Optical Resolution of the α-Tocopherol Spiro Dimer and Demonstration of its Fluxional Nature

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A model compound (**1b**) for the oxidative dimer of α-tocopherol (vitamin E) (**1a**) has been shown to undergo fluxion by NMR spectroscopy through a magnetization transfer experiment. This compound has also been resolved at low temperature using an optically active HPLC column. Its rate of racemization parallels the fluxion process suggesting a biradical intermediate and free radicals are shown to be present in non-degassed solutions of (**1b**). Its crystalline form has been examined with solid-state NMR spectroscopy and X-ray crystallography.

Fluxional molecules have fascinated chemists since 1961 when the possibility of valence tautomerism between two identical structures was first mentioned by Vogel.[1] Bullvalene and cyclooctatetraene, in their degenerate Cope rearrangements,[2] are perhaps the best known of these interesting molecules. Originally, their reorganization was believed to be independent of solvent and not susceptible to catalysis, but today many exceptions to this generalization are known.[2] The identity of reactant and product makes these reactions difficult to study except by NMR spectroscopy and the most thoroughly studied examples are those for which the rates fall in the time window accessible by this technique.[3]

Most compounds showing fluxion are synthetic and often they have been specifically tailored to enhance the effect. However, many years ago two of us (H. A. L. and H. M. F.) reported[4] the same spectral properties in a natural product, *i.e.*, the oxidative dimer of α-tocopherol [vitamin E (**1a**)]. In this compound, the ^{1}H NMR lines associated with the methyl groups of the aromatic and dienone rings were unexpectedly broad. Using the more easily available model compound (**1b**),[5] we showed that considerable sharpening of the lines was obtained at lower temperatures. To explain this phenomenon, we proposed that the substances were undergoing the fluxional change (**2a**) $\rightleftharpoons$ (**2b**) *i.e.*, a 1,3-dioxa-[3,3]-sigmatropic rearrangement,[6] although the orbital overlap in the system appeared unfavourable for such a concerted process.

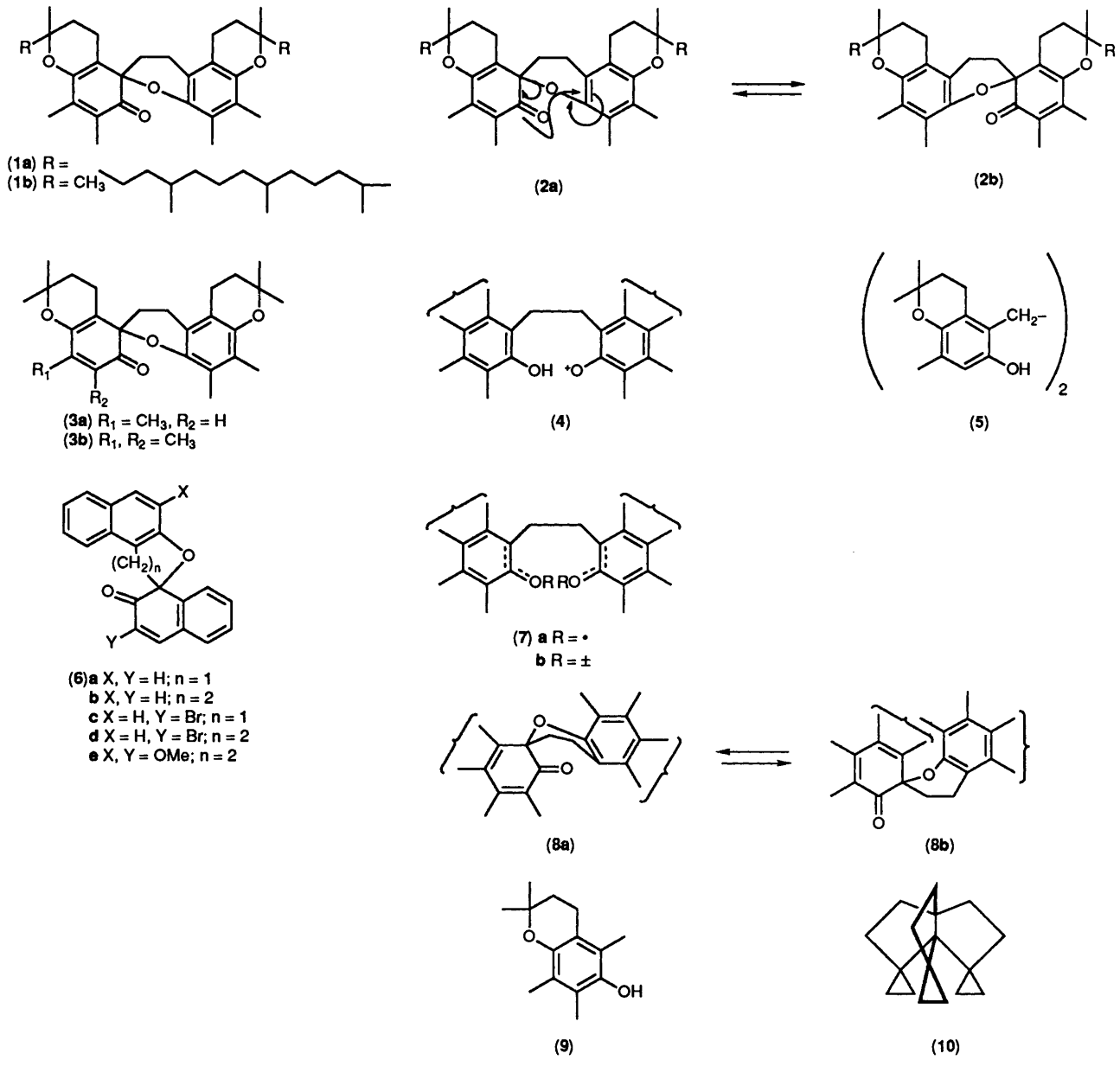
A later report by Swedish workers attempting to extend the NMR observations to the simple homologues (**3a**) and (**3b**)[7] was also difficult to explain. Both of these compounds showed sharp lines that were not broadened even on heating, although sample decomposition limited the experiments to a maximum of 77 °C. Since the non-degenerate reaction of (**3b**) should produce two detectable products, this finding was particularly important. Chauhan *et al.*[8] later reformulated the reaction as a heterolytic process involving the univalent oxygen cation (phenoxylium ion) (**4**) because they observed even broader NMR lines on addition of trichloroacetic acid. These workers also found the system to be solvent independent and lacking in ESR or CIDNP signals. Supporting the heterolytic mechanism, they also found that the time for complete reduction of (**1b**) to bisphenol (**5**) by ascorbic acid[9] was accelerated from 12 h to 5 s in the presence of an acid. On the other hand, addition of excess pyridine to the acid solution in the NMR tube was reported to restore the signal only to its original level of broadening. The original broadening therefore remains unexplained; clearly it could not have been due to traces of acid in the solvents.

The phenoxylium ion mechanism has itself been criticized by Dixie and Southerland[10] who examined the effect of steric factors on the reaction using the spiro dienes (**6a–e**), one of which (**6b**) had been shown by Chauhan not to undergo the rearrangement. In this series, only brominated analogues (**6c**) and (**6d**) underwent rearrangement and the presence of the five-membered ring reduced the rate considerably [$k = 1.4 \times 10^{-5}$ s^{-1} at 138 °C, (ΔG^* 33.5 kcal mol^{-1}) *vs.* $k = 0.35 \times 10^{-5}$ s^{-1} at 50 °C, (ΔG^* 27.0 kcal mol^{-1}), all in $C_6D_5NO_2$]. Furthermore, these reactions were found *not* to be catalysed by trifluoroacetic acid although methoxy substituents as in (**6e**) did accelerate the reaction ($\Delta G^* = 25.2$ kcal mol^{-1}). All of these effects are once again in agreement with a concerted [3,3]-sigmatropic rearrangement. Dixie and Southerland also recalled our observation[5] that the geminal methyl groups of (**1b**) remain a doublet during the rearrangement and pointed out that this is inconsistent with an achiral diradical or dipolar intermediate (**7a**) or (**7b**).

In view of these reports, we decided to establish more firmly the fluxional nature of (**1b**) through a simple magnetization transfer experiment,[11] used so successfully in establishing the fluxional nature of bullvalene[12–14] and barbaralone.[15] This experiment would also rule out any more trivial explanation such as the existence of a conformational equilibrium such as (**8a**) $\rightleftharpoons$ (**8b**). Furthermore, since a biradical intermediate such as (**7a**) does not entirely rule out a fairly rigid transition-state geometry (at least in an all-carbon analogue),[16] solutions of (**1b**) were re-examined by ESR spectroscopy. Finally, information about the motion of (**1b**) in its crystal state was sought using solid-state ^{13}C NMR spectroscopy and X-ray crystallography.

Experimental

Preparation of the dimer (**1b**) has been described in detail previously.[17] For these studies, the compound was carefully purified by chromatography over silicic acid followed by



recrystallization at low temperature from pentane. Various m.p.s have been reported in the range from 77–79 °C[17] to 120.5–127 °C.[18] Our compound melted at 122–124 °C on a Kofler hot-stage apparatus.

HPLC chromatography was carried out with a Waters system using a Pirkle ionic type 1-A column (Regis Chemical Inc., Morton Grove, IL) with heptane–propan-2-ol (95:5) as the solvent.

Both liquid and solid-state NMR experiments were carried out on a Varian XL-300 spectrometer equipped for the latter with a ^{13}C solid state probe. The liquid-state magnetization-transfer experiment used the three-pulse sequence:[19] $\pi/2 - t_1 - \pi/2 - \tau_{mix} - \pi/2 - t_2$(acquire). Here t_1 is incremented to produce a matrix for 2D Fourier transformation and τ_{mix} is the mixing time during which the exchange process is monitored. The original pulse sequence was modified to perform ^1H spin decoupling. All experiments were performed at 25 °C in the phase-sensitive mode using the hypercomplex transform method of States *et al.*[20] with 1 024 complex points in t_2 and 128 complex points in t_1 which were zero-filled to produce a 2 048 × 512 matrix.

EPR measurements were made using a Varian E-109 spectrometer with 100 kHz field modulation. The sample temperature was regulated by a nitrogen gas flow system and was held within ±0.05 °C.

X-Ray measurements were made using an Enraf–Nonius CAD-4 diffractometer (Cu-K_α X-radiation) and a Huber precession camera (Mo-K_α X-radiation).

^{13}C *NMR Magnetization Transfer.*—The critical experiment undertaken to determine the fluxional nature of (**2a**) ⇌ (**2b**) involved examining magnetization transfer in solution between the individual carbon atoms in the molecule by two-dimensional exchange spectroscopy (NOESY). Thus, if carbon atoms at *i* and *j* interconvert *via* chemical exchange during τ_{mix}, cross peaks will be observed at the intersections of the respective chemical shifts ω_i and ω_j. The usual 1D spectrum appears along the diagonal axis of the 2D NOESY spectrum (Figure 1). For short mixing times, τ_{mix}, the intensities of these cross peaks will be proportional to $k_{ij}\tau_{mix}$, where k_{ij} is the rate constant for the intramolecular exchange reaction.

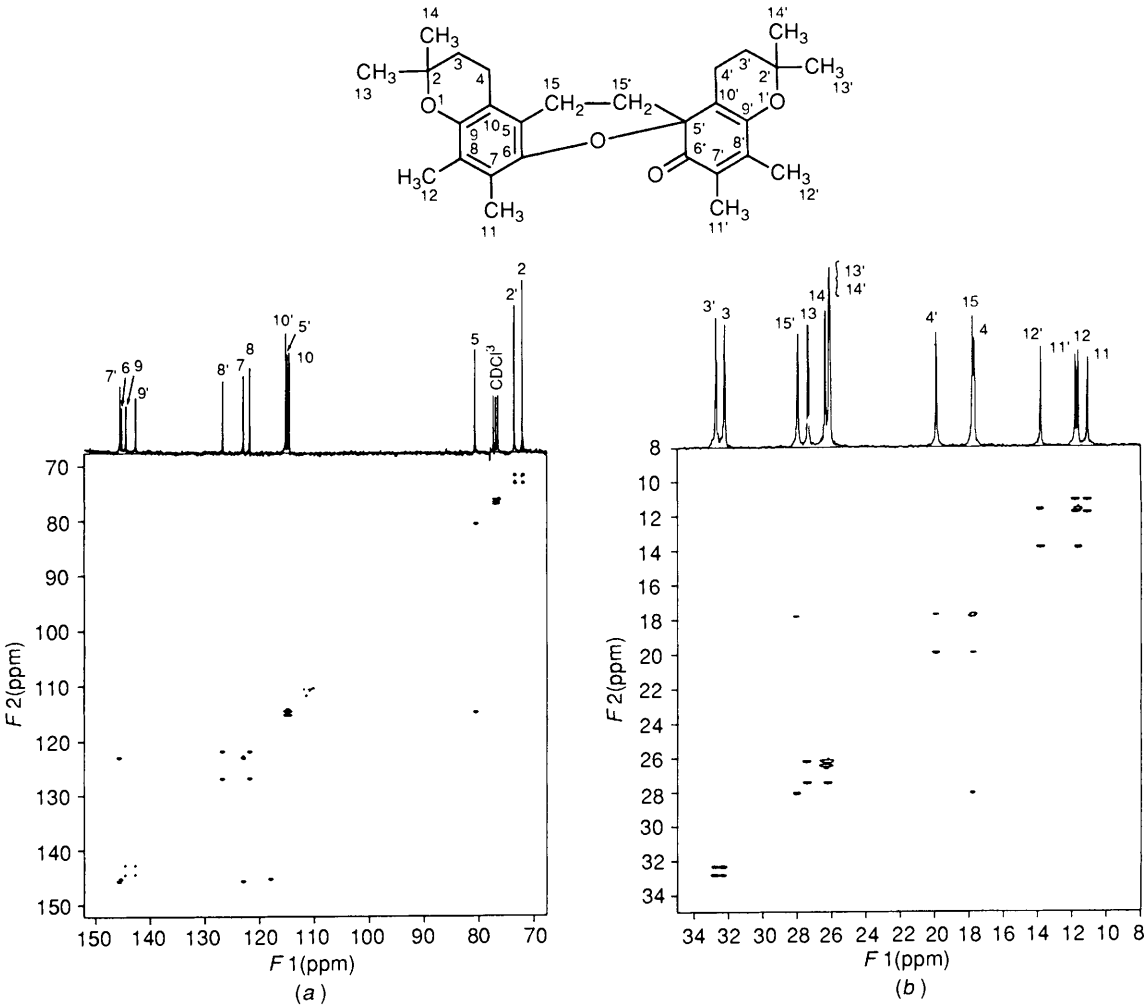


Figure 1. Two-dimensional ^{13}C NOESY spectrum of (**1b**): (*a*) aromatic and other carbons; (*b*) aliphatic carbons.

Table.

T/°C	$k_{(2a)\rightarrow(2b)}$/s^{-1}
0	6.1×10^{-4}
11	5.0×10^{-3}
25	4.3×10^{-1}

Figure 1, showing the 2D NOESY spectrum run with a value of τ_{mix} = 125 ms, is separated into two segments, (**A** and **B**), corresponding to the aliphatic and aromatic regions of the ^{13}C spectrum, respectively. The spectral assignments were made using standard 2D methods[19] and are principally based on the one-bond ^{1}H–^{13}C chemical-shift correlation spectrum. The distinction between prime and non-primed carbon atoms was based in part on chemical shift and is subject to modification. From the ratios of the integrated intensities of the cross peaks to their parent diagonal peaks in the NOESY spectra, k_{ij} values in chloroform and cyclohexane are estimated to be 1.2 and 0.3 s^{-1}, respectively, at 25 °C. The rate constant measured in cyclohexane compares fairly well with the rate constant measured for racemization (Table, see above) which was determined in heptane–propan-2-ol (95:5) at 25 °C.

Optical Resolution of (**1b**).—The chemical nature of (**1b**) did not appear to allow any convenient points for attachment of an optically active resolving agent. The ketone group is too hindered to react with the usual carbonyl reagents and its rather unstable nature militated against the usual conditions employed in such resolutions. Therefore we elected to use an optically active HPLC column[21] (Pirkle ionic type 1-A) using heptane–propan-2-ol (95:5) as the solvent. Figure 2 shows the results of this chromatography as the temperature was lowered from 60 to 10 °C. Near room temperature (30 °C) resolution was achieved but the raised valley between the two peaks is clear evidence of the existence of a dynamic process,[22] *i.e.*, racemization. At 60 °C the more strongly retained component was no longer detectable. Lowering the temperature to 10 °C completely separated the components and the peak areas were found in a 1:1 ratio as expected for resolution of a racemate. Upon reinjection at 30 °C each of these separated peaks showed the same raised valley behaviour as seen in Figure 2.

When larger samples of the individual peaks were collected at solid CO_2 temperature and their rotations determined in a chilled polarimeter, approximately equal but opposite rotations were obtained: $[M]^{5890}_{10\,°C}$ +3 960° (*c*, 0.112) for the early-eluting isomer and $[M]^{5890}_{10\,°C}$ −3 670° (*c*, 0.0348) for the late-eluting isomer and $[M]^{5460}/[M]^{5890}$ + 1.38 in each case. As the solutions warmed in the polarimeter tube, loss of optical activity was observed and a series of rates were determined (Table) leading to an approximate value for ΔG^{*} of 20 kcal mol^{-1} in the solvent heptane–propan-2-ol (95:5).

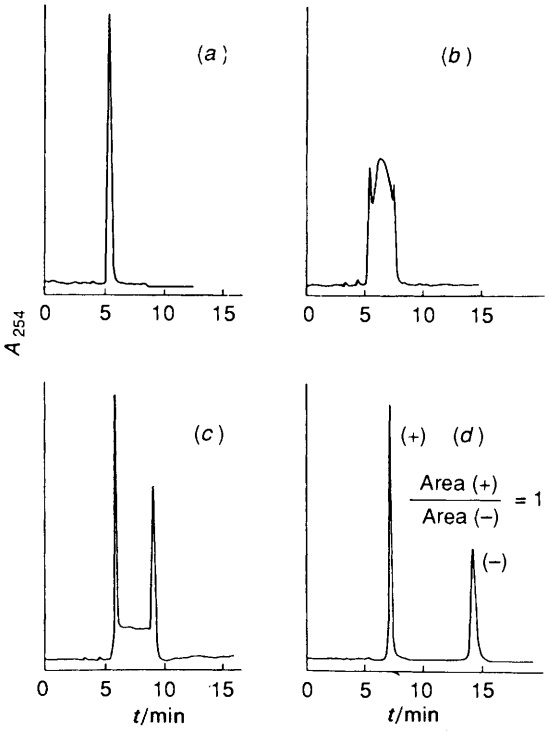


Figure 2. HPLC of (**1b**) at various temperatures. See Experimental for details. (*a*) 60; (*b*) 40; (*c*) 30; (*d*) 10 °C.

X-Ray Examination of (**1b**).—Crystals were apparently well-formed yellow plates, but preliminary diffractometric investigations using Cu-K_α X-radiation gave inconsistent unit-cell dimensions. The very wide X-ray reflections with half widths of 2° instead of the more usual 0.3–0.5° could have caused the inconsistencies but, in our experience, the most usual reason for such behaviour is twinning. The investigation was continued by photographic methods using a precession camera and Mo-K_α radiation. Photographs could be interpreted as showing two superimposed triclinic nets with a c^* axis in common and two b^* axes inclined at about 15° to each other. Since, according to Donnay and Donnay,[23] the only allowed operations for triclinic twinning are 180° rotations, a suitable mechanism is rotation about the a axis bringing b into $-b$ and c into $-c$. Since a is perpendicular to b^* and c^* by definition, and the latter two reciprocal axes are not orthogonal, rotation around a could bring only one axis into coincidence with itself.

Combination of photographic and diffractometric evidence allowed the deduction of a set of triclinic unit-cell dimensions: a = 6.64(2), b = 12.29(2), c = 15.71(2) Å, α = 97.0(1), β = 93.7(1), γ = 92.7(1)°. The low precision was caused by partial overlap and difficulties in centring the broad X-ray peaks. The *ca.* 15° angle between the nets seen on precession photographs is consistent with the measured α angle since $2(\alpha - 90)$ is 14°. In addition to overlap, the X-ray intensities fell off very rapidly as the Bragg angle increased and the number of measurements possible would probably be insufficient to allow a direct-methods structure determination. The density calculated for a molecular weight of 438 Da and one molecule in the unit cell is 0.57 g cm^{-3} but the measured density was 0.97 g cm^{-3}. The calculated density for Z = 2 is 1.14 g cm^{-3} and the agreement is still remarkably poor, although the presence of two molecules in the unit cell is much more probable than one. Solid-state NMR data (see below) also favours the presence of two distinct molecular environments appearing in equal fractions within the lattice.

The most usual reason for a bimolecular triclinic unit cell when crystals are obtained from a racemic solution is that the crystals are racemates and the space group is $P\bar{1}$, but spontaneous resolution with two identical molecules in space group $P1$ would also be possible. Real spontaneous resolution has been observed many times but it is also possible for resolution to take place into microscopic or even submicroscopic domains. Such domain resolution can be difficult to detect as was the case for hexahelicene where the apparent resolution was later shown to be caused by the presence of domains visible after suitable etching.[24] In this case, all axes overlapped exactly since the space group was $P2_12_12_1$ and the X-ray intensity data showed no unusually rapid fall-off. No domains were visible in the present case even with careful microscopic examination. The packing at a domain boundary might be less efficient than in the bulk crystal thus lowering the density but the fraction of the crystal that forms boundaries should be small and the observed density should be in reasonable agreement with that calculated.

Another possibility, less commonly observed, would be that the crystals were a racemic mixture with any one molecule having a random choice of being a (+)- or (−)-enantiomer. Such disorder might cause a rapid fall-off of X-ray intensity, but the measured and calculated crystal densities should agree reasonably well. Furthermore, the two distinguishable molecular environments indicated by solid-state NMR spectroscopy (see below) are difficult to reconcile with such packing. However, the transition from a (+)- to a (−)-enantiomer essentially corresponds to the reversal of the direction of an axis and this is what happens in a twin. Thus, when a mistake is made, one axis is reversed and growth might continue in the sense determined by the new direction. If the domains were defined by an exact small number of cells, say n, the crystal would be ordered with one cell axis n times as long as that measured, but the ratio of the two possible environments would be 1:(n − 1). The NMR results suggest $n \approx 2$. However, there is apparently a lack of order since the X-ray reflection peaks are wide and there is no indication of a supercell. Thus it is possible that the width of two cells is only an average. A Poisson distribution with a mean of 2 would allow a domain as wide as 8 with a finite probability (*ca.* 0.1%). If the average domain size were small, a considerable fraction of the crystal could be involved in inefficient domain boundary packing and the measured density would be significantly lower than calculated, as is observed.

Solid-state NMR Examination of (**1b**).—The ^{13}C NMR spectrum of crystalline (**1b**), obtained by sample spinning at the magic angle and dipolar ^{1}H decoupling, is shown in Figure 3 and is comparable to the equivalent solution spectrum (Figure 1). One notable feature is the splitting of the peak at 78 ppm which is assigned to the spiro carbon atom 12. The two different environments implied for this one atom of the molecule can hardly be unique and it seems likely that the resonances of the other carbons are simply not resolved at this field strength. Since the two peaks are comparable in area (Figure 3), the spectra probably represent two molecules exposed to very slightly different environments within the crystal in accordance with the X-ray findings above.

EPR Examination of (**1b**).—In a model experiment, a concentrated (1 mol dm^{-3}) solution of the 'monomer' (**9**) in chloroform at room temperature showed a well-resolved septet hyperfine pattern with 0.5 mT splitting, consistent with a hyperfine interaction with the six equivalent aromatic methyl protons. With time, at room temperature, the intensity showed an increase by 30% in 40 min. Addition of a drop of glacial acetic acid increased the signal intensity by 2.5; however, the signal then decreased and further addition of acetic acid was no longer

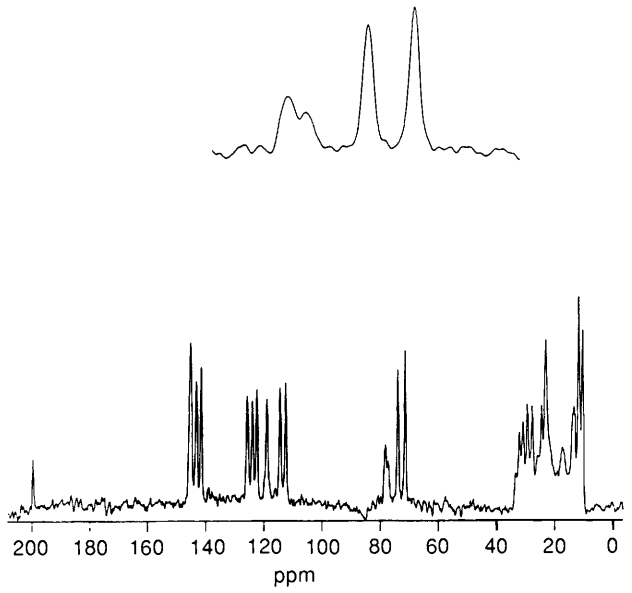


Figure 3. ^{13}C NMR TOSS (total suppression of spinning side bands) spectrum of crystalline (**1b**) with dipolar ^{1}H decoupling.

effective. Addition of an excess of pyridine did not greatly affect this intensity.

A relatively concentrated (0.5 mol dm^{-3}) chloroform solution of the oxidative dimer (**1b**) similarly showed a five-line hyperfine pattern with 0.45 mT splitting. The pattern may be interpreted as being due to a doublet of quartets from one of the bridge methylene protons and the aromatic methyl group adjacent to the oxygen if these have coupling constants of comparable magnitude. Coupling to only one of the bridge methylene protons suggests that this particular radical species is still constrained, more like (**1b**) than the biradical (**7a**). Addition of two drops of trichloroacetic acid caused a dramatic increase in intensity with concomitant loss of the hyperfine structure, perhaps because of an excessive radical concentration and exchange interaction. Diluting with chloroform recovered some of the hyperfine structure but resulted in considerable broadening of the peaks. Addition of an excess of pyridine reduced the signal by 60%, while raising the temperature to 46 °C doubled it.

It is well known that addition of an acid to oxygenated species causes broadening of NMR lines. In fact, this effect has been observed specifically with (**9**) where it was ascribed to the presence of cation radicals.[25] Presumably these were formed by reaction with aerial oxygen as was later found to be the case in 1,2,4,5-tetramethoxybenzene.[26] Reaction with O_2 may be facilitated in highly oxygenated aromatics such as (**9**) and (**1a–b**). In any case, our results regarding the presence of radicals in solutions of (**1b**) disagree with those of Chauhan *et al.*[8] who failed to detect any radicals. It is possible that their solutions were not sufficiently concentrated to detect this species.

Discussion

Two-dimensional ^{13}C magnetization transfer spectroscopy unequivocally demonstrates that the interconversion (**2a**) $\rightleftharpoons$ (**2b**) occurs in ordinary $CDCl_3$ solutions of (**1b**). The corresponding exchange rate is comparable to the rate of racemization measured by the loss of optical activity. Furthermore, EPR results show that free radicals are present in these solutions. The relationship of radical formation to the process of interconversion has not yet been established but the loss of optical activity suggests that the interconversion proceeds through a symmetrical intermediate, perhaps the biradical (**7a**). It was originally thought that the observation of two peaks from the *gem*-dimethyl groups at temperatures between 30 and 70 °C implied a concerted mechanism[5] and this was again stressed by Dixie and Southerland.[10] However, the ^{13}C magnetization transfer studies clearly show that the reaction actually is in the slow-exchange limit, at least at room temperature. Unfortunately, heating (**1b**) to temperatures much higher than 50 °C results in partial decomposition.

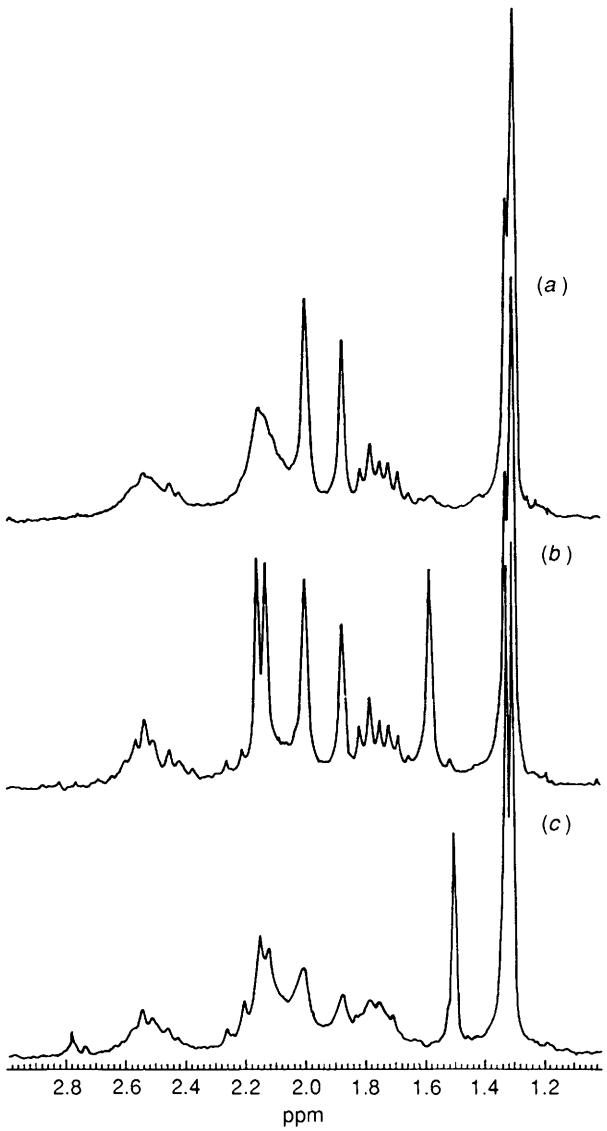


Figure 4. ^{1}H NMR spectrum of (**1b**) in (*a*) non-degassed $CDCl_3$, 25 °C; (*b*) $CDCl_3$ degassed by freeze–thawing, 25 °C; (*c*) degassed $CDCl_3$ heated to 50 °C.

Since radicals are often formed by the action of dissolved oxygen on highly oxygenated aromatic compounds such as (**1b**), we have reinvestigated its ^{1}H NMR spectrum. A $CDCl_3$ solution of (**1b**) was carefully degassed by repetitive freeze–thawing. Figure 4 compares the spectrum of the resulting solution with that from a sample prepared in the usual way (open to air). Degassing markedly sharpens the proton resonances [Figure 4(*b*)], especially in the case of the peak at 1.58 ppm which is assigned to one of the angular methyls; the other three angular methyl proton resonances are found at 1.30–1.34 ppm. Previous spectra on a non-degassed sample, obtained at 60 MHz in $CDCl_3$,[5] did not detect this resonance, although all four angular

methyl resonances were clearly visible in C_6D_6. The two methyl resonances around 2.14 ppm are assigned to the aromatic ring by analogy to their shifts in (**9**)[25] and the two methyl resonances at 1.88 and 1.95 ppm correspond to those on the dieneone double bond. The line broadening observed in the non-degassed sample [Figure 4(*a*)] cannot be caused by an exchange process with a rate constant of *ca.* 1 s^{-1} as measured in the ^{13}C magnetization transfer experiment. Instead, this broadening is likely to be associated with a relaxation process due to the dissolved oxygen complexing with the heavily oxygenated aromatic system.

The above conclusion contrasts with our earlier interpretation[5] of the line broadening as resulting from chemical exchange. In the spectrum of the degassed sample run at a slightly higher temperature [50 °C, Figure 4(*c*)] all of the proton lines are once again broadened, except for the *gem*-dimethyls which remain relatively sharp. The implication here is that, even in the *absence* of oxygen, radicals are again present and that they now affect both aromatic and dienone parts of the molecule. A diradical intermediate such as (**7a**) is one possibility. Thus, the effect of the dissolved oxygen [Figure 4(*a*)] and the putative radical formation [Figure 4(*c*)] do not appear to be related, although further experimentation will be necessary here. Steric crowding does seem to be an important factor in these systems as evidenced by the aforementioned broadening observed in spectra of bromo- and methoxy-analogues (**6d**) and (**6e**)[10] as well as the failure of (**3a**) and (**3b**) [in comparison to (**1b**)] to show this property.[7]

The data presented in this study all point to a radical intermediate, although they do not entirely rule out the concerted mechanism originally proposed. Further experiments on related model compounds are in progress to resolve this problem. However, these results do demonstrate that re-examination of reported fluxional systems is necessary, preferably including ^{13}C magnetization transfer NMR spectroscopy.

The complexity of (**1b**) is retained in its crystalline form where NMR indicates separate environments for two molecules as evidenced by the doubling of the resonances of the asymmetric carbon atom. Certainly it would be more satisfying if this doubling was observed in more than one of the carbon resonances. However, it is reasonable if not essential that the carbon atom affected is the one for which the spatial (not necessarily electrical) environment is the most asymmetric. The X-ray and density measurements are also consistent with the presence in the crystal of extremely small ordered domains of individual enantiomers the average size of which is two unit cells. It is unlikely that the conversion of one enantiomer into another could take place within the crystal, and the X-ray results do not support the total randomization expected from such a process. On the other hand, conversion occurs at a fairly rapid rate in the solution from which the crystal is being formed, and it is perhaps not surprising that the resulting crystal is not well ordered.

At least one other example of a fluxional system involving optical activity has been discussed recently.[27] The very crowded chiral hydrocarbon (**10**) undergoes inversion in a stepwise rather than concerted process. In this case, the chirality is a conformational feature and no bonds need be formally broken in its inversion. In vitamin E itself, the side chains are chiral so the analogous product (**1a**) must, in fact, be a mixture of isomers. Apparently, (**1a**) is the only existing example of a naturally occurring molecule exhibiting the fluxion phenomenon. The biological implications of this behaviour are under investigation.

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