

127. Conformational Analysis of 1,2:3,4-Diepoxides: *Ab Initio* and Semiempirical Molecular-Orbital Calculations

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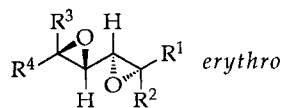
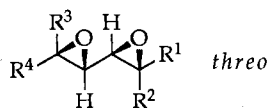
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Using semiempirical and *ab initio* procedures, the most stable conformations of *meso*- and *rac*-bioxirane and of some substituted 1,2:3,4-diepoxides were calculated. For *threo*-diepoxides (having the same relative configurations as *rac*-bioxirane, **3**), two stable conformations with CCCC dihedral angles of *ca.* 90° and *ca.* 270° were found. For *erythro*-diepoxides (derivatives of *meso*-bioxirane, **4**) the calculations suggest three preferred conformations with corresponding dihedral CCCC angles of *ca.* 90°, *ca.* 180°, and *ca.* 270°. The calculations are in fair agreement with the experimental data available for the unsubstituted compounds **3** and **4**.

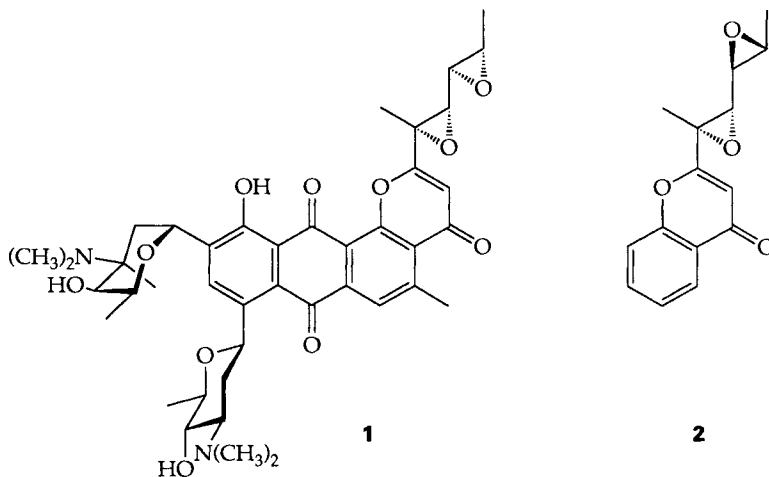
Introduction. – In the course of our work on ‘open-chain²⁾ 1,2:3,4-diepoxides [2] [**3**], X-ray structure analyses of the antitumor antibiotic hedamycin (**1**) [**4**] and of the similarly substituted 4*H*-chromen-4-one **2** [**5**] were obtained. The side chains of both compounds have the same constitution but differ in the relative configurations. Surprisingly, the crystal structures revealed that the side chains of **1** and **2** adopted virtually the same conformations in terms of CCCC torsion angles around the inter-epoxide bond, apparently irrespective of the different relative configurations. What are the parameters that govern the internal rotation around the inter-epoxide bond in 1,2:3,4-diepoxides? To answer this question, we calculated the energy profile for this internal rotation with semiempirical methods for the bioxiranes **3** and **4** as well as for the more complex compounds **5–12**, some of which resemble the partial structures found in **1** and **2**. In the



	R ¹	R ²	R ³	R ⁴		R ¹	R ²	R ³	R ⁴
3	H	H	H	H	4	H	H	H	H
5	CONH ₂	H	H	Me	9	CONH ₂	H	H	Me
6	CO ₂ Me	Me	H	Me	10	CO ₂ Me	Me	H	Me
7	CONH ₂	Me	Me	Me	11	CONH ₂	Me	Me	Me
8	CONH ₂	Et	<i>t</i> -Bu	H	12	CONH ₂	Et	<i>t</i> -Bu	H

¹⁾ From the Ph. D. thesis of *M. N.* [1].

²⁾ We call diepoxides ‘open-chain’ diepoxides, if they are not part of a larger ring system.



vicinity of stable conformations, additional *ab initio* SCF calculations were performed to refine the results.

1,2:3,4-diepoxides (bioxiranes) are isoelectronic with bicyclopropyls. Several experimental [6] and computational [7] studies on the conformations of bicyclopropyls have been reported in the literature, but only little is known about the conformations of diepoxides [8–12]. In contrast to bicyclopropyl (13), three stereoisomers of bioxirane are known: the two enantiomers of the chiral form **3** (with *threo*-configuration³) and the *meso*-form **4** (with *erythro*-configuration). Correspondingly, more complex diepoxides can be considered as belonging either to the *threo*-series (such as hedamycin (**1**)) or to the *erythro*-series (such as **2**).



Computational Methods. – Semiempirical calculations utilizing the PCILO [13] [3] as well as the MNDO and the AM1 hamiltonian (AMPAC program package [14]) were performed. To obtain the energy profile for the internal rotation around the inter-epoxide bond, the dihedral CCCC angle⁴ was changed in steps of 10° (in some cases 5° in the vicinity of the energy minimum) and the remaining structure relaxed for each angle. In this way, not only the most stable conformations but also the rotational barriers between them were found. Subsequently, *ab initio* SCF optimizations for the most stable conformations found by the above procedure were performed with the GAUSSIAN88 [15] and GAUSSIAN90 program packages [16] on a VAX-8840 and a CRAY-2 computer, applying the 3-21G basis set. Finally, single-point calculations with the 6-31G* basis set were

³) To distinguish between the different relative configurations, the prefixes '*threo*' and '*erythro*' are used depending on whether the C-atoms involved in the inter-epoxide bond have the same relative configurations as C(2) and C(3) in *threo* or *erythro*, respectively.

⁴) The signs of the dihedral angles (torsion angles) are given in accordance with IUPAC recommendations (*i.e.* positive for clockwise rotation, see rule E-5.4).

carried out at the AM1 (6-31G*||AM1) and at the 3-21G (6-31G*||3-21G) optimized structures to test the influence of the basis set on the relative energies of the conformations. For compounds **3** and **4**, the basis 6-31G** was used in addition. For the most highly substituted compounds (**8** and **12**), *ab initio* optimizations were not feasible; therefore, onyl single-point calculations with the 3-21G basis set were performed at the MNDO (3-21G||MNDO) and AM1 structures (3-21G||AM1). In general, the results depend only little on the method applied, an indication that the results obtained are quite reliable. All calculations were carried out for the enantiomers shown above (**3–12**).

Results and Discussion. – *threo-Diepoxides*. Some years ago, *Smith* and *Kohl* [9] published an electron-diffraction study of compound **3**. Two conformations with angles of 170° and 315° were detected in the gas phase, the latter conformation being present only in 'smaller amounts'. In a recent study, *Su et al.* [11] concluded from IR, *Raman*, and microwave spectra (and thus confirmed the original findings of *Lüttke* and *de Meijere* [8]), that only one conformation with a dihedral CCCC angle of 235° exists for **3** in the solid state, whereas, in the liquid and in the gas phase, an additional conformation with a dihedral angle of *ca.* 105° is present. *Gatti* and *Demarco* [10] performed CNDO calculations and predicted three conformations with dihedral angles of 15°, 75°, and 235° (the latter being the most stable) in equilibrium with each other. The discrepancy between the experiments and these early calculations for the gas phase is not surprising, as it is well known today that the CNDO approximation does not take into account in an appropriate way the dipole-dipole interactions responsible for the dihedral angle, thus also leading to wrong rotational barriers. This was one of the reasons to implement the NDDO methods (retaining dipole-dipole interactions) as the MNDO [17] and later the AM1 [18] parametrization.

The results of our own calculations in terms of conformations and their relative energies are summarized in *Table 1*. The conclusion is that, independent of the substitu-

Table 1. *Stable Conformations Calculated for the threo-Diepoxides, Characterized by the CCCC Angles ϕ*
(the relative energy of the most stable conformer was set to zero)

Compound	AM1		3-21G		6-31G* AM1		6-31G* 3-21G	
	Con- former $\phi/^\circ$	Rel. energy $\Delta E/$ $\text{kJ}\cdot\text{mol}^{-1}$	Con- former $\phi/^\circ$	Rel. energy $\Delta E/$ $\text{kJ}\cdot\text{mol}^{-1}$	Con- former $\phi/^\circ$	Rel. energy $\Delta E/$ $\text{kJ}\cdot\text{mol}^{-1}$	Con- former $\phi/^\circ$	Rel. energy $\Delta E/$ $\text{kJ}\cdot\text{mol}^{-1}$
3	84	2.2	84	0.0	94 ^{a)}	0.0 ^{a)}	84	0.3
	267	0.0	256	14.6	242 ^{a)}	3.1 ^{a)}	256	0.0
5	90	3.6	86	0.0	90	0.0	86	0.0
	270	0.0	257	13.4	270	3.7	257	1.8
6	110	2.2	99	0.0	110	0.0	99	5.6
	260	0.0	267	8.5	260	2.6	267	0.0
7	130	3.6	115	0.0	130	3.0	115	5.5
	260	0.0	272	3.6	260	0.0	272	0.0
8	150	7.0			150 ^{b)}	18.5 ^{b)}	150 ^{c)}	22.9 ^{c)}
	270	0.0			270 ^{b)}	0.0 ^{b)}	270 ^{c)}	0.0 ^{c)}

^{a)} Calculation with 6-31G** basis set including full geometry optimization. ^{b)} 3-21G||MNDO Calculation.

^{c)} 3-21G||AM1 Calculation.

tion pattern, the *threo*-compounds adopt two different conformations (see *Newman* projections below). One of them has a dihedral CCCC angle ϕ between 80° and 150° , increasing monotonously with higher substitution; the second has an angle ϕ of *ca.* 260° independent of the degree of substitution, but varying between 240° and 270° according to the method and basis set used. As an example, the energy profile for the dihedral angle ϕ in **3** is shown in *Fig. 1*.

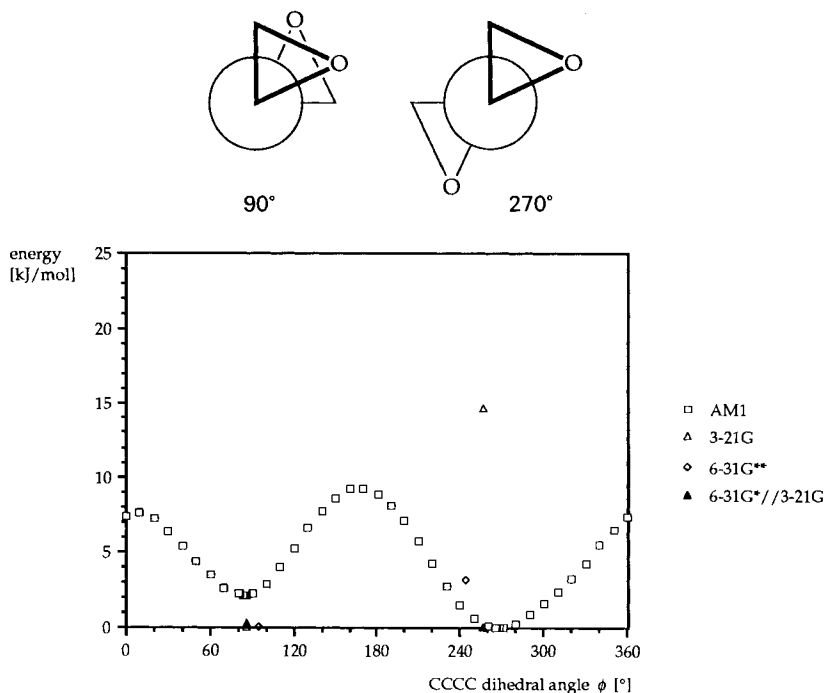


Fig. 1. Energy profiles of **3** as calculated by different methods. The points for 3-21G and 6-31G** show local minima on the profiles. Note that the point for 3-21G at 84° is nearly hidden by the one for 6-31G**//3-21G.

An inspection of framework molecular models of *threo*-diepoxides suggests a stable *transoid*-conformation with $\phi \approx 240^\circ$ and a stable *gauche*-conformation with $\phi \approx 120^\circ$, probably slightly distorted due to interaction of the oxygen lone-pairs. The second conceivable *gauche*-conformation is destabilized as the substituents R^2 and R^3 are directly pointing towards each other.

Overall, we have a rather clear cut picture regarding the structures, and we are quite confident that the two conformations indicated by the calculations are qualitatively correct, although the size of the angles may quantitatively change a little. We are less confident about the relative energies of the two conformations. We would have preferred to perform all optimizations with the 6-31G** basis set, but this was – with regard to the CPU time available – not feasible. The results for **3** with this basis set as well as the single-point calculations with the 6-31G* basis set suggest that the stabilities obtained with the 3-21G basis set are too unfavourable for the conformation with $\phi \approx 270^\circ$.

Overall, we would estimate that the two conformations have a very similar energy for the less substituted compounds, and that the smaller angle is preferred for the more highly substituted ones. *Su et al.* [11] estimated from their measurements for **3** that the conformation with the larger dihedral angle is *ca.* 1 kJ/mol more stable, which is in fair agreement with the 3 kJ/mol calculated with the 6-31G** basis set. Between these conformations, rotational barriers of 8–12 kJ/mol at an angle between 150 and 210° and of 8 kJ/mol (for **3**) – 70 kJ/mol (for **8**) between 350 and 40° were found. For compounds **7** and **8**, the rotational barrier would be high enough (40–70 kJ/mol) to prevent free rotation through a full 360° at room temperature.

erythro-Diepoxides. For compound **4**, measurements of two groups [8] [12] showed that in the crystal only a *trans*-conformation with a dihedral CCCC angle of 180° exists, whereas in the liquid state an equilibrium with two (degenerate) additional *gauche*-conformations with estimated angles of 60° and 300°, respectively, were found by *Arony et al.* [12] from *Kerr*-effect measurements. They estimated the *trans/gauche* ratio to be 20:80.

Table 2. *Stable Conformations Calculated for the erythro-Diepoxides, Characterized by the CCCC Angles ϕ*
(the relative energy of the most stable conformer was set to zero)

Compound	AM1		3-21G		6-31G** AM1		6-31G** 3-21G	
	Con- former $\phi/^\circ$	Rel. energy $\Delta E/$ $\text{kJ}\cdot\text{mol}^{-1}$	Con- former $\phi/^\circ$	Rel. energy $\Delta E/$ $\text{kJ}\cdot\text{mol}^{-1}$	Con- former $\phi/^\circ$	Rel. energy $\Delta E/$ $\text{kJ}\cdot\text{mol}^{-1}$	Con- former $\phi/^\circ$	Rel. energy $\Delta E/$ $\text{kJ}\cdot\text{mol}^{-1}$
4	110 ^{a)}	1.0	75	0.0	69 ^{b)}	0.0 ^{b)}	75	6.2
	180	0.0	180	2.4	180 ^{b)}	3.7 ^{b)}	180	0.0
	250 ^{a)}	1.0	285	0.0	291 ^{b)}	0.0 ^{b)}	285	6.2
9	90	1.3	70	0.0	85	3.2	70	1.8
	190 ^{a)}	0.7	186	8.5	190	0.0	186	0.0
	260	0.0	284	1.9	255	5.7	284	2.8
10	120	0.0			120	1.2		
			179	5.2			179	0.0
	250	0.3	275	0.0	250	0.0	275	4.3
11	120	0.2	92	0.0	120	1.9	92	1.5
	240	0.0	254	0.4	235	0.0	254	0.0
12	110	0.2			120 ^{c)}	3.0 ^{c)}	110 ^{d)}	0.1 ^{d)}
	230	0.0			230 ^{c)}	0.0 ^{c)}	230 ^{d)}	0.0 ^{d)}

^{a)} Shoulder. ^{b)} Calculation with 6-31G** basis set including full geometry optimization. ^{c)} 3-21G||MNDO Calculation. ^{d)} 3-21G||AM1 Calculation.

The results of our own calculations in terms of conformations and their relative energies are summarized in *Table 2*. For compounds **4**, **9**, and **10**, three conformations are predicted. However, if the H-atom in position R³ of the diepoxide (**4**, **9**, and **10**) is replaced by an alkyl group (**11** and **12**), there remain only two minima in the energy profile. Note that two of the three conformations of **4** are degenerate due to symmetry. Framework molecular models of this compound suggest that a *trans*- as well as two *gauche*-conformations should be stable, the latter being perhaps slightly destabilized sterically.

For **4**, the optimizations with the 6-31G** and 3-21G basis sets agree with the experiments cited, whereas the semiempirical and single-point calculations predict reversed relative stabilities of the conformers. The calculated energy difference, however, is small enough so that the relative stabilities could as well be reversed.

Whereas for **4**, **9**, and **10**, conformations between 70–120°, 180–190°, and 250–285° were found (see *Newman* projections below), **11** and **12** show only stable conformations between 90–120° and 230–255°. Fig. 2 shows how flat the potential is between 60° and 300°.

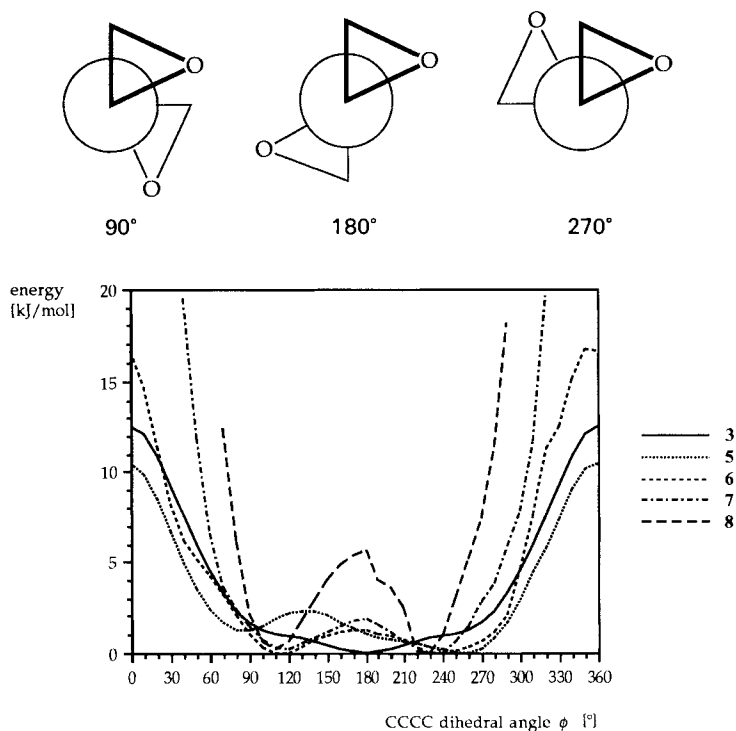


Fig. 2. Energy profiles calculated by AM1 for the different erythro-compounds

As shown in *Table 2*, the smaller angle of the *gauche*-conformation increases only slightly from *ca.* 70° (3-21G) in the less substituted compounds to *ca.* 90° (3-21G) in the more highly substituted substances. The angle of the *transoid*-conformation is roughly independent of the substitution in those compounds where it corresponds to a local energy minimum. The relative stabilities of the different stable conformations found depend much on the method and basis set applied, but overall it seems that they have very similar energies.

For **4**, **9**, and **10**, rotational barriers of 5–20 kJ/mol, and for **11** and **12** of *ca.* 10 kJ/mol at 180° and 40–70 kJ/mol at 360° were found. This means that the free rotation through a full 360° around the inter-epoxide bond is also hindered for the *erythro*-compounds at room temperature.

Conclusion. – For the unsubstituted *threo*- and *erythro*-diepoxides, **3** and **4**, respectively, our calculations predict conformations which are in agreement with the available experimental data. The scarce experimental as well as the calculated data in addition show that, for each of these two molecules, the stable conformations have similar energies. A comparison of the results of our calculations for the diepoxides with IR, X-ray, and electron-diffraction data for substituted bicyclopropyls (where dihedral angles around 60°, 180°, and 300° are reported [6]) again shows fair agreement. This agreement for the unsubstituted compounds on the one hand and the only slight dependence of the calculations on the applied method (AM1, *ab initio*) and basis set (3-21G, 6-31G*) on the other hand make us quite confident that the most stable conformations of substituted 1,2:3,4-diepoxides can be correctly predicted.

Finally, the question asked in the introduction, why hedamycin (**1**) and the similarly substituted model compound **2** adopt the same conformations in the crystal, can now be answered in a plausible way: our calculations show that the observed conformations for **1** with a torsion angle around the inter-epoxide bond of 252° (*i.e.* –108°) and that of **2** with 271° each correspond quite well to one of the minima on the energy profiles of *ent*-**6**⁵) and **10**, respectively. The fact that **1** and **2** crystallized in these specific conformations with almost identical torsion angles (and did not adopt one of the other conformations that appear to be stable according to our calculations) must be either due to a coincidence or to the specific interactions in the solid state.

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⁵) Note that **1** and **6** have opposite absolute configurations.

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