

## **meso-Tetrahydropyranylperoxides: Molecular Structures in Solution, in the Crystal, and by DFT Calculations and Their Isomerization to the Racemate**

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The crystalline peroxide **3a** is the main product (out of 10 theoretically possible) from the aerial peroxidation of all-*cis*-2,4,6-trimethyltetrahydropyran (**2a**). It has a similar structure both in solution and in the crystal as shown by nuclear Overhauser effects and X-ray analysis, respectively. Theoretical calculations at a density functional theory level (B3LYP/6-31G\*\*) provide insight into the stabilities of the different stereoisomers of this peroxide, accounting for the facile, acid-catalyzed isomerization from the *meso* form to the racemate. Peroxide **3b**, which is the 2-*tert*-butyl analogue of **3a**, out of 22 theoretically possible isomers, crystallizes in a similar *meso* form. As a result of crystal packing effects and the intrinsically (axial) chiral peroxy “chromophore” that deviates slightly from the antiperiplanar conformation, both enantiomeric forms of **3b** are encountered in the lattice.

### Introduction

Peroxides have attracted considerable attention, and a vast amount of literature exists dealing with both experimental and theoretical studies; they are currently of interest for high-energy materials.<sup>1</sup> A special class of peroxides is represented by the ether peroxides in which the peroxy-bond links two carbon atoms adjacent to the ethereal oxygen atom. The secondary ozonides can be considered the simplest case of ether peroxides where the 1,2,4-trioxolane ring is responsible for the increased reactivity. The alkoxy groups stabilize the peroxy-linkage so that ether peroxides are more stable than the common dialkylperoxides.<sup>2</sup> It is usually accepted that alkyl ethers possessing  $\alpha$ -hydrogen atoms form peroxides, and these are potentially hazardous, leading sometimes to powerful explosions in distillation stills. Few such peroxides have been isolated and structurally characterized, mainly because of their ill-defined and oligomeric nature.

We have previously shown that by the catalytic (Pd/C) hydrogenation of pyrylium salts bearing 2,6-dialkyl-substituents (**1**) one may conveniently obtain, in prepara-

tively useful yields, the correspondingly substituted all-*cis*-tetrahydropyrans **2**.<sup>3,4</sup> If the initial pyrylium salt has 2,6-diaryl substituents<sup>3,5</sup> or is polycyclic,<sup>4</sup> the hydrogenation is less chemoselective leading to complicated mixtures.

Two crystalline peroxides (**3a** and **3b**) stemming from the aerial oxidation of the tetrahydropyrans **2a** and **2b** were isolated (Scheme 1), and their structures were solved from X-ray diffraction data, NOE constraints in solution, and theoretical calculations in the gas phase. Both crystal structures display a diaxially linked peroxy-bridge between two tetrahydropyran rings, having a *meso* configuration. The calculations for **3a** prove that the *meso* peroxide is indeed the most stable form out of 10 envisageable stereoisomers (of an all-*cis*-2,4,6-trisubstituted tetrahydropyran peroxide with an  $\alpha$ - $\alpha$  linkage having identical 2- and 6-substituents). This product is also kinetically favored and should predominate in the crude peroxide mixture, a fact which rationalizes its preferential appearance. Furthermore, an isomerization of the *meso* peroxide **3a-A** occurs easily, upon acid catalysis, leading to the racemate **3a-C/3a-D**, which according to the DFT calculations lies 1.8 kcal/mol higher in energy. A plausible mechanism for this isomerization is also proposed.

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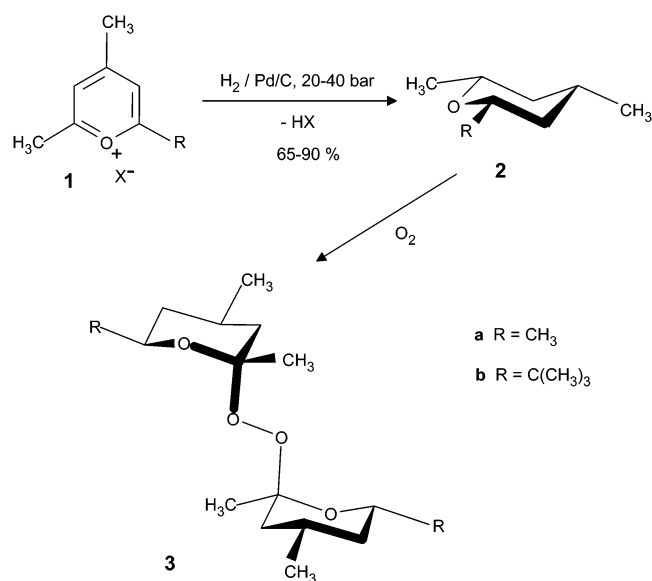
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## SCHEME 1

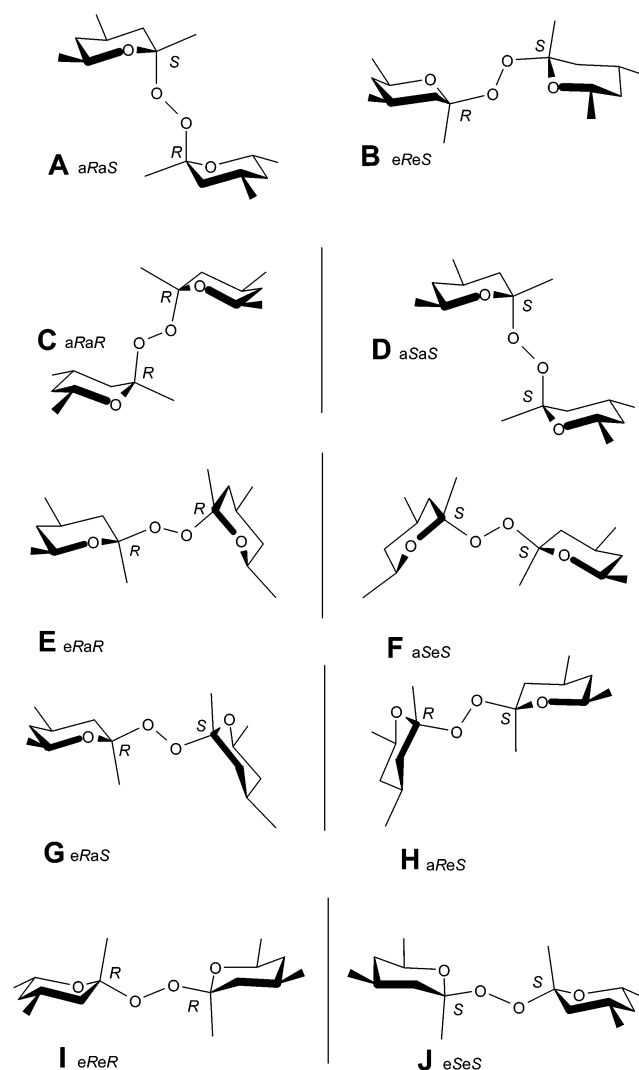


## Results and Discussion

**Peroxide Formation.** The tetrahydropyrans **2** precipitate crystalline peroxides **3** upon exposure to air. However, **2** are stable for years if distilled from sodium metal or lithium aluminum hydride under argon and kept in sealed ampules containing a trace of hydroquinone. The distillation residue of **2**, when left exposed to the atmosphere for several days, also forms solid colorless peroxides. Attempts to speed up the process by passing a current of air or oxygen through **2a** or by adding Mn(II), Mo(III), or Co(II) salts (which in other cases have been found to catalyze the peroxidation of alkenes and/or aromatics) were unsuccessful. The peroxidation rate of **2** was usually very slow so that it was necessary to leave them in sealed vessels (to avoid evaporation) under air for several weeks before the formed peroxide was filtered off and if necessary purified by column chromatography on silica gel. Bulky  $\alpha$ -tetrahydropyranic substituents prevent the peroxidation. Thus, we were unable to observe peroxide formation from 2,6-diisopropyl- or 2,6-di-*tert*-butyl-4-methyltetrahydropyrans.

The aerial auto-oxidation of **2a** is probably initiated by abstraction of a hydrogen atom from the 2- and 6-positions only if these are sterically uncumbered and leads to enantiomeric radicals in equal amounts. The reaction with molecular oxygen O<sub>2</sub> (<sup>3</sup> $\Sigma_g^-$ ) generates hydroperoxy radicals in which the axial products should predominate.<sup>6,7</sup> According to the low-temperature EPR study of Bartlett and Guaraldi,<sup>8</sup> these hydroperoxy radicals dimerize to form tetroxides, which in turn eject molecular oxygen to generate oxy radicals which finally can dimerize to peroxides. The structure of the final peroxides should thus be determined kinetically by the formation of the hydroperoxy radicals.

## SCHEME 2



## Molecular Structure of Peroxide 3a in Solution.

A crystalline peroxide was isolated from a bottle containing about 75 mL of tetrahydropyran **2a** and formed large rhombic plates, which after recrystallization from *n*-hexane melted at 130–132 °C (with decomposition). At least two other peroxides were present in minor amounts in the initial mother liquor as shown by TLC. Theoretically, there are 10 possible stereoisomers of an all-*cis*-2,4,6-trisubstituted tetrahydropyran peroxide with an  $\alpha$ - $\alpha$  linkage having identical 2- and 6-substituents (Scheme 2). If the 2- and 6-substituents are different (as in **3b**, *vide infra*) 22 stereoisomers are possible. The main geometrical feature is the axial (a) or equatorial (e) position of the peroxo-bridge, which induces both anomeric and *exo*-anomeric effects.<sup>9</sup> Molecular mechanics calculations using the MM+ force field,<sup>10,11</sup> which have

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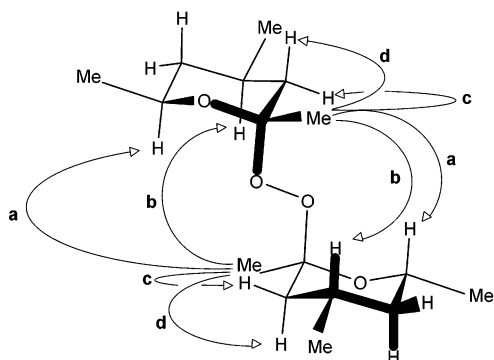
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**FIGURE 1.** Solution structure and observed NOEs in peroxide **3a**. The distances in the B3LYP/6-31G\*\* optimized structure were as follows: (a) 2.76 Å; (b) 3.08 Å; (c) 2.63 Å; and (d) 2.97 Å. The distances were measured from the respective proton for which an NOE was observed to one of the three hydrogen atoms, which was closest, in the 2/2' methyl groups, which were irradiated. The corresponding distances in the crystal of **3A-a** are (a) 2.727/2.969 Å; (b) 3.216 Å; (c) 2.506/3.091 Å; and (d) 2.569/2.853 Å. The two distances refer to different protons of the 2/2' methyl groups that were closest.

been shown after slight modifications to adequately describe the geometries and even heats of formation of saturated cyclic compounds and of dialkylperoxides,<sup>12,13</sup> indicate that the most stable configuration is **3a-A** with an  $\alpha$ - $\alpha$  diaxial peroxy bridge in the *meso* form and not the chiral forms (**3a-C** or **3a-D**, Scheme 2). As this seemed an interesting result, higher level density functional theory (DFT) calculations were performed in order to gain further insight into the nature of this phenomenon (see below) and to understand the kinetic versus the thermodynamic control of the peroxide formation.

Strong nuclear Overhauser effects (NOEs) were observed in the proton spectra of peroxide **3a** in CDCl<sub>3</sub> solution (Figure 1). Thus, upon irradiation of the 2-methyl protons at  $\delta = 1.40$  ppm, about 10% enhancement is observed for the axial protons in the 6-position of the oxane ring at 3.90 ppm (arrow **a**) and about 6% for both of the protons in position 3 (arrows **c** and **d** in Figure 1), at 1.00 ppm (axial) and 1.77 ppm (equatorial). If the 2-methyl group is equatorial and the peroxy-linkage is diaxial (as in **3a-A**, **3a-C**, and **3a-D**) then the signal of the 3-axial proton should be enhanced but the 6-axial proton in the same oxane ring should be NOE silent as it is more than 4.5 Å distant. The size of the NOEs at the axial protons in positions 4 and 6 indicate that these are interezidial NOEs, i.e., NOEs between the methyl in position 2 and the axial protons in positions 4' and 6'. Obviously, the distance dependence is not so important as the fact that the methyls in positions 4 and 6 have a large contribution to the relaxation from the vicinal protons. The observed enhancement must thus be due to the methyl group in position 2 in the other tetrahydropyran ring across the peroxy-bridge. One cannot presume, however, that if the methyl in position 2 passes close enough to the axial protons in positions 4' and 6' with the right frequency, a large NOE should be expected,

even if for most of the time the methyl is remote from these axial protons. This restricts the conformational space theoretically possible by the free rotation of the relatively rigid tetrahydropyran rings around the two C–O bonds and one O–O bond. Attempts to observe a splitting of signals upon addition of the chiral shift reagent Eu(tfc)<sub>3</sub>, {tris[3-trifluoromethyl-hydroxymethylene)-(+)–camphorato]–europium}, even at high molar ratios, were unsuccessful. If a splitting had been encountered in this experiment it would have been clear structural proof for the racemic mixture **3a-C** + **3a-D**. This “negative result experiment” is compatible with the *meso* form **3a-A** configuration.

**Acid-Catalyzed Isomerization of *meso* Peroxide **3a-A** to Racemate **3a-C/3a-D**.** Heating a chloroform solution of the plates of **3a** with catalytic amounts of trifluoroacetic acid causes the *meso* peroxide to isomerize to at least two other peroxides, which were separated by column chromatography on silica gel. The first peroxide fraction afforded a colorless solid (mp 55–57 °C), which exhibited a <sup>1</sup>H NMR spectrum very similar to that of the parent *meso* peroxide **3a-A**. There were slight chemical shift differences, notably for the 6-proton, which appeared at 4.06 ppm (instead of 3.95 ppm in **3a-A**). Also the <sup>13</sup>C NMR spectra are quite similar but not identical, as seen in the spectra of a mixture. The much lower melting point than for **3a-A** was a strong indication that this fraction must be a racemate. This was eloquently demonstrated by the addition of the chiral shift reagent Eu(tfc)<sub>3</sub> at high molar ratios, which causes the 2-methyl singlet to split into two equal signals while the 6-proton multiplet shifts to about 6.5 ppm and broadens considerably with loss of its fine structure. This result confirms the presence of the racemic form of the diaxially peroxy-linked tetrahydropyranic compounds **3a-C** + **3a-D** (Scheme 2). The peroxide fraction that eluted later showed complicated NMR spectra from which a structural assignment was not possible and probably contained a mixture of axial–equatorial peroxy-bridged tetrahydropyrans.

A more in depth study of this intriguing isomerization was performed using a milder acid, namely, acetic acid, to slow the kinetics and allow convenient investigations by NMR methods. Thus the transformation of **3a-A** in a mixture of C<sub>6</sub>D<sub>6</sub>/CD<sub>3</sub>COOD (3:1) was monitored by NMR overnight (Supporting Information Figures S1 and S2). In CDCl<sub>3</sub>/CD<sub>3</sub>COOD (3:1) almost the same kinetics are encountered, thus excluding any aberrant solvent effects, but the chemical shift separation of the signals in the crude reaction mixture was worse. Only three compounds were found in both of these cases in the crude reaction mixture in a concentration exceeding 2% mol of the total tetrahydropyranic concentration, namely, the starting **3a-A** and two new compounds displaying similar spectra. The product having the most upfield signal for the 2-methyl group (product **4**) reaches a steady concentration in the first 2 h. Both products display a single set of signals for H-6 (Supporting Information, Figure S1) and the methyl in position 2 (Supporting Information, Figure S2); therefore they are not compounds having two different tetrahydropyran units, like **3a-E/F** and **3a-G/H**.

The proton chemical shifts assignments for the tetrahydropyranyl moieties in the three compounds have been

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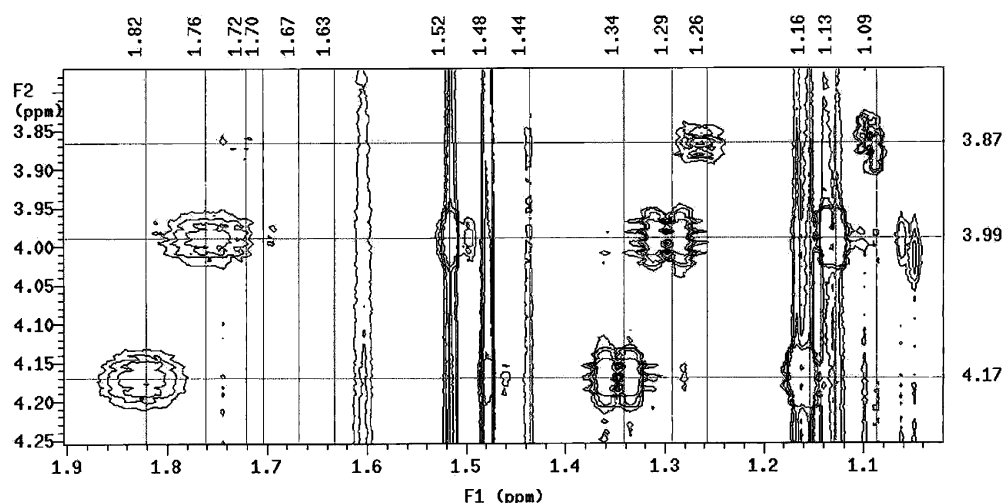
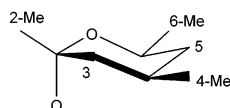


FIGURE 2. Expansion of the NOESY spectrum of the reaction mixture from the isomerization of **3a** in  $C_6D_6/CD_3COOD$  (3:1).

**SCHEME 3. Proton Chemical Shifts ( $\delta$ , ppm) in the Peroxide Isomerization Mixture**



	H-3 <sup>a</sup>	H-3 <sup>c</sup>	H-4 <sup>a</sup>	H-5 <sup>a</sup>	H-5 <sup>c</sup>	H-6 <sup>a</sup>	2-Me	4-Me	6-Me
<b>3a-A</b>	0.90	1.70	1.76	0.65	1.29	3.99	1.52	0.65	1.13
<b>3a-C, 3a-D</b>	0.91	1.67	1.82	0.66	1.34	4.17	1.48	0.63	1.16
<b>4</b>	0.89	1.63	1.76	0.61	1.26	3.87	1.44	0.61	1.09

made on the basis of the  $^1H$ – $^1H$  correlations seen in the DQCOSY spectrum of the mixture and are given in Scheme 3.

The similarity of the chemical shifts in the three compounds, particularly for the methyl in position 2, indicates that in all of them the methyls are all-*cis*, discarding further possible structures such as **3a-B** or **3a-I/J**.

The product other than **4** displays NOEs between the methyl in position 2 and H-4 and H-6 as **3a-A** does, and therefore this product was assigned as the racemate **3a-C/3a-D**. Product **4** does not display these NOEs (Figure 2). Compound **4** is 2,4,6-trimethyl-2-acetoxy-*d*<sub>3</sub>-tetrahydropyran, as inferred also from a *m/z* = 160 for the peak corresponding to the same concentration in GC–MS as seen in the NMR spectra for compound **4**.

Additionally, two samples of **3a** in benzene having  $C_6D_6:CD_3COOD$  ratios of 3:1 and 12:1 when reaching equilibrium displayed ratios of **3a-A**:(**3a-C**+**3a-D**):**4** of 1:0.7:0.4 and 1:0.7:0.1, respectively. Thus, as expected, by reducing the acid concentration, less acetate **4** is formed, while the ratio *meso*/racemate is unaffected. No strange kinetic effects are here to be suspected so this ratio must reflect the thermodynamic stability, which translates at equilibrium at 25 °C to an  $\Delta G$  value of 0.23 kcal/mol in favor of the *meso* peroxide. This value is overestimated by the DFT calculations (*vide infra*), which were, however, performed in the absence of solvation. A plausible mechanism for this isomerization is depicted in Scheme 4<sup>14</sup> and involves protonation at one of the two

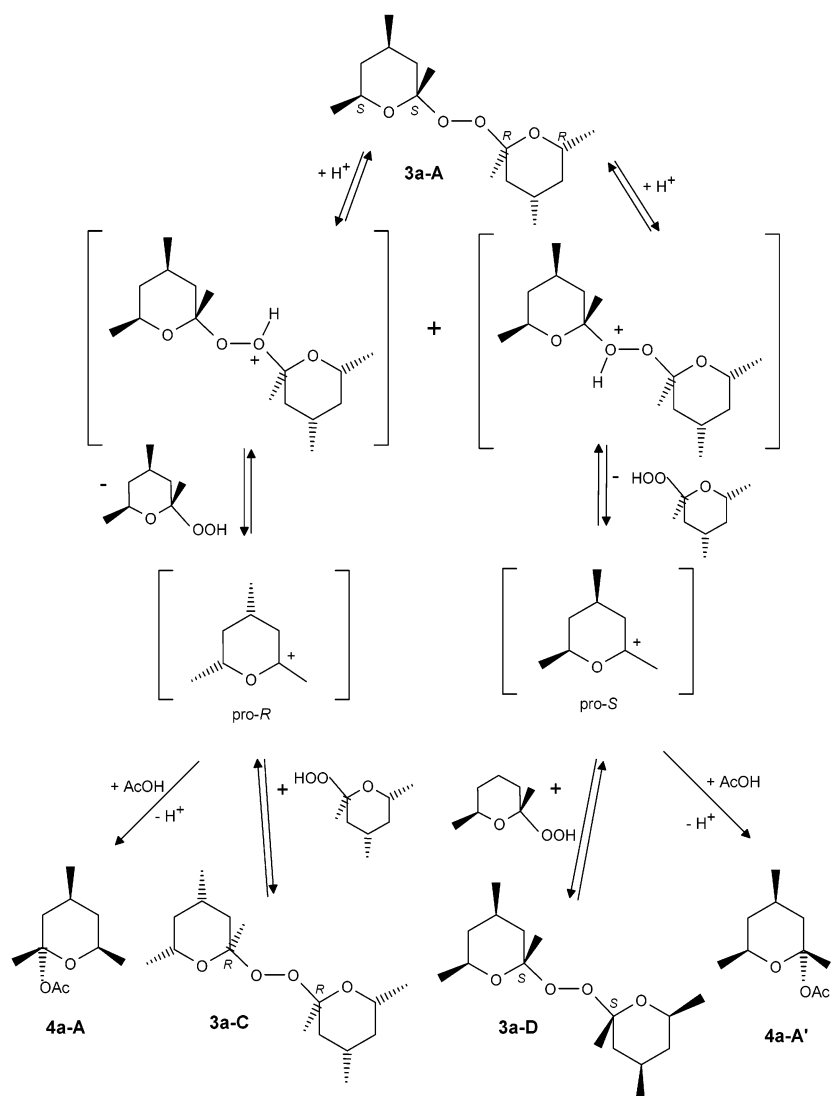
oxygen atoms in the peroxy-bridge followed by formation of a hydroperoxide. Recombination with either hydroperoxide then gives back the *meso* peroxide **3a-A** or the chiral peroxide **3a-C**. The enantiomer **3a-D** can be formed in equal probability by the initial protonation of the other oxygen atom in the peroxy-bridge, thus accounting for the racemate formation. In the presence of carboxylic acids in excess, the intermediate cation is trapped and results in ester formation (as is the case for **4**).

In the absence of acids no isomerization occurs. Thus the initial aerial peroxidation that leads predominantly to axial oxy radicals and for which there is essentially no barrier for dimerization will produce a statistical mixture **3a-C/3a-A/3a-D** in a 1/2/1 ratio. The more symmetric, less soluble *meso* isomer crystallizes out from this mixture.

**DFT Calculations on Peroxides 3a and Attempts to Estimate the Anomeric Effect.** Initial molecular mechanics calculations within the PCMODEL program<sup>10</sup> (employing the MM+ force field, which is derived from the Allinger MM2 force field) have allowed a systematic exploration of the energy surface dependence of the three dihedral angles that permit free rotation of the two tetrahydropyran rings [O(1)C(1)O(2)O(2a), C(1)O(2)O(2a)C(1a), and O(1a)C(1a)O(2a)O(2)]. Evidently, some conformations are strongly disallowed as a result of the overlap of the two tetrahydropyran rings. The most stable conformation proved to have a 180° dihedral angle of the central peroxy-bond with a rather shallow dependence on the other two dihedral angles. Subsequent extensive minimizations within the program package HyperChem<sup>11</sup> (also with the MM+ force field) have led to the most stable conformations for all isomeric peroxides **3a**, which are depicted in Scheme 2. However, the geometry of the most stable structure, which corresponds to that of **3a-A**, deviated somewhat from the geometry encountered in the crystal (*vide infra*). Especially the peroxy-bond with about 1.32 Å appeared much too short. This shed doubts on the accuracy of the calculation method or suggested that unexpected crystal packing effects were operating. Earlier molecular mechanics

(14) We thank a kind anonymous referee for suggesting this mechanism.

## SCHEME 4



calculations have been shown to describe correctly the geometries and even heats of formation for dialkylperoxides only after slight modifications of the force field.<sup>12,13</sup> To estimate the kinetic *versus* thermodynamic control of peroxide formation we performed also higher level calculations and the results are summarized in Table 1. As starting geometries, the MM+ optimized structures were used.

All reported energies were computed at fully optimized geometries using a hybrid density function B3LYP<sup>15,16</sup> with a 6-31G\*\*<sup>17</sup> basis set using the JAGUAR ab initio program package.<sup>18</sup> Previous work on peroxides using wave function based ab initio methods<sup>19,20</sup> suggest that the basis set is more than adequate. Studies on simpler peroxides using DFT methods have also been performed.<sup>21,22</sup> The basis set dependency for cyclic peroxides

has been fairly recently investigated for a high-energy, shock-sensitive triperoxide.<sup>23</sup> Generally smaller basis sets are required in density functional methods compared to traditional wave function based ab initio methods as dynamic correlation effects are treated implicitly in the functional rather than explicitly in the basis-set-dependent expansion of the wave function. The geometry of **3a-A** was found to be in excellent agreement with the crystal structure described below (e.g., O–O bond length 1.474 vs 1.477 Å, dihedral angle 179.4° vs 180°) and is considerably better than those from the BLYP method (using the same basis set). The relative energies of the various isomers (Table 1) can be rationalized well with the established concepts of the anomeric effect.<sup>9</sup> Given the similarity of the computed structures, zero-point corrections, which were not considered in this study, are not likely to contribute discernible differential effects to the reported energies.

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**TABLE 1.** Calculated Energies and Geometries of Peroxides **3a** and Model Compounds **4a–6a**

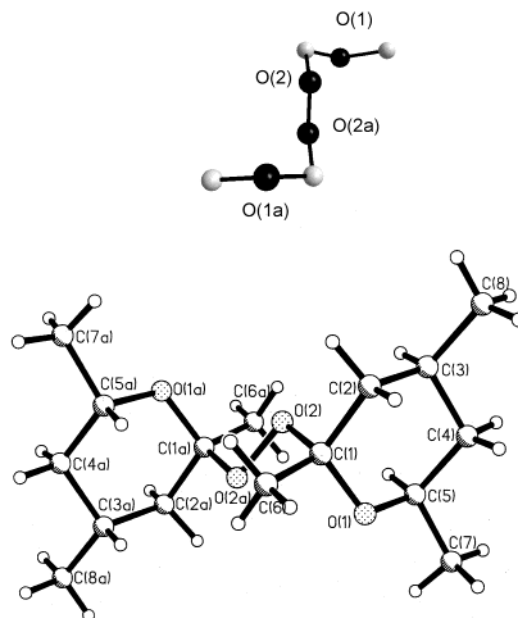
compd	total energy (hartree)	rel energy (kcal/mol)	OCOO (deg)	COOC (deg)	OOCO (deg)	O–O (Å)
<b>3a-A</b>	-928.6549	0	60.4	-179.5	-60.7	1.4746
<b>3a-A<sup>a</sup></b>	-928.6498	3.20	-177.5	179.6	177.4	1.4718
<b>3a-C</b>	-928.6520	1.82	59.0	173.9	-179.2	1.4727
<b>3a-G</b>	-928.6467	5.15	-72.2	132.2	73.9	1.4685
<b>3a-B</b>	-928.6443	6.65	70.8	134.6	-69.7	1.4710
<b>3a-E</b>	-928.6442	6.71	-179.5	156.3	58.4	1.4683
<b>3a-I</b>	-928.6402	9.22	-179.1	153.4	68.6	1.4690
<b>4a-A</b>	-617.6185	0				
<b>4a-B</b>	-617.6134	3.24				
<b>5a-A</b>	-464.9687	0				
<b>5a-B</b>	-464.9683	0.24				
<b>6a-A</b>	-540.1029	0				
<b>6a-B</b>	-540.0993	2.26				

<sup>a</sup> Local minimum with a conformation other than that encountered in the crystal. The crystal geometry of **3a-A** has the three dihedral angles OCOO, COOC, and OOCO as 60.60°, 180.00°, and -60.60°, respectively, and the O–O bond length is in the crystal 1.477(6) Å.

The least stable structure was found to be **3a-I** involving two equatorial peroxy-linkages. An estimation of the anomeric effect was attempted by optimizing the geometries and calculating the energies, with the same methods, for the axial (**A**) and equatorial (**B**) 2-acetoxy-(**4a**) 2-hydroxy- (**5a**), and 2-hydroperoxy-substituted 2,4,6-trimethyltetrahydropyran (**6a**), which are represented in the Supporting Information, Figure S3. Models **5a–6a** were investigated also in order to correlate the theoretical results with formation of the acetate **4**. The results are given in Table 1 and show that although the 2-hydroxy group counteracted by the 2-methyl group has only a relatively small axial preference, in contrast the 2-hydroperoxy group in an axial position leads to an energy decrease of 2.26 kcal/mol compared to that in an equatorial position. In both geometries **6a-A** and **6a-B** a hydrogen bond seems to operate between the tetrahydropyran oxygen atom and the hydroperoxide hydrogen with distances of 2.22 and 2.18 Å, respectively, so that the energetic preference for **6a-A** is not solely due to an *exo*-anomeric effect.<sup>24,25</sup> As the axial hydroperoxides are the precursors for the peroxides with axial peroxy-bonds, which also prove to be more stable, we can conclude that these are both the kinetically *and* the thermodynamically favored products.

**Crystal Structures of Peroxides 3a and 3d from X-ray Diffraction Analyses.** Confirmation of the preferential formation of the *meso* peroxide diastereomer came from investigations of the crystal structures by diffraction methods.

**Molecular Structure of Peroxide 3a.** The large plates of **3a** obtained after several months from the aerial peroxidation of **2a** proved unsuitable for X-ray diffraction as there was a large degree of twinning and the crystals were too soft for cutting. However, slow diffusion of *n*-hexane into a benzene solution of similar plates of **3a**



**FIGURE 3.** Molecular structure with atom numbering of the *meso* peroxide **3a-A**. Oxygen atoms are dotted circles. Note in the inset the *antiperiplanar* conformation of the C(1)–O(2)–O(2a)–C(1a) bonds, which makes achiral the otherwise intrinsically chiral peroxy-linkage. In the inset, oxygen atoms are represented as darker spheres compared to the carbon atoms.

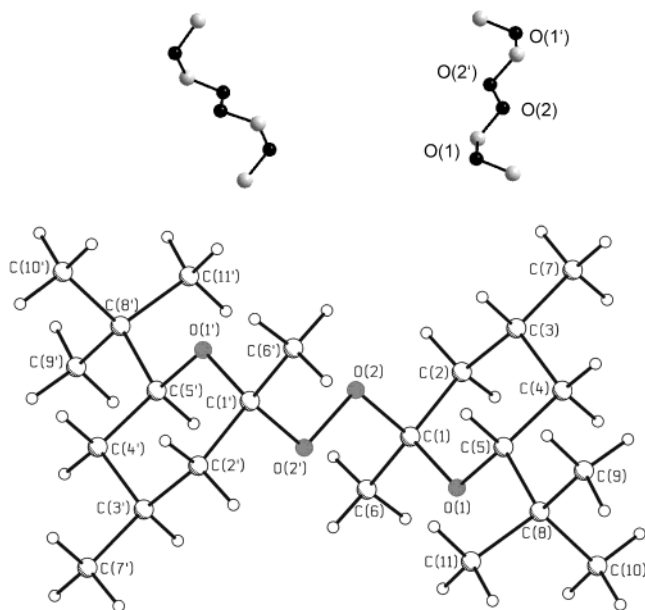
provided suitable crystals for X-ray analysis. The structure was solved by direct methods and gave unambiguous proof of the *meso*-diaxially peroxy-linked bistetrahydropyran **3a-A**. The molecule has an inversion center so that only half of it was considered in the initial computations. The final structure was obtained by symmetrization. Figure 3 shows the molecular structure the atom numbering. The thermal ellipsoids show relatively loosely attached methyl groups hinged to a more rigid tetrahydropyran core (Supporting Information, Figure S4). Crystallographic details are given in Tables 2–7 in the Supporting Information.

The distance in the crystal structure of **3a** between the 6'-axial proton and one of the 2-methyl protons (from the other tetrahydropyran ring) is 2.727 Å. This distance must be approximately the same in CDCl<sub>3</sub> solution in order to account for the observed NOE of 10% over the peroxy-bridge (arrow **a** in Figure 1). Thus, the solution structure must be similar to the one encountered in the crystal as shown in Figure 1, where the observed NOE effects upon irradiation of the 2-methyl singlet are indicated together with the distances in the optimized structure at the B3LYP/6-31G\*\* level (solvent interactions neglected), which fit the X-ray data much better than the ones obtained by molecular mechanics. Also given in the caption of Figure 1 are the corresponding distances from the X-ray data. A good fit exists between the solution structure obtained from the NOE constraints and the crystal structure.

**Molecular Structure of Peroxide 3b.** Part of the crude hydrogenation mixture of **1b**, which by GC–MS contained ~45% tetrahydropyran **2b**, was not distilled but kept in a vial with a plastic cap. After more than a year, small peroxide needles of **3b** were visible at the air–liquid interface. These were collected, and their

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**FIGURE 4.** Molecular structure of **3b**. Only one of the two enantiomeric molecules present in the unit cell is shown together with the atom numbering. Oxygen atoms are depicted as gray spheres. In the inset the first three atoms connected to the peroxo-bond are shown for both enantiomorphs. In the inset, oxygen atoms are represented as darker spheres compared to the carbon atoms.

structure was determined by direct X-ray methods. Analogously with **3a**, the structure proved to be the *meso* form also with the diaxial peroxo-bridge. In this case selectivity was achieved by preferential axial peroxidation of the 6-methyl-substituted  $\alpha$ -carbon and by locking the conformation of the oxane ring with the bulky 2-*tert*-butyl group. It is quite surprising that crystallization occurred in this complex mixture and that only one out of the 22 possible stereoisomers crystallized. Again, probably the higher symmetry forces it to crystallize more easily. The crystal structure together with atom numbering is presented in Figure 4. Crystallographic details are given also in the Supporting Information.

Crystal packing effects probably cause the C(1)O(2)O(2')C(1') dihedral angle of the peroxo-bridge in **3b** to deviate from antiperiplanarity, and as a result the structure becomes chiral. Both chiral forms are encountered so that the unit cell contains two molecules that have superimposable tetrahydropyran rings in which the peroxo-bridge has enantiomeric conformations with dihedral angles of  $178.81^\circ$  and  $-177.06^\circ$ . As this small difference is barely visible to the eye, only the right-handed form is presented in Figure 4. In the inset only the first three atoms connected to both sides of the peroxide bond are shown for both enantiomeric conformers. Attempts to solve the structure in a higher symmetry space group than  $P\bar{1}$  did not converge satisfactorily. The O(2)–O(2') bond is only 0.002 Å longer than in **3a**, confirming the similarity of the two crystal structures.

Interestingly, the fact that an achiral compound (as *meso*-**3b**) crystallizes in chiral conformations and that both enantiomeric forms are present in the crystal is not usually encountered, as only few examples (about 40 inorganic, the most notable being quartz, and 30 organic)

are known. These are reviewed in ref 26 and are not uncommon for peroxides, as even hydrogen peroxide or dibenzoylperoxide possess this property. A search in the Cambridge Structural Database for crystal structures of ether peroxides has revealed only one related tetrahydropyranyl structure, namely, the bis-peroxide of 2-methyl tetrahydropyran, which also has diaxial peroxo-bridges.<sup>27</sup>

## Conclusions

The fact that the *meso* peroxides are formed with such high diastereoselectivity by the aerial peroxidation of substituted tetrahydropyrans has been hereby proven, and it arises both as a result of the kinetic control of the reaction as well as their higher stability. An easier crystallization of the higher symmetry *meso* compound **3a-A** occurs, whereas in the case of *meso*-**3b** the symmetry is broken by crystal lattice effects so that both enantiomeric forms are present. Furthermore, isomerization from the *meso* form to the racemate, which is acid-catalyzed, is a “clean” reaction. As *meso* peroxide **3a** is easily available in large quantities, a preparatively useful spin-off of our study may be envisaged, namely, performing the isomerization reaction to the racemate in the presence of a chiral carboxylic acid would lead to diastereomeric esters of type **4**, which could be easily separated. Taking into account that these are equilibrium reactions, one can expect exclusive formation of one diastereomer, provided that the energy difference between the two diastereomers is high enough. Chiral 2-hydroxy-tetrahydropyranyl residues could thus be accessed and put synthetically to use in stereoselective transformations or resolutions of racemates. The tetrahydropyranyl group is well-established as an alcohol protective group since the works of Marc Julia, but starting from  $\Delta^2$ -dihydropyran and thus without the stereochemical touch.

Attempts to separate the enantiomers **3a-C** and **3a-D** by preparative TLC on acetylcellulose failed. Preparative chiral HPLC could, in principle, lead to their isolation in pure form. This may prove useful as it will allow determination of the circular dichroism (CD) spectra of the individual enantiomers. Comparison with the conformation encountered in the crystal for the *meso* form would thus be possible, a fact that could lead to a correlation between the sign of the Cotton effects and the absolute configuration for the peroxide “chromophore”, which is intrinsically chiral having axial chirality. For the related dithiane chromophore such a rule was derived and explained on the basis of simple MO theory by Sznatzke.<sup>28</sup> More recently, ab initio calculations have predicted that a torsion angle between  $0^\circ$  and  $90^\circ$  around the peroxo-bond (C–O–O–C) in dimethyl peroxide should lead to a positive Cotton effect.<sup>29,30</sup> Free rotation around

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the peroxy-bridge leads to racemization, but in cyclic compounds or when this rotation is hindered by other means, enantiomers could be isolated. As peroxides are common natural compounds, especially of marine origin, either from metabolic pathways or as artifacts of their subsequent oxidation during the isolation procedures, a rule that allows the assignment of the absolute configuration from CD spectra would be of interest. Tedious crystallizations to obtain X-ray suitable crystals, which also require milligram quantities of compounds, could thus be circumvented, and CD spectra of nano- to microgram quantities would furnish the absolute configuration. The drawback of the peroxide chromophore (compared to the related dithianes) is, however, a very low extinction coefficient for the forbidden  $n-\sigma^*$  transition, which tails into the 250–350 nm range. This fact may lead to small  $\Delta\epsilon$  values, i.e., small Cotton effects, which might hamper these analyses and make the correlation with the absolute configuration difficult.

## Experimental Section

**General Remarks.** NMR spectra were recorded at 300, 400, and 500 MHz (with an indirect detection probe) in  $\text{CDCl}_3$  and were referenced to the solvent signals. Column chromatography was performed on silica gel (0.040–0.063 mm). Analytical thin-layer chromatography was performed on ready made plates coated with silica gel either on aluminum or on glass. The tetrahydropyrans and their peroxides were visualized by spraying with either a “Mo-Cer” reagent  $\{\text{Ce}(\text{SO}_4)_2/\text{H}_3\text{P}(\text{Mo}_3\text{O}_{10})_4/\text{H}_2\text{SO}_4/\text{H}_2\text{O} = 1:2.5:11:94 \text{ (by weight)}\}$  or a  $\text{KMnO}_4$  solution (3 g  $\text{KMnO}_4$ , 5 mL 5%  $\text{NaOH}$ , 20 g  $\text{K}_2\text{CO}_3$ , and 200 mL  $\text{H}_2\text{O}$ ) followed by heating.

**meso-Bis-2,2'-[(Z,Z,Z)-2,4,6-trimethyltetrahydropyranyl]-peroxide (3a-A).** The tetrahydropyran **2a**,<sup>3,31,32</sup> after standing for several months, gave large crystalline plates that were freed from residual oil. Mp 127–128 °C (dec with gas evolution) or 130–132 °C (dec) after recrystallization from *n*-hexane.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ , ppm: 0.79 (6H, d,  $J = 6.5$  Hz, 4-Me and 4'-Me), 0.80 (2H, dd,  $J = 11.8$  and 12.7 Hz, H-5<sup>a</sup> and H-5<sup>a'</sup>), 1.05 (2H, t,  $J \approx 12.5$  Hz, H-3<sup>a</sup> and H-3<sup>a'</sup>), 1.18 (6H, d,  $J = 6.3$  Hz, 6-Me and 6'-Me), 1.42 (6H, s, 2-Me and 2'-Me), 1.57 (2H, d of m,  $J(5^e-5^e) = -13.1$  Hz, H-5<sup>e</sup> and H-5<sup>e'</sup>), 1.84 (2H, d of m, H-3<sup>e</sup> and H-3<sup>e'</sup>), 1.90 (2H, broad m, H-4<sup>a</sup> and H-4<sup>a'</sup>), 3.97 (2H, sextet of d, 6-H<sup>a</sup> and 6'-H<sup>a'</sup>).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$ , ppm: 21.75 (6-Me and 6'-Me), 22.14 (4-Me and 4'-Me), 25.10 (2-Me and 2'-Me), 25.74 (C-4 and C-4'), 41.29 (C-5 and C-5'), 41.62 (C-3 and C-3'), 66.66 (C-6 and C6'), 102.21 (C-2 and C-2'). IR ( $\text{CCl}_4$ )  $\tilde{\nu}$   $\text{cm}^{-1}$ : 845 m, 890 m, 965 m, 992 m, 1015 m, 1052 m, 1104 m, 1145 mw, 1152 mw, 1175 ms, 1204 s, 1230 mw, 1380 s, 1396 mw, 2860 w, 2885 w, 2942 ms, 2966 ms. EI-MS (%): 128 (9), 127 (100,  $\text{M}/2 - \text{O}_2^+$ ), 109 (5), 83 (7), 69 (19), 55 (9), 43 (70), 41 (5). UV (cyclohexane),  $\lambda_{\text{max}}$  (log  $\epsilon_{\text{max}}$ ): 218 (1.89), 280–320 (tail). (MeOH),  $\lambda_{\text{max}}$  (log  $\epsilon_{\text{max}}$ ): 209 (2.37), 250–300 (tail).  $\text{C}_{16}\text{H}_{30}\text{O}_4$  (MW = 286.41), calcd C 67.10, H 10.56; found C 67.42, H 10.64. Crystallographic data (excluding structure factors) for **3a-A** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 152999. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [FAX (internat.) + 44-1223/336-033; E-mail deposit@ccdc.cam.ac.uk]. Structure factors are available upon request from the corresponding author.

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(±)-*rac*-Bis-2,2'-[(Z,Z,Z)-2,4,6-trimethyltetrahydropyranyl]peroxide (**3a-C** and **3a-D**). By standing for 10 days in  $\text{CDCl}_3$  the *meso* peroxide **3a-A** isomerizes slowly and new signals appear in the  $^1\text{H}$  NMR spectrum, especially visible at 4.06 ppm. Preparatively, 0.3418 g of crystalline peroxide **3a-A** was dissolved in 10 mL of chloroform, 5 drops of trifluoroacetic acid were added, and then the mixture was heated to reflux for 0.5 h. Column chromatography on silica gel with petroleum ether with increasing amounts (1%, 2%, 5%, etc.) of diethyl ether separates a peroxide fraction (0.124 g) that crystallizes and has mp = 55–57 °C and  $R_f = 0.33$  (on  $\text{SiO}_2$  elution with petroleum ether/diethyl ether 9:1, v/v) while the initial *meso* peroxide is eluted later and has  $R_f = 0.27$ .  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ , ppm: 0.80 (2H, m, H-5<sup>a</sup> and H-5<sup>a'</sup>), 0.84 (6H, d,  $J = 6.6$  Hz, 4-Me and 4'-Me), 1.05 (2H, t,  $J \approx 12.5$  Hz, H-3<sup>a</sup> and H-3<sup>a'</sup>), 1.18 (6H, d,  $J = 6.3$  Hz, 6-Me and 6'-Me), 1.44 (6H, s, 2-Me and 2'-Me), 1.60 (2H, d of m, H-5<sup>e</sup> and H-5<sup>e'</sup>), 1.81 (2H, d of m, H-3<sup>e</sup> and H-3<sup>e'</sup>), 1.90 (2H, broad m, H-4<sup>a</sup> and H-4<sup>a'</sup>), 4.06 (2H, sextet of d, 6-H<sup>a</sup> and 6'-H<sup>a'</sup>).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ , ppm: 21.85 (6-Me and 6'-Me\*), 22.05 (4-Me and 4'-Me\*), 24.80 (2-Me and 2'-Me), 25.51 (C-4 and C-4'), 41.30 (C-5 and C-5'), 41.78 (C-3 and C-3'), 66.50 (C-6 and C6'), 102.27 (C-2 and C-2').

**meso-Bis-2,2'-[(Z,Z,Z)-6-(2,2-dimethylethane-1-yl)-2,4-dimethyltetrahydropyranyl]-peroxide (3b).** This peroxide could not be obtained analytically pure because of the minute amount of crystals that were formed in the crude hydrogenation mixture of **1b**.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$ , ppm: 0.75 (2H, dd,  $J = 12.0$  and 12.5 Hz, H-5<sup>a</sup> and H-5<sup>a'</sup>), 0.82 (6H, d,  $J = 6.3$  Hz, 4-Me and 4'-Me), 0.88 (18 H, s, C(CH<sub>3</sub>)<sub>3</sub>), 1.00 (2H, t,  $J \approx 13.0$  Hz, H-3<sup>a</sup> and H-3<sup>a'</sup>), 1.40 (6H, s, 2-Me and 2'-Me), 1.70 (2H, d of m, H-3<sup>e</sup> and H-3<sup>e'</sup>), 1.80 (2H, broad m, H-4<sup>a</sup> and H-4<sup>a'</sup>), 3.44 (2H, dd,  $J = 11.5$  and 1.7 Hz, 6-H<sup>a</sup> and 6'-H<sup>a'</sup>). The H-5<sup>e</sup>, H-5<sup>e'</sup> multiplet was covered by the residual water signal at 1.53 ppm). Crystallographic data (excluding structure factors) for **3b** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 161312. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [FAX (internat.) + 44-1223/336-033; E-mail deposit@ccdc.cam.ac.uk]. Structure factors are available upon request from the corresponding author.

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**Supporting Information Available:** NMR spectra monitoring the isomerization of **3a**; optimized geometries by DFT for **4a**, **5a** and **6a**; ORTEP plot of the crystal structure of **3a** in a different orientation than that shown in Figure 3 as well as Tables 2–11 with atomic coordinates and selected bond lengths and angles for **3a** and **3b**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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