Density Functional Study of the Oxy-*Cope* Rearrangement[1])

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With the goal of explaining the very large rate acceleration in the anion-assisted *Cope* rearrangement, the behavior of the prototypes of the *Cope* rearrangements, namely hexa-1,5-diene (**4**), hexa-1,5-dien-3-ol (**5**), and the oxy anion **6** of the latter were compared. For this purpose, two-dimensional DFT (hybrid B3LYP functionals with 6-31G* basis set) potential-energy surfaces (PESs) were computed, based on two interatomic distances. As the reliability of DFT/B3LYP-computed energies can not be taken for granted, we first performed model computations on the experimentally well-studied bridged homotropylidenes **1**–**3**. Then, the transition states of the *Cope* rearrangements of 3-methylhexa-1,5-dien-3-ol (**7**), (2*Z*,4*Z*,7*Z*)-cyclonona-2,4,7-trien-1-ol (**9**), 1-methoxy-2-*endo*-vinylbicyclo[2.2.2]oct-5-en-2-*exo*-ol (**11**), and (1*S*,2*R*)-2-hydroxy-1-methyl-2-vinylbicyclo[4.4.0]dec-6-en-8-one (arbitrary numbering; **13**) and of their oxy anions **8**, **10**, **12**, and **14**, respectively, were computed by the same method. These examples were chosen because kinetic data have been measured for most of them (except for **13** and **14**) and/or because they furnished already important contributions to the discussion of the character of the *Cope* rearrangement. The computation of $\Delta G^{\neq}$ for a given temperature allowed to calculate the rate constants at that temperature for the different rearrangements and to compare them with the experimental data. In the cases of the neutral and anionic oxy-*Cope* rearrangements, the equation $\Delta\Delta G^{\neq} = 2.3026 \cdot RT \cdot \Delta pK_a$ suggested a correlation between the difference in the pK_a values of the pair of reactants and the pair of transition states and the change of the two free energies of activation.

Introduction. – According to *Swaminathan* [1], the first example of an oxy-*Cope* rearrangement documented in the literature seems to be the thermal conversion of (2*E*,6*E*)-octa-2,6-diene-4,5-diol to a substituted cyclopentenecarboxaldehyde reported by *Urion* [2] in 1934. The correct oxy-*Cope* mechanism was first described in 1964 by *Berson* and *Jones* [3]. The enormous rate acceleration of 10^{10}–10^{17} for the oxy-*Cope* rearrangement by deprotonation of the OH group in hexa-1,5-dien-3-ol was first documented by kinetic measurements by *Evans* and *Golob* in 1975 [4]. Five years later, *Evans* and *Nelson* [5] were able to conclude from their experiments with a 1,5-diene carrying stereogenic centers at both the C(3) and C(4) positions that in the change from OH to O^-, the stereochemical fidelity was maintained.

Swaminathan et al. [6] had used this same base-catalyzed rearrangement in 1962 for a then novel ring enlargement. *Swaminathan* and co-workers [7] studied the rearrangement of one enantiomer of the system, for which a concerted rearrangement would have given a specific optically active compound, whereas a racemic product would be expected if a non-concerted mechanism were operative. The fact that the diastereoisomer with reversed configuration at the OH-substituted C-atom also gave the

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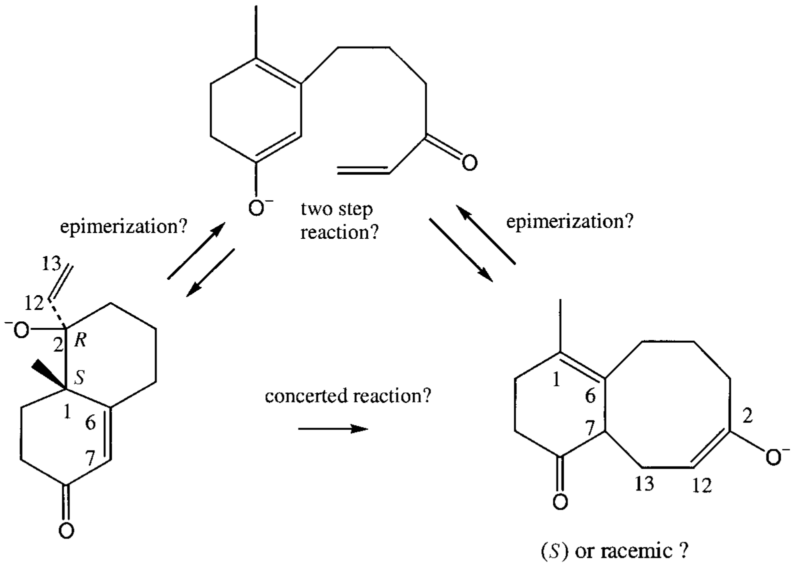
[1]) Preliminary results presented at the Poster Session of the International 'Conference on Reactive Intermediates and Reaction Mechanisms', Centro Stefano Franscini, Ascona, Switzerland, July 12–17, 1998.

rearrangement product under the KOH/aqueous MeOH reaction conditions suggested that a non-concerted path might be involved, or that base-catalyzed epimerization might have preceeded or followed a concerted oxy-*Cope* process (see *Scheme 1*).

Scheme 1



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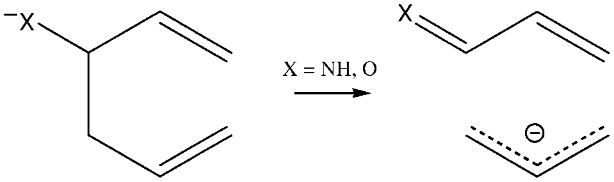
Since the starting alcohol was recovered with little loss of optical activity and with no evidence of formation of the racemic alcohol, the assumption of a reversible equilibrium between reactant and intermediate state had to be ruled out. In the same way, the possibility of a racemization of the product had to be discounted since the chiral product could be recovered unaffected [7]. This leaves two reaction mechanisms as highly probable: the concerted and the two-step reactions shown in *Scheme 1.*

Bunnage and *Nicolaou* [8] recently summarized two different effects by which the rate acceleration of the oxy-*Cope* reaction might be modulated: *a*) by the degree of alkoxide-metal dissociation, with a maximum acceleration obtained with a more 'naked' anion, and *b*) by the addition of [18]crown-6 as a ionophore. These two effects are merely different aspects of the same thing, *i.e.* of the difference in anionic character measured by alkoxide-metal dissociation in a favorable solvent, or driven by the addition of a crown ether. They rationalized the rate enhancement by the degree of conjugation of the substituent in the ground state relative to the transition state of the reaction. This stabilization of the oxy anion in the transition state relative to the ground state, according to *Bunnage* and *Nicolaou* [8], leads to a decrease in the free energy of activation $\Delta G^{\neq}$ and an increase in the rate for the reaction.

Evans and *Baillargeon* [9] attributed the acceleration to a bond-weakening effect of the anionic alkoxy group on the adjacent C(3)–C(4) bond. This was compared to model computations on methanol and methoxide by *Goddard* and co-workers [10]. Interestingly, however, no rate acceleration was observed in the *Cope* reaction with an

NH^- substituent despite the fact that calculations suggest that there should be the same bond-weakening effect as that produced by O^-. Recently, *Houk*, *Meyers*, and co-workers [11] rationalized the absent rate acceleration by calculations based on an intermediate complex of allyl anion and 'acrolein imine' (= prop-2-en-1-imine; *Scheme 2*). As a mater of fact, this intermediate complex corresponds to the one proposed for O^- by *Swaminathan* and co-workers [6][7] for O^- who believed that the additional carbonyl group (see *Scheme 1*) delocalized the anionic charge and caused a switch to an ionic mechanism.

Scheme 2



We present here density-functional theory (DFT) calculations for oxy-*Cope* and anion-accelerated *Cope* rearrangements for which, in most of the cases, some kinetic date a are available, and a new qualitative model that rationalizes the rate acceleration.

Computational Method. – The reliability of DFT-/B3LYP-computed [12] energies cannot be taken for granted, because the method essentially is parametrized. Therefore, we first performed model computations on the experimentally well-studied bridged homotropylidenes **1**–**3** before we attacked our actual problem. The fast and reversible valence isomerizations in barbaralane (= tricyclo[3.3.1.$0^{2,8}$]nona-3,6-diene; **1**)[2]), methylenebarbaralane (**2**), and barbaralone (**3**) are particularly interesting from the mechanistic point of view because they have a low barrier and are degenerate (*Scheme 3*). Our *ab initio* and DFT calculations of the potential-energy surfaces (PESs) of the three compounds **1**–**3** established the consistency of the experimental and DFT results, which was encouraging in view of our ultimate goal. Experimental activation parameters for the degenerate rearrangements of **1**–**3** are summarized in *Table 1.*

CASPT2N Studies on hexa-1,5-diene by *Borden* and co-workers [22] on the influence of the correlation energy indicated a concerted *Cope* reaction with synchronous breaking and forming of the bonds in the transition structure. DFT Computations of the B3LYP/6-31G* type by *Houk* and co-workers [23] confirmed this result. The energies for the chair- and boat-form transition states were in excellent agreement with the experimental results [24][25]. *Jiao* and *Schleyer* [26] also attained good agreement with the experimental data by means of one-determinant method which included electron correlation (*e.g.*, MP4SDTQ/31G*). According to them, the prototype of the *Cope* rearrangement is not a diradical, but rather an aromatic mechanism. *Davidson* and co-workers [27] developed MP2 methods for multireference wave functions, which corrected the overestimation of the diradical character of the CASSCF wavefunction. When this error was corrected, the *Dewar*-type diradical

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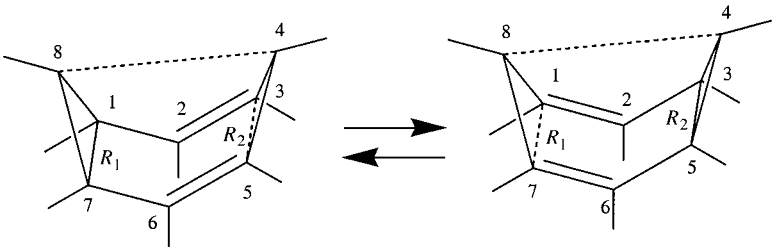
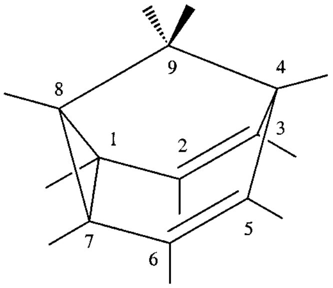
[2]) The numbering of the barbaralane skeleton is arbitrary.

Scheme 3





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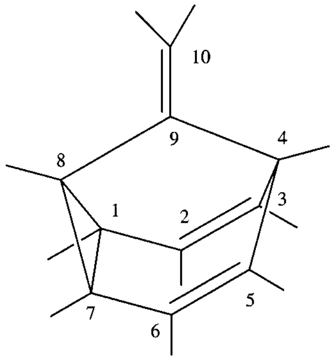

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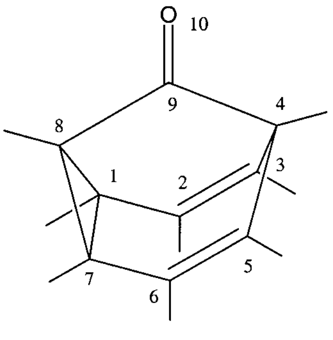

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intermediate no longer occurred as a minimum on the PES, and the aromatic transition state moved to shorter bond length. Some of these *ab initio* calculations were summarized by *Borden* and *Davidson* [28] and *Baumann* and *Voellinger-Borel* [29]. The most recent quantum-chemical computations [22][23][26–29] excluded with certainty the first of three possible mechanisms, namely *a*) *via* an intermediate state (IS) with the interatomic distances $R_1 \approx R_2$ (see *Scheme 3*) being short, *b*) *via* the aromatic six-electron transition state (TS), or *c*) *via* two more-or-less separated allyl radicals (IS with $R_1 \approx R_2$ being long).

Table 1. *Experimental Kinetic Parameters for the* Cope *Rearrangement of* **1**–**3**

	Ref.	$\log_{10}A$ [kcal mol^{-1}]	E_a [kcal mol^{-1}]	k [s^{-1}]	$\Delta G^{\neq}$ [kcal mol^{-1}]	$\Delta H^{\neq}$ [kcal mol^{-1}]	$\Delta S^{\neq}$ [e.u.]	T [°C]
1	[13]	13.6 ± 0.3	8.6 ± 0.2	$1.73 \cdot 10^{7}$	–	–	–	–
	[14]	5.7 ± 0.3	10.4 ± 0.3	$2.60 \cdot 10^{7}$	–	9.8 ± 0.3	11.5 ± 0.3[a])	0
		–	–	$0.99 \cdot 10^{6}$	–	–	–	-40
	[15]	12.90	7.71	–	7.60	7.32	-0.73	–
	[16]	13.19 ± 0.03	8.22 ± 0.02	$1.48 \cdot 10^{7}$	7.67 ± 0.06	7.81 ± 0.02	0.49 ± 0.14[a])	25
	[17]	–	–	–	7.74	7.69 ± 0.09	-0.80 ± 0.48	-73
2	[18]	13.7	10.5	–	9.5	10.0	2.3	-89.5
	[16]	13.28 ± 0.02	9.55 ± 0.02	$1.98 \cdot 10^{6}$	8.86 ± 0.05	9.12 ± 0.02	0.9 ± 0.1	25
3	[19]	–	8.1 ± 0.4	–	–	–	–	–
	[18]	–	–	–	10.5	–	–	-41
	[20]	–	11.5 ± 0.1	–	10.1 ± 0.1	10.9 ± 0.1	2.7 ± 0.7	–
	[21]	–	–	–	10.2 ± 0.1	–	–	-93.2
	[16]	12.84 ± 0.01	10.06 ± 0.02	$2.90 \cdot 10^{5}$	9.99 ± 0.03	9.55 ± 0.02	-1.50 ± 0.06	25

[a]) It is noteworthy that $\Delta S^{\neq}$ determined by ^{1}H-NMR and the actual ^{13}C-NMR value differ strongly from each other (11.5 and 0.49 e.u.). The results of [14] had only preliminary character, and the measured data of [16] are the most recent and reliable values.

In the present work, the PESs of the *Cope* rearrangements of **1**–**3** were computed either with UMP2/3-21G or with B3LYP/6-31G* geometries. With the first-mentioned geometries, single-point UHF/6-31G** computations were performed to generate the NOs, and subsequently, UNO-CASSCF/6-31G** calculations furnished the energies (for details of the UNO-CASSCF/6-31G** method, see *Yamaguchi* [30] and *Pulay* and co-workers [31]). All calculations were performed with 'Gaussian94' [32], and structures depicted with 'Molden' [33].

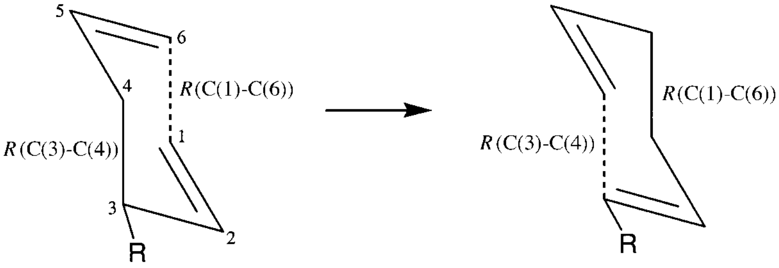
The numerical results of the computations for **1**–**3** are collected in *Table 2*. The B3LYP/6-31G* computations were in good agreement with the experimental results, whereas the CASSCF/6-31G**-computed heat of formations of the UMP2/3-21G-computed structures of the TSs of C_{2v} symmetry were too high. The interatomic distances $R_1 = R_2$ (see *Scheme 3*) determined on the CASSCF/6-31G** PESs for the TS were with *ca.* 2.2 Å, longer than those of the B3LYP/6-31G* method ($R_1 = R_2 = 2.083$ (**1**), 2.065 (**2**), and 2.059 Å (**3**)). This means that the reaction has more synchronous [34] character than reflected in the UMP2/3-21G-based geometries, which are more similar to two weakly coupled allyl radicals (IS with $R_1 \approx R_2$ being long) [29]. The force-constant matrices were diagonalized, and only one negative eigenvalue was found, in agreement with *McIver* and *Komornicki* [35]. The B3LYP/6-31G* enthalpies of activation for **1**–**3** were in agreement with our experimental results for these molecules (see *Tables 1* and *2*), and the entropies of activation of -1.97, -1.93, and -1.72 e.u. were close to zero, like our measured values ($+0.49$, $+0.9$, and -1.5 e.u.) given in *Table 1*. The DFT-computed differences of the reaction rates (*Table 2*) satisfactorily reproduced the experimental values (*Table 1*). These results encouraged us to use the DFT/B3LYP method for our actual problem. In addition to this fact, we recognize that promising results were recently obtained by *Borden* and *Houk*, and co-workers [36] and *Paquette* and *Houk*, and co-workers [37] for *Cope* and oxy-*Cope* reactions that validate this choice of computational method.

Table 2. *B3LYP/6-31G*-Computed Kinetic Parameters for the* Cope *Rearrangement of* **1**–**3** (*T* 298.15 K)

	$\log_{10}A$	E_a [kcal mol^{-1}]	k [s^{-1}]	$\Delta G^{\neq}$ [kcal mol^{-1}]	$\Delta H^{\neq}$ [kcal mol^{-1}]	$\Delta S^{\neq}$ [e.u.]
1	12.73	7.06	$3.60 \cdot 10^7$	7.14	6.55	– 1.97
2	12.81	7.88	$3.94 \cdot 10^6$	8.45	7.88	– 1.93
3	12.41	9.48	$7.90 \cdot 10^5$	9.40	8.89	– 1.72

Potential-Energy Surfaces. – In a first step, we extended the method just-presented to define PESs for the *Cope* rearrangements of hexa-1,5-diene (**4**; R = H), hexa-1,5-dien-3-ol (**5**; R = OH), and its oxy anion **6** (R = O$^-$). As *Minkin et al.* [38] stated, the reaction-coordinate method often employed in practical calculations may be incorrect in some cases. Only when the internal coordinate being varied is really sufficiently close to the genuine reaction coordinate, does this method locate the TS correctly. On the other hand, possible transition states can be more reliably identified on two-dimensional PESs. For this purpose, DFT (hybrid B3LYP functionals [11] and the 6-31G* basis set) computations were performed, based on the two interatomic distances *R*(C(1)–C(6)) and *R*(C(3)–C(4)), as shown in *Scheme 4*. These were chosen because they correspond to the bonds formed (*R*(C(1)–C(6))) and broken (R(C(3)–C(4))) during the reaction. The calculations were performed with 'Gaussian94' [32].

Scheme 4



4 R=H

5 R=OH

6 R=O$^-$

The surface for dienol **5** appeared to be slightly perturbed (TS: *R*(C(1)–C(6)) = 2.050 Å, *R*(C(3)–C(4)) = 2.006 Å, chair) in comparison with the symmetrical surface of diene **4** (TS: *R*(C(1)–C(6)) = *R*(C(3)–C(4)) = 1.967 Å; chair), whereas that of oxy anion **6** was strongly asymmetrical (TS: *R*(C(1)–C(6)) = 3.219 Å, *R*(C(3)–C(4)) = 2.310 Å; chair), as illustrated in *Fig. 1*.

It is also probable that the degree and character of this asymmetry determines the reaction pathway. Therefore, we studied, in addition to the above prototypes, the transition states of the *Cope* rearrangement of 3-methylhexa-1,5-dien-3-ol (**7**), (2*Z*,4*Z*,7*Z*)-cyclonona-2,4,7-trien-1-ol (**9**), 1-methoxy-2-*endo*-vinylbicyclo[2.2.2]oct-5-en-2-*exo*-ol (**11**), and (1*S*,2*R*)-2-hydroxy-1-methyl-2-vinylbicyclo[4.4.0]dec-6-en-8-one (arbitrary numbering; **13**) and of their oxy anions **8**, **10**, **12**, and **14**, respectively (see *Figs. 2–5*). As for **5** and **6**, we found also for **7**, **9**, **11**, and **13** slightly perturbed TSs (TS

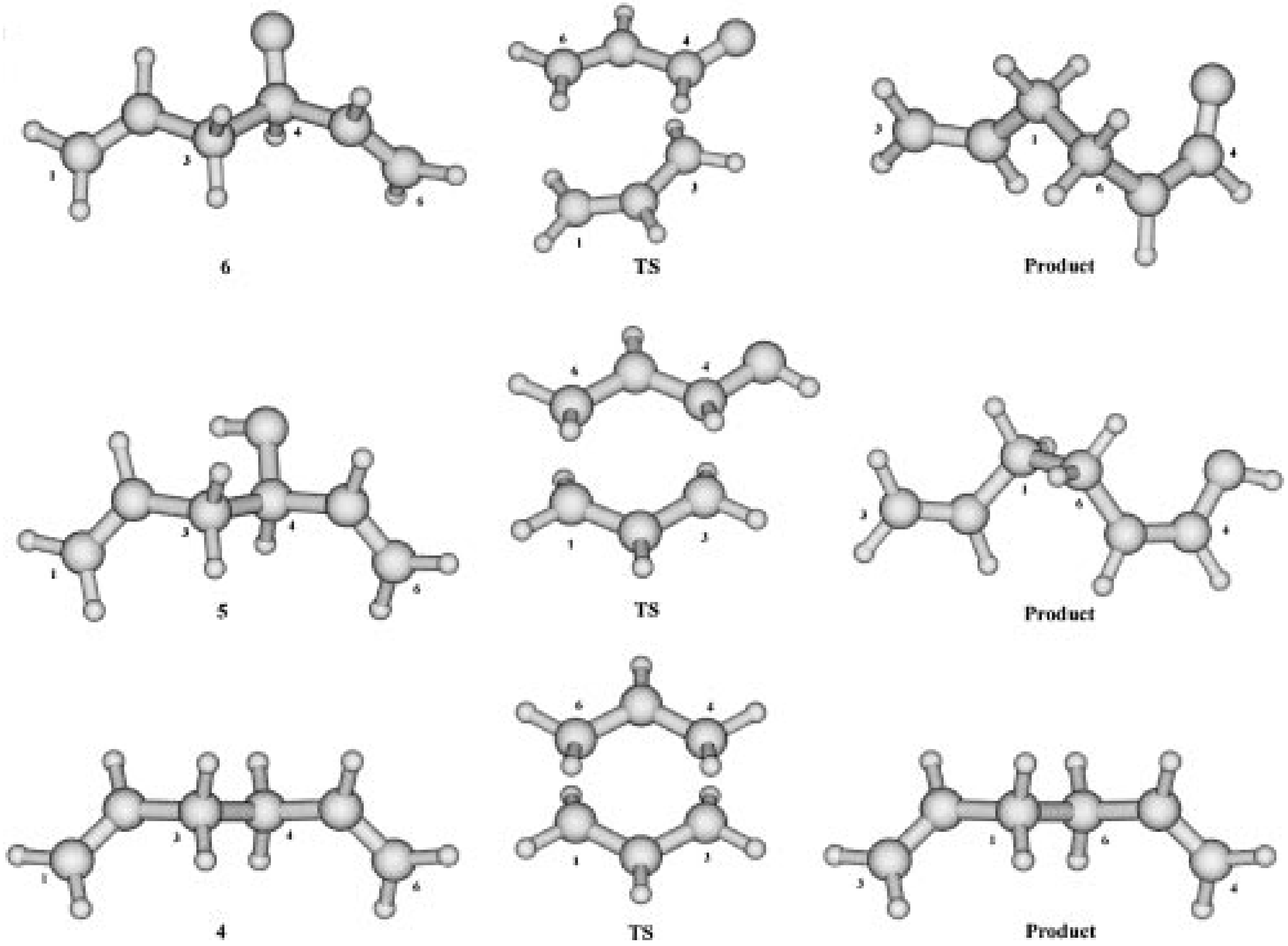


Fig. 1. Cope *rearrangement of hexa-1,5-diene* (**4**), *of hexa-1,5-dien-3-ol* (**5**), *and of its oxy anion* **6**. Diene **4**: $R(C(1)-C(6)) = 5.752$ Å, $R(C(3)-C(4)) = 1.548$ Å, TS from **4**: $R(C(1)-C(6)) = R(C(3)-C(4)) = 1.967$ Å, chair; product from **4**: $R(C(1)-C(6)) = 1.548$ Å, $R(C(3)-C(4)) = 5.752$ Å. Dienol **5**: $R(C(1)-C(6)) = 5.611$ Å, $R(C(3)-C(4)) = 1.552$ Å; TS from **5**: $R(C(1)-C(6)) = 2.050$ Å, $R(C(3)-C(4)) = 2.006$ Å, chair; product from **5**: $R(C(1)-C(6)) = 1.553$ Å, $R(C(3)-C(4)) = 5.530$ Å. Oxy anion **6**: $R(C(1)-C(6)) = 5.900$ Å, $R(C(3)-C(4)) = 1.604$ Å; TS from **6**: $R(C(1)-C(6)) = 3.219$ Å, $R(C(3)-C(4)) = 2.310$ Å, chair; product from **6**: $R(C(1)-C(6)) = 1.562$ Å, $R(C(3)-C(4)) = 5.159$ Å. Numbering of TSs and products corresponds to that of the reactants.

from **7**: R(C(1)−C(6)) = 2.078 Å, R(C(3)−C(4)) = 2.045 Å, chair, TS from **9**: R(C(3)−C(7)) = 2.155 Å, R(C(1)−C(9)) = 2.100 Å, boat; TS from **11**: R(C(5)−C(10)) = 2.209 Å, R(C(1)−C(2)) = 2.186 Å, boat; TS from **13**: R(C(7)−C(13)) = 2.809 Å, R(C(1)−C(6)) = 2.811 Å, boat), whereas the ones for **8**, **10**, **12**, and **14** were strongly asymmetrical (TS from **8**: R(C(1)−C(6)) = 3.409 Å, R(C(3)−C(4)) = 2.241 Å, chair; TS from **10**: R(C(3)−C(7)) = 2.957 Å, R(C(1)−C(9)) = 1.977 Å, boat; $\mathrm{TS_1}$ from **12**: R(C(5)−C(10)) = 3.752 Å, R(C(1)−C(2) = 2.187 Å, boat $\mathrm{TS_1}$ from **14**: R(C(7)−C(13)) = 5.633 Å, R(C(1)−C(2)) = 1.717 Å, chair-like). For **12** and **14**, we found non-concerted pathways. In the case of **12**, the IS was characterized by the relevant bond length R(C(5)−C(10)) = 3.207 Å, and R(C(1)−C(2)) = 3.261 Å, and by a 3.0 kcal $\mathrm{mol^{-1}}$ lower energy than the reactant oxy anion **12**. For **14** ((1*S*,2*R*)-configuration), the most favorable reaction pathway showed, when carried out with NaOMe/MeOH or KOMe/THF, the above-described intermediate state IS, which had biradical character, with R(C(7)−C(13)) = 4.312 Å and R(C(1)−C(2)) = 4.837 Å, and which was 11.5 kcal $\mathrm{mol^{-1}}$ lower in energy than the reactant oxy anion **14**, as predicted by *Swaminathan* and co-workers. According to the latter, the reaction is concerted when carried out with chiral substrates and KH/THF [7]. In view of the fact that [3,3]-sigmatropic rearrangements occur in a suprafacial manner, the chirality center 7 in the product from **14** must have (*S*)-configuration (*cf. Scheme 1*). The more stable the intermediate product, the more probable are racemic products. The computed structures of the TSs and the IS are illustrated in *Fig. 5*.

Thermochemistry. – The translation of the PESs to kinetic parameters that can be compared to experiment was done by solving the vibrational problem at each minimum and TS. A scaling factor of 0.9804 was used for the frequencies, as suggested by *Wong* [39].

The computed data were compared with the published experimental data for the condensed phase (see *Table 3*). For all the computed species, we found a high rate acceleration of the reaction when going from the oxy-*Cope* to the anion-assisted oxy-*Cope* rearrangement: $k(\mathbf{6})/k(\mathbf{5}) = 1.56 \cdot 10^{20}$, $k(\mathbf{8})/k(\mathbf{7}) = 1.10 \cdot 10^{20}$, $k(\mathbf{10})/k(\mathbf{9}) = 8.04 \cdot 10^{20}$, $k(\mathbf{12})/k(\mathbf{11}) = 2.00 \cdot 10^{23}$, and $k(\mathbf{14})/k(\mathbf{13}) = 8.01 \cdot 10^{24}$. For the neutral systems, our computed data for the gas phase corresponded rather well to the experimental data for the condensed phase, with exception of the value for compound **7**: $\Delta H^{\neq}$ of **4** 33.3 *vs.* 33.5, of **7** 30.4 *vs.* 20.5, and of **9** 31.3 *vs.* 33.9 kcal $\mathrm{mol^{-1}}$; E_a of **11** 33.9 *vs* 35.9 kcal $\mathrm{mol^{-1}}$. For the anionic species, the computed and experimental data were less similar, though always with the correct trend, *i.e.*, being much smaller than those for the neutral systems: $\Delta H^{\neq}$ of **8** 5.5 *vs.* 12.6; and of **10** 3.2 *vs.* 14.8 kcal $\mathrm{mol^{-1}}$; E_a of **12** 2.7 *vs.* 18.2 kcal $\mathrm{mol^{-1}}$. This deviation could be due to the difference of the data for the gas and those for the condensed phase. Then this would mean that, in the gas phase, the reactions would be obviously more accelerated than in the condensed phases chosen for the experiments.

Discussion. – The *Mulliken* population analysis (see *Fig. 6*) indicated increasing heterolytic character for the TSs when going from **4** to **6**.

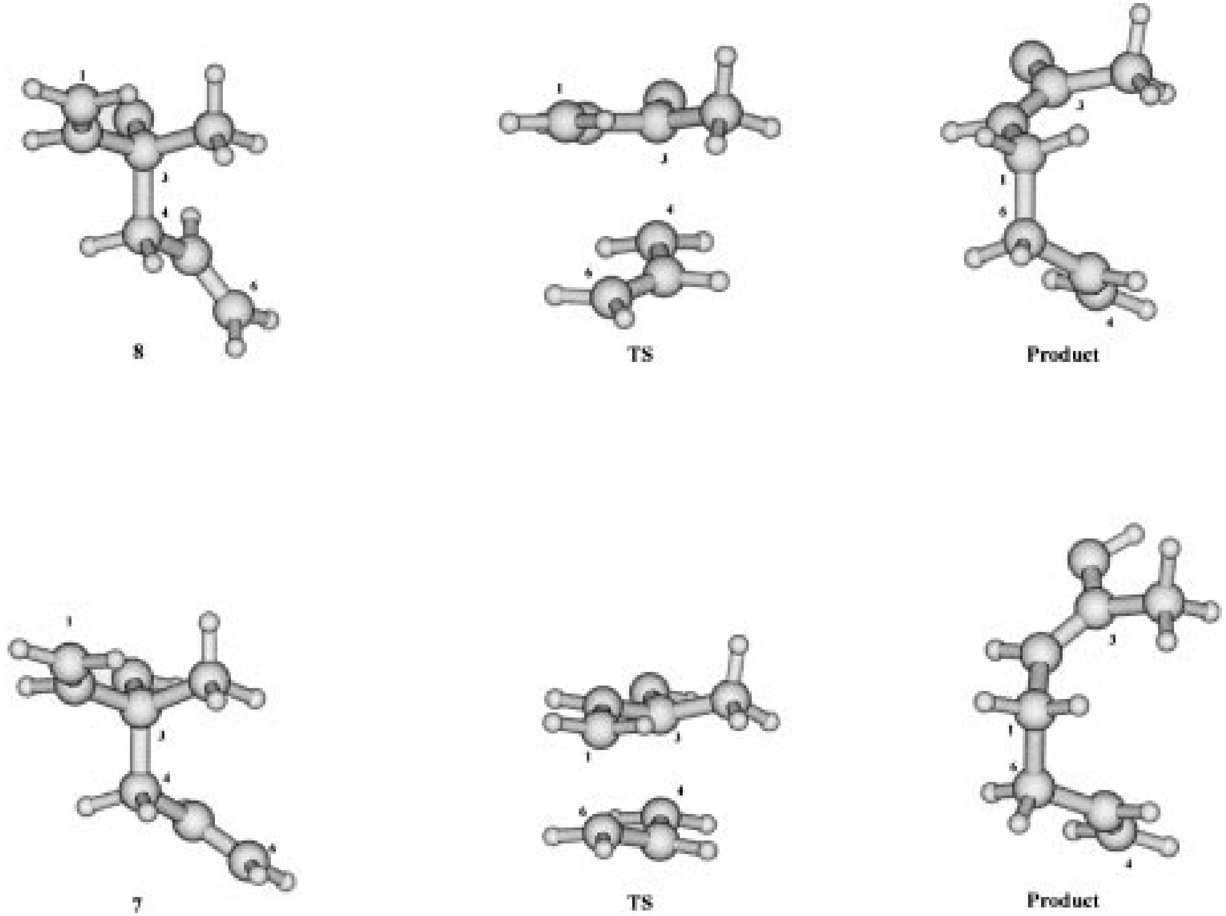


Fig. 2. Cope *rearrangement of 3-methylhexa-1,5-dien-3-ol* (**7**) *and oxy anion* **8**. Dienol **7**: R(C(1)−C(6)) = 5.710 Å, R(C(3)−C(4)) = 1.563 Å; TS from **7**: R(C(1)−C(6)) = 2.078 Å, R(C(3)−C(4)) = 2.045 Å, chair; product from **7**: R(C(1)−C(6)) = 1.553 Å, R(C(3)−C(4)) = 5.508 Å. Oxy anion **8**: R(C(1)−C(6)) = 6.012 Å, R(C(3)−C(4)) = 1.613 Å; TS from **8**: R(C(1)−C(6)) = 3.409 Å, R(C(3)−C(4)) = 2.241 Å, chair; product from **8**: R(C(1)−C(6)) = 1.562 Å, R(C(3)−C(4)) = 5.192 Å. Numbering of TSs and products corresponds to that of the reactants.

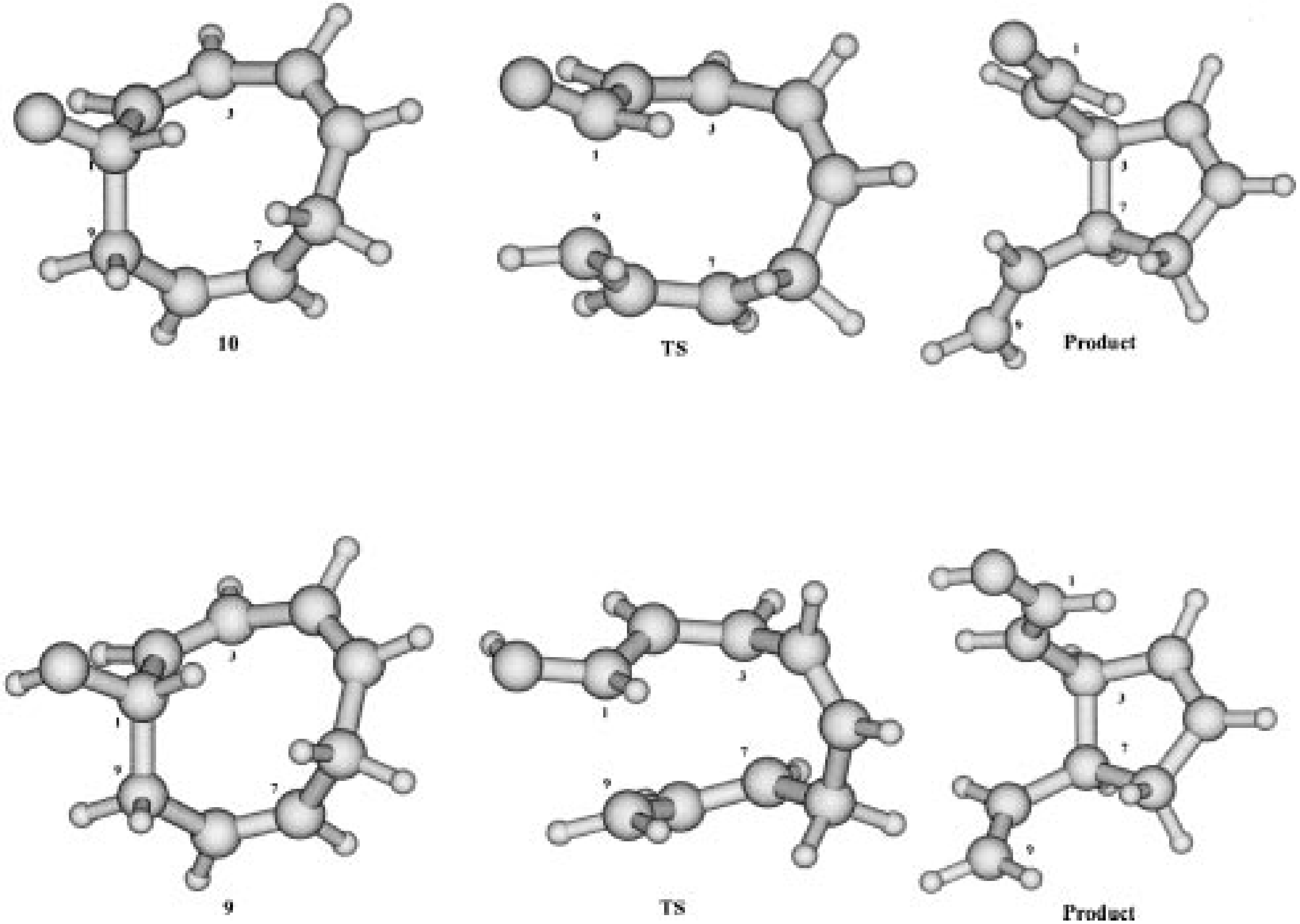


Fig. 3. Cope *rearrangement of (2*Z*,4*Z*,7*Z*)-cyclonona-2,4,7-trien-1-ol* (**9**) *and the oxy anion* **10**. Trienal **9**: *R*(C(3)–C(7)) = 3.016 Å, *R*(C(1)–C(9)) = 1.569 Å; TS from **9**: *R*(C(3)–C(7)) = 2.155 Å, *R*(C(1)–C(9)) = 2.100 Å, boat (the chair configuration is 1.17 kcal mol^{-1} lower in energy but sterically unfavorable); product from **9**: *R*(C(3)–C(7)) = 1.584 Å, *R*(C(1)–C(9)) = 4.471 Å. Oxy anion **10**: *R*(C(3)–C(7)) = 3.070 Å, *R*(C(1)–C(9)) = 1.689 Å; TS$_1$ from **10**: *R*(C(3)–C(7)) = 2.957 Å, *R*(C(1)–C(9)) = 1.977 Å, boat (the chair configuration is 2.31 kcal mol^{-1} higher in energy and sterically unfavorable); IS from **10**: *R*(C(3)–C(7)) = 2.957 Å, *R*(C(1)–C(9)) = 1.977 Å; TS$_2$ from **10**: *R*(C(3)–C(7)) = 2.957 Å, *R*(C(1)–C(9)) = 1.977 Å; product from **10**: *R*(C(3)–C(7)) = 1.600 Å, *R*(C(1)–C(9)) = 4.512 Å. Numbering of TSs and products corresponds to that of the reactants.

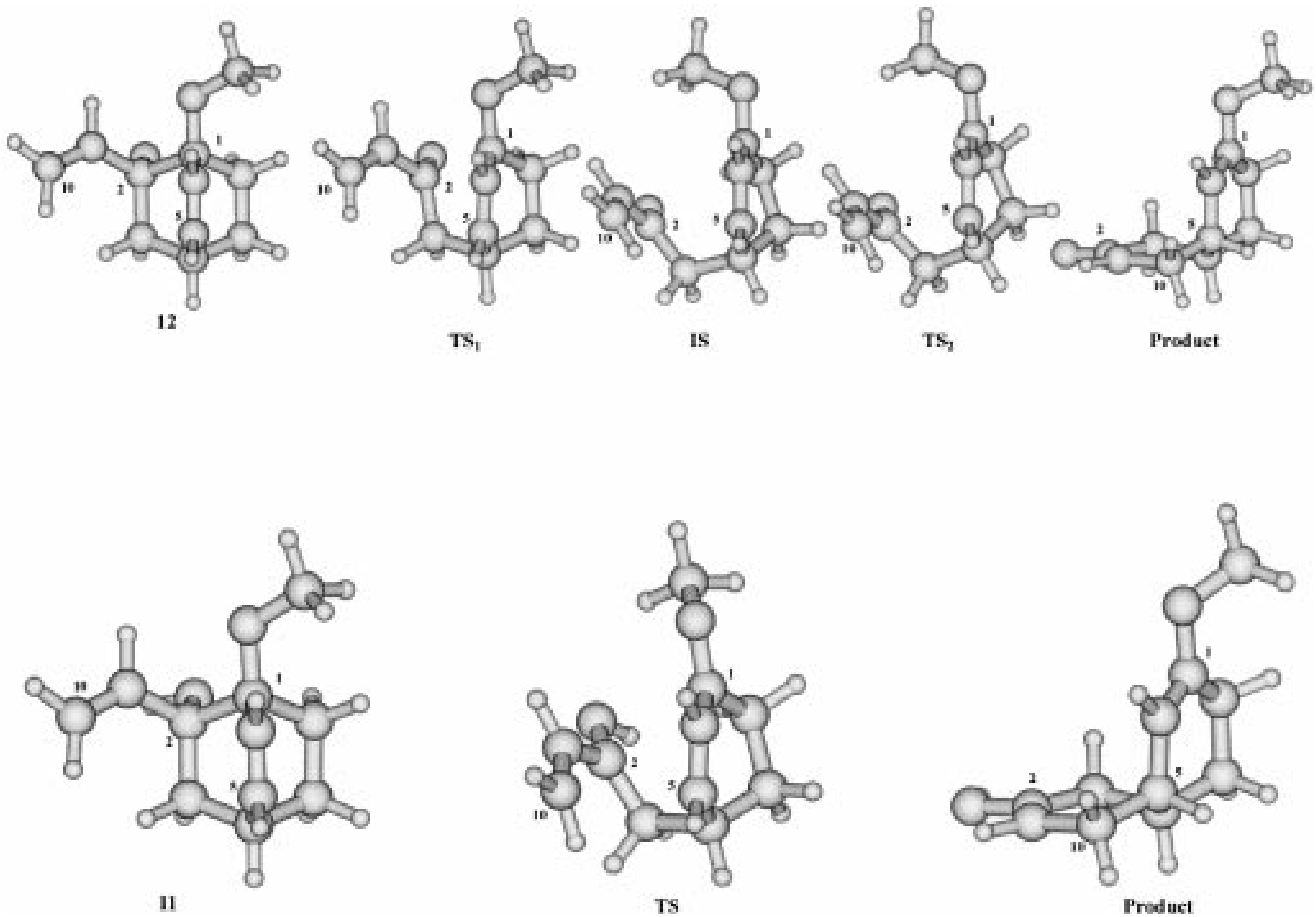


Fig. 4. Cope *rearrangement of 1-methoxy-2-*endo-*vinylbicyclo[2.2.2]oct-5-en-2-*exo-*ol* (**11**) *and the oxy anion* **12**. Enol **11**: $R(\mathrm{C}(5)-\mathrm{C}(10)) = 4.070$ Å, $R(\mathrm{C}(1)-\mathrm{C}(2)) = 1.579$ Å; TS from **11**: $R(\mathrm{C}(5)-\mathrm{C}(10)) = 2.209$ Å, $R(\mathrm{C}(1)-\mathrm{C}(2)) = 2.186$ Å, boat; product from **11**: $R(\mathrm{C}(5)-\mathrm{C}(10)) = 1.544$ Å, $R(\mathrm{C}(1)-\mathrm{C}(2)) = 4.137$ Å. Oxy anion **12**: $R(\mathrm{C}(5)-\mathrm{C}(10)) = 4.077$ Å, $R(\mathrm{C}(1)-\mathrm{C}(2)) = 1.687$ Å; TS$_1$ from **12**: $R(\mathrm{C}(5)-\mathrm{C}(10)) = 3.752$ Å, $R(\mathrm{C}(1)-\mathrm{C}(2)) = 2.187$ Å, boat; IS from **12**: $R(\mathrm{C}(5)-\mathrm{C}(10)) = 3.207$ Å, $R(\mathrm{C}(1)-\mathrm{C}(2)) = 3.261$ Å; TS$_2$ from **12**: $R(\mathrm{C}(5)-\mathrm{C}(10)) = 2.819$ Å, $R(\mathrm{C}(1)-\mathrm{C}(2)) = 3.453$ Å, boat; product from **12**: $R(\mathrm{C}(5)-\mathrm{C}(10)) = 1.539$ Å, $R(\mathrm{C}(1)-\mathrm{C}(2)) = 4.199$ Å. The actual orientation of the MeO group corresponds to the energy minima of the different structures. Numbering of TSs and products corresponds to that of the reactants.

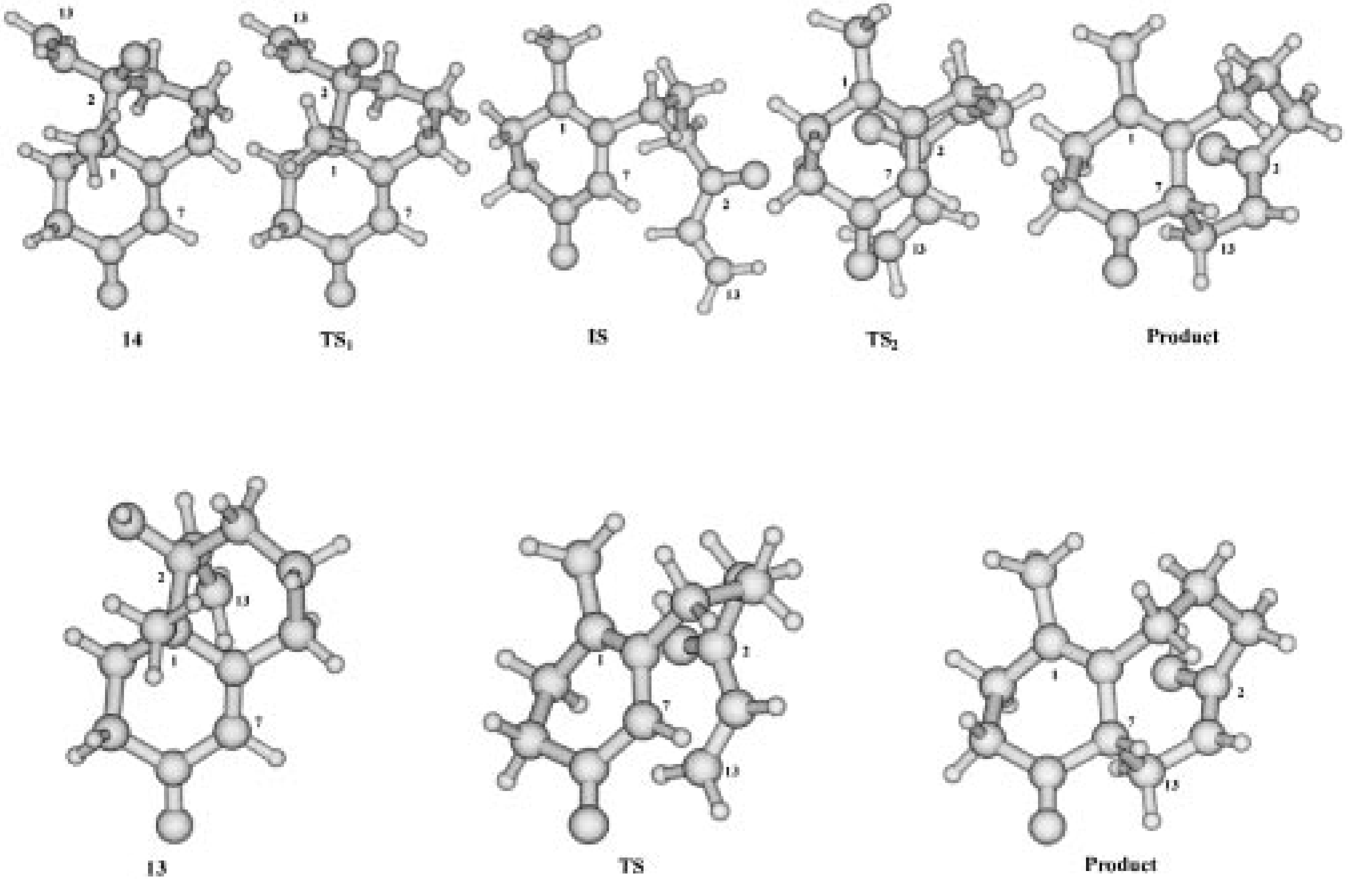


Fig. 5. Cope *rearrangement of (1*S*,2*R*)-2-hydroxy-1-methyl-2-vinylbicyclo[4.4.0]dec-6-en-8-one* (arbitrary numbering; **13** *and the oxy anion* **14**). Hydroxy-enone **13**: $R(C(7)-C(13)) = 3.897$ Å, $R(C(1)-C(2)) = 1.573$ Å, TS from **13**: $R(C(7)-C(13)) = 2.809$ Å, $R(C(1)-C(2)) = 2.811$ Å, boat; product from **14** ((*S*)-configuration): $R(C(7)-C(13)) = 1.584$ Å, $R(C(1)-C(2)) = 3.782$ Å). Oxy anion **14** ((1*S*,2*R*)-configuration): $R(C(7)-C(13)) = 5.720$ Å, $R(C(1)-C(2)) = 1.695$ Å; TS$_1$ from **14**: $R(C(7)-C(13)) = 5.633$ Å, $R(C(1)-C(2)) = 1.717$ Å, chair-like; IS from **14**: $R(C(7)-C(13)) = 4.312$ Å, $R(C(1)-C(2)) = 4.837$ Å; TS$_2$ from **14**: $R(C(7)-C(13)) = 3.642$ Å, $R(C(1)-C(2)) = 3.886$ Å, boat-like; product from **14** (*S*)-configuration): $R(C(7)-C(13)) = 1.620$ Å, $R(C(1)-C(2)) = 3.627$ Å. Numbering of TSs and products corresponds to that of the reactants.

Table 3. *B3LYP/6-31G*-Computed and Measured (*in parentheses*) Kinetic Parameters of the* Cope *Rearrangement of* **4**–**14** (*T* 298.15 K)

	ΔH_R a) [kcal mol^{-1}]	$\Delta H^{\neq}$ [kcal mol^{-1}]	$\Delta S^{\neq}$ [e.u.]	$\Delta G^{\neq}$ [kcal mol^{-1}]	k [s^{-1}]	E_a [kcal mol^{-1}]	$\log_{10}A$
4	0.0	33.3 (33.5)b)	– 10.0 (– 13.8)b)	36.3	$1.63 \cdot 10^{-14}$ ($1.54 \cdot 10^{-15}$)b)	33.9	11.0 (10.4)b)
5	– 3.2	31.4	– 8.1	33.8	$1.05 \cdot 10^{-12}$	32.0	11.5
6	– 21.0	6.2	– 0.1	6.3	$1.64 \cdot 10^{8}$	6.8	12.8
7	– 7.1	30.4 (20.5)c)	– 7.0 (– 15.2)c)	32.5 (25.0)c)	$8.63 \cdot 10^{-12}$	31.0	11.7
8	– 23.8	5.5 (12.6)c)	0.9 (– 28.3)c)	5.2 (21.0)c)	$9.47 \cdot 10^{8}$	6.1	13.4
9	– 1.5	31.3 (33.9)d)	– 0.3	31.3 (34.4)d)	$5.82 \cdot 10^{-11}$	31.9 (34.5)d)	13.2
10	– 19.9	3.2 (14.8)d)	1.0	2.9 (21.3)d)	$4.68 \cdot 10^{10}$	3.8 (15.4)d)	13.5
11	– 18.1	33.4	– 1.2	33.8	$1.06 \cdot 10^{-12}$	33.9 (35.9)e)	12.9
12	– 29.2	2.1	0.4	2.0	$2.11 \cdot 10^{11}$	2.7 (18.2)e)	13.3
13	– 9.7	36.2	1.0	35.9	$2.67 \cdot 10^{-14}$	36.8	13.5
14	– 14.9	1.5	– 1.8	2.0	$2.14 \cdot 10^{11}$	2.1	12.8

a) Enthalpy change associated with the reaction. b) [24]. c) [40]. d) [41]. e) [4].

At the limit of a complete heterolysis, which would be more closely approached in polar solvent than in the gas phase (this computation), a simple relationship between the rate acceleration and the difference in ΔpK_a between each pair of reactant/transition state can be postulated3). The relation of *Eqn. 1* stems from the correlation between the large difference in the pK_a values of the pair of reactants and the pair of transition states and the remarkable change $\Delta\Delta G^{\neq}$ in the free energies of activation of the *Cope* reactions of the molecules **5** and **6**. Because **5** and **6** show some heterolytic character, we approximated the difference in the free energies of activation by the difference of the pK_a values of allyl alcohol [43] and protonated crotonaldehyde [44], *i.e.*, by *Eqn. 2*.

$$\Delta\Delta G^{\neq} = 2.3026 \cdot RT \cdot \Delta pK_a \tag{1}$$

$$\Delta pK_a(\text{exp.}) = (15.6 - (-4.8)) = 20.4 \tag{2}$$

As the experimental pK_a values of our compounds are not available, we computed these values by the program 'SPARC' [45], which predicts the values strictly from molecular structure by means of reactivity models. The program was trained on 2400 compounds and tested on 4338 pK_as for 3685 compounds. The root-mean-square deviation for the acids and the amino reaction center is in the region of 0.35 pK_a units. 'SPARC' predicted the following pK_a values: **5**, 16.6; **7**, 18.2; **9**, 16.7; **11**, 16.2; **13**, 18.4. With the computed differences of the enthalpies of reaction when going from the alcohol to the oxy anion and with *Eqn. 1*, we found the following shifts for our 5 compounds: 20.2, 20.0, 20.8, 23.3, and 24.9 kcal mol^{-1}. With these shifts, we predicted the following pK_as for the oxy anions (in parentheses the corresponding 'SPARC' values are given): **6**, – 3.6 (– 5.5); **8**, – 1.8 (– 5.2); **10**; – 4.1 (– 5.2); **12**, – 7.1 (– 4.9); **14**, – 6.5 (– 4.9). These values are astonishingly close to each other when we keep in mind

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3) This idea was put forward independently by *Golob* [42].

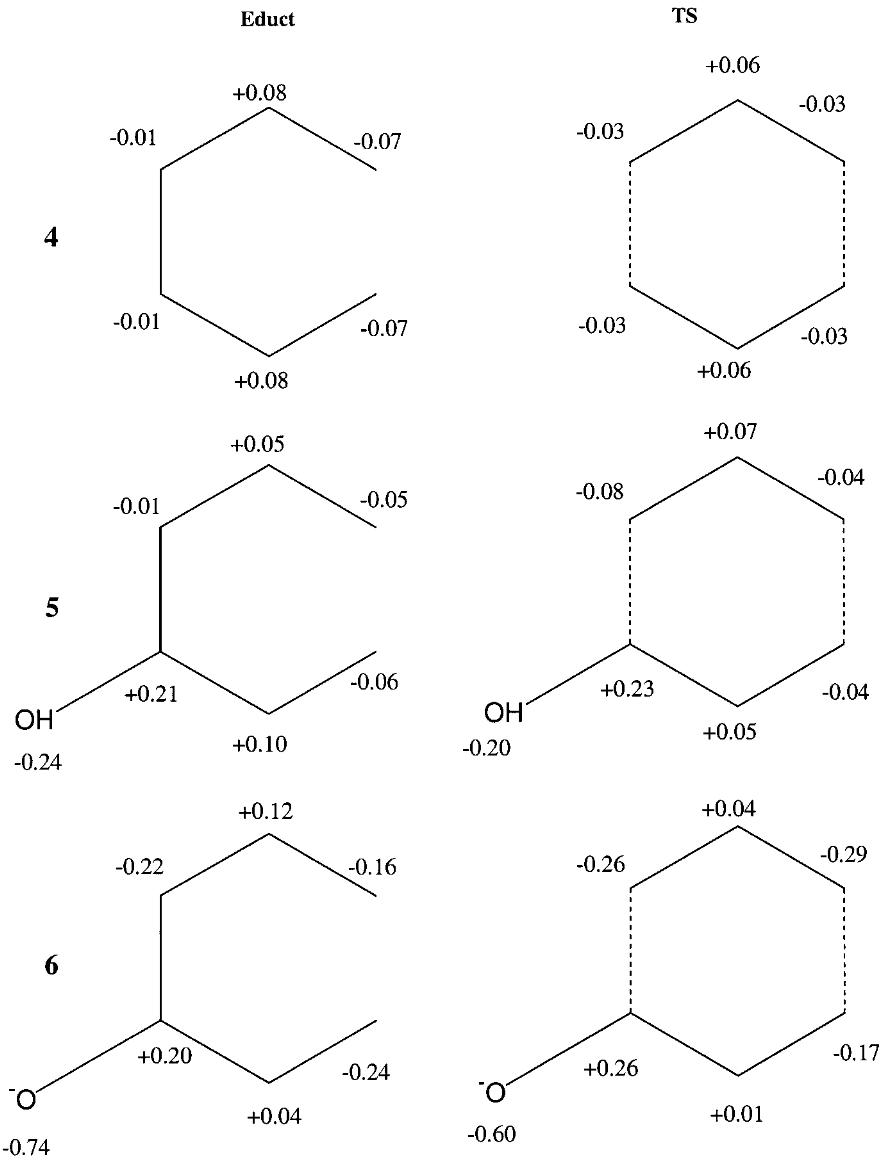

Fig. 6. Mulliken *population analysis for the transition structures reached from* **4**–**6**

that we are considering very large pK_a shifts. The deviations of the experimental enthalpies of activation from the calculated ones may eventually be attributed to the solvation effects.

In *Fig. 7*, the computed thermochemical cycle for the *Cope* reaction of **5** and **6** is depicted. The proton affinities (*PA*) and the $\Delta G^{\neq}$ values correspond to the computational results of this work. It is noteworthy to mention that the *PA* value for the

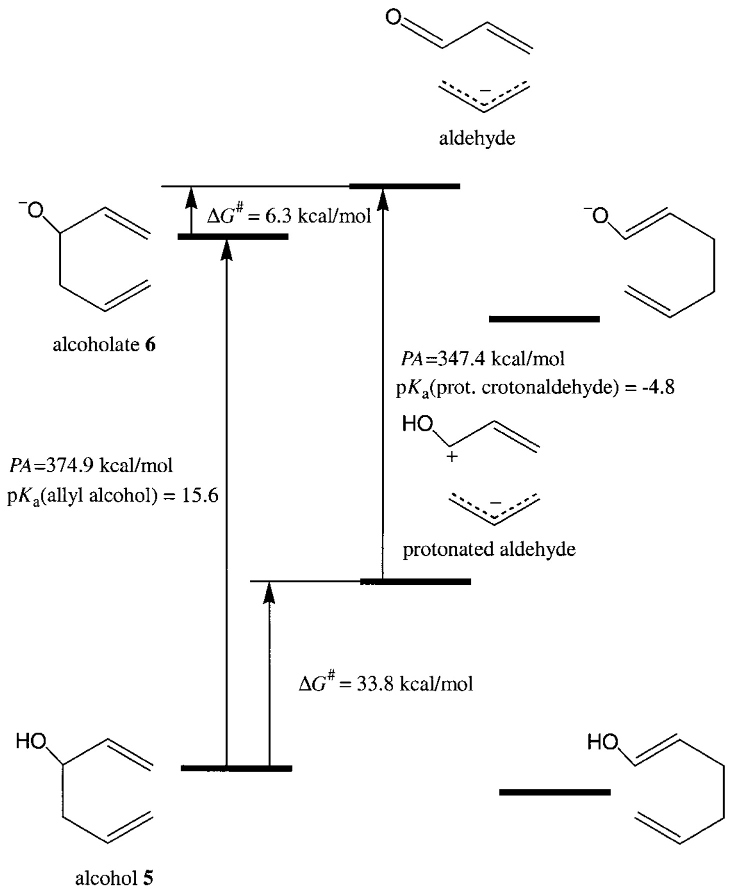

Fig. 7. *Thermocycle for the gas-phase* Cope *rearrangements of the alcohol and the alkoxide.* $\Delta\Delta G^{\neq} \sim \Delta pK_a$. The experimental p$K_a$ values are taken from [43] and [44], the $\Delta G^{\neq}$ and PA values are computed in this work by B3LYP/6-31G* (see also *Table 3*).

protonation of the TS (347.4 kcal/mol) does not correspond to the experimental *PA* of crotonaldehyde at 373 K in the gas phase (186.1 kcal/mol) [46]. This deviation must be attributed to the additional stabilization of the protonated aldehyde by the allyl anion as the computed value for crotonaldehyde is rather close to the experimental value: 193.5 kcal/mol. Our model gives support to the idea of an intermediate complex proposed by *Swaminathan* and co-workers [6] [7] (*Scheme 2*) favored by the additional carbonyl group (see *Scheme 1*), which delocalizes the anionic charge and causes a switch to the ionic mechanism proposed in [6] [7]. As can be seen from *Table 3*, the enthalpy of reaction in the cases of the four examples (namely **7**, **9**, **11**, and **13** and their oxy anions **8**, **10**, **12**, and **14**) are equally strongly changed. The correlation of $\Delta\Delta G^{\neq}$ in the oxy-*Cope* *vs.* the anion-accelerated *Cope* rearrangement with the difference in pK_a between allyl alcohol and protonated crotonaldehyde would seem to assume a stepwise 'heterolytic' mechanism for the oxy-*Cope* rearrangement of **4**–**6**, as the *Mulliken* population analysis suggested. Even if complete heterolysis does not occur, the correlation should work as long as the fully charge-separated structures are energetically close to the actual transition states. For the oxy anions, the transition states do indeed resemble the limiting structures in *Fig. 7*.

Our model gives a reasonable explanation for the two main effects leading to the rate acceleration found by *Evans* and *Golob* [4] and summarized by *Bunnage* and *Nicolaou* [8]: *a*) the degree of alkoxide-metal dissociation, with a maximum acceleration obtained with a more 'naked' anion and *b*) the amount of added [18]crown-6 as a ionophore in that the degree of ion pairing should influence the thermochemical cycle in *Fig. 7*.

The computations were performed on the workstation cluster in our laboratory (including IBM and DEC workstations), which was installed by *Supercomputing Systems AG*, Zurich. We would like to thank Prof. *John Baldwin*, Syracuse University, for carefully reading our manuscript and for his useful advice. The literature search of Mr. *Josef Meienberger* is gratefully acknowledged.

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