p)$, for parallel, is the minor partner of the line labeled $CH_2(a)$, for antiparallel, of the C5,C15 pair and lies at 35.8 ppm in the solid, to be compared with the 34.5 ppm shift observed in solution. Likewise the two accidentally coincident methyl lines labeled Me(p) are the minor partners of the nearly coincident pair C8,C18 labeled Me(a) and appear at 27.8 ppm in the solid, to be compared with the 26.5 ppm shift in solution[19] (the 27.8 ppm solid-state signal has been unambiguously assigned to a methyl group by means of the nonquaternary suppression sequence). It thus seems that the proportion of the **1c** conformer in the crystal (about 23%) is somewhat higher than in solution, where it is expected to be about 14% at the same temperature (−40 °C).[9]

The shape of the exchanging lines labeled "p" and "a" were computer simulated at three different temperatures (0, 15, and 25 °C), providing rate constants from which a $\Delta G^{\ddagger} = 14.8$ kcal mol^{-1} was derived (Figure 4). As expected this value is quite higher than that measured in solution ($\Delta G^{\ddagger} = 8.4$ kcal mol^{-1}) since the interconversion barriers are known to increase by a few kcal mol^{-1} in the solid,[20] due to the additional resistance to the internal molecular motions generated by the crystal lattice.

In the −40 °C spectrum (as well as in those at lower temperatures) a number of low-intensity lines (about 5%), which disappear in a reversible manner on warming the sample, were also observed: one such line (starred) is visible in the spectral range displayed in Figure 4. The position of this line (34.3 ppm) lies in the same region[19] where the C6,C16 methine signal of the *M* atropisomer **1b** was identified in the solution spectra at −40 °C (38.2 ppm as in Figure 1). Thus, we were tempted to interpret this signal as due to the presence, in the crystal, of the *M* atropisomer **1b** in an amount somewhat larger than

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[16] Hill, H. D.; Zens, A. P.; Jacobus, J. *J. Am. Chem. Soc.* **1979**, *101*, 7091.

[17] (a) Casarini, D.; Lunazzi, L.; Macciantelli, D. *J. Org. Chem.* **1988**, *53*, 177. (b) Casarini, D.; Lunazzi, L.; Foresti, E.; Macciantelli, D. *J. Org. Chem.* **1994**, *59*, 4637.

[18] The pairs of carbon atoms might still display isochronous ^{13}C signals in the solid only in the case that the 2-fold symmetry axis (which in dicarvone is perpendicular to the C1−C11 bond) is coincident with a C_2 crystallographic axis,[17a] a situation which does not apply in the present case.[3]

[19] The shift deviations are due not only to the different temperatures and phases, but also to the different methods employed to determine the shifts in solution and in the solid state (for the latter see the Experimental Section).

[20] Miller, R. D.; Yannoni, C. S. *J. Am. Chem. Soc.* **1980**, *102*, 7396. Elguero, J.; Fruchier, A.; Pellegrin, V. *J. Chem. Soc., Chem. Commun.* **1981**, 1207. Riddell, F. G.; Arumagam, S.; Anderson, J. E. *J. Chem. Soc., Chem. Commun.* **1991**, 1525. Lambert, J. B.; Xue, L.; Howton, S. C. *J. Am. Chem. Soc.* **1991**, *113*, 8958. Barrie, P. J.; Anderson, J. E. *J. Chem. Soc., Perkin Trans. 2* **1992**, 2031. Riddell, F. G.; Arumagam, S.; Harris, K. D. M.; Rogerson, M.; Strange, J. H. *J. Am. Chem. Soc.* **1993**, *115*, 1881. Riddell, F. G.; Cameron, K. S.; Holmes, S. A.; Strange, J. H. *J. Am. Chem. Soc.* **1997**, *119*, 7555. Casarini, D.; Lunazzi, L.; Mazzanti, A. *J. Org. Chem.* **1998**, *63*, 9125.

Table 1. Assignment of ^{13}C and ^{1}H Shifts (ppm from TMS) of Dicarvone in CD_2Cl_2 at 20 °C

^{13}C shift	position	^{1}H shift	^{13}C shift	position	^{1}H shift
16.134	10, 20	1.69 (2 Me)	114.284	9, 19	4.76, 4.84 (2 CH_2=)
19.354	8, 18	1.62 (2 Me)	135.732	7, 17	
31.783	5, 15	2.18, 2.42 (2 CH_2)	143.118	4, 14	6.66 (2 CH=)
48.635	6, 16	3.41 (2 CH)	146.523	3, 13	
49.749	1, 11	2.55 (2 CH)	200.360	2, 12	

that observed in solution (i.e., 5% vs 0.5% at −40 °C).[21] If this is the case, this line should exchange with that of its major partner *P* (**1a**) lying at much lower field: in solution this separation was found to be 795 Hz. Although we could not unambiguously identify the corresponding major partner in the solid, the major CH lines are indeed observed at about 1000 Hz downfield (the expected four lines for the CH carbons of **1a** appear as a pair of 1:3 lines due to overlapping). Computer simulation indicates that in such a situation rate constants of 5−10 s^{-1} are sufficient to broaden the minor line to the point of making the signal invisible. Since at temperatures higher than 0 °C these minor lines do disappear, the corresponding $\Delta G^{\ddagger}$ should be approximately 15−16 kcal mol^{-1}. Such a value is again larger than that determined in solution for the *P*,*M* interconversion (13.3 kcal mol^{-1}), for the same reasons mentioned above.[20] This fact can be taken as an additional indication that the proposed interpretation is not unreasonable.

Finally it should be mentioned that there is an apparent contradiction between the results of the two types of measurements carried out in the solid state. Whereas in the X-ray diffraction solely the antiparallel conformer **1a** had been observed,[3] the solid-state NMR spectra indicate the presence of at least two conformers (**1a** and **1c**) in a not negligible proportion (probably there is also a small amount of the third conformer **1b**). Such a result is independent of the way the dicarvone is crystallized, in that identical NMR spectra were obtained even when we examined crystals purposely grown with the same techniques and in the same solvent used for the X-ray study. With the purpose of gaining a better understanding of this situation, we repeated the X-ray diffraction measurement by selecting a single crystal from the very same batch we had prepared for the solid-state NMR spectra. In this diffraction experiment we collected 10 times the number of reflections with respect to the precedent investigation,[3] and obtained again the same single structure **1a**, with very good agreement indices (see the Experimental Section). As previously observed,[22] also in the present determination the anisotropic displacement factors were found very similar for all the atoms involved: accordingly the X-ray measurement does not provide any evidence for the presence of a substantial amount of a second conformer. This result might possibly be explained by considering that the solid comprises a relatively large number of well-ordered crystals containing only the single conformer **1a**, but also a not negligible amount of crystals with a certain degree of disorder where, in addition to **1a**, also the other conformer **1c** (and possibly **1b**) is trapped. The latter crystals are never selected for an X-ray determination since only the well-ordered crystals are invariably chosen to obtain good diffraction patterns. As a consequence, the information contained in the less ordered crystals is lost in the X-ray measurement, but not in the NMR spectrum, where an indiscriminate bulk of all the crystals (and powder) can be examined. This points out the usefulness of the combined use of both techniques, since solid-state NMR reflects the situation occurring in the whole solid, which is not necessarily the same situation that comes about when a single ordered crystal is examined by X-ray diffraction.

Experimental Section

The details of the preparation and the identification data of dicarvone (**1**) have been previously reported.[3] The assignments of the ^{1}H and ^{13}C signals at +20 °C (see Table 1) were achieved (at 400 and 100.6 MHz, respectively) by making use of DEPT, NOE, COSY, and 2D-heterocorrelation (gradient-selected HSQC pulse sequence) experiments. The samples for the measurements below −100 °C were prepared by connecting to a vacuum line the NMR tubes containing dicarvone dissolved in CD_2Cl_2, and condensing therein twice as much an amount of gaseous CHF_2Cl by means of liquid nitrogen. The tubes were subsequently sealed in vacuo and introduced into the precooled probe of the 300 MHz spectrometer operating at 75.45 MHz for ^{13}C. The temperatures were calibrated by substituting the sample with a precision Cu/Ni thermocouple before the measurements. The high-resolution ^{13}C NMR solid-state CP-MAS spectra were also obtained at 75.45 MHz. The sample, a white crystalline powder, was packed in a 7 mm zirconia rotor spun at the magic angle with a speed of 3.7 kHz. The number of transients (128−256) was varied to achieve good signal-to-noise ratios in the VT experiments. The chemical shifts were measured, by replacement, with respect to the lower frequency signal of the adamantane (29.4 ppm). The cooling was achieved by means of a flow of dry nitrogen, precooled in a heat exchanger immersed in liquid nitrogen. The temperatures of the solid-state spectra were calibrated by using the shift dependence of the ^{13}C lines of 2-chlorobutane absorbed on solid dicalite, assuming a dependence equal to that observed in neat liquid, which had been previously calibrated by the same Cu/Ni thermocouple. Total line shape simulations for both the solution and solid-state spectra were achieved by using a computer program based upon the Bloch equations.[5] The number of reflections collected in the X-ray diffraction was 26343, 15407 of which were used; the crystal data were found to be the same as in ref 3. The number of independent reflections was 3201, with the final conventional R factor equal to 0.049 for the 1413 reflections having $F \geq 4\sigma(F)$; 199 was the total number of refined parameters.

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(21) The possibility of these 5% lines being due to impurities was excluded. Not only do they appear and disappear in a reversible manner on varying the temperature, but a ^{13}C spectrum (in $CDCl_3$) of the very same crystals examined in the CP-MAS experiment showed that the impurities do not exceed 1.5%, an amount definitely too small to be detectable with the signal-to-noise ratio of the −40 °C spectrum of Figure 4.

(22) Private communication of Dr. G. Valle, CNR, Padua.