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The Dowd–Beckwith ring expansion: a theoretical study

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Abstract—UB3LYP/6-311++G(d,p) and ROMP2/6-311++G(d,p)//UB3LYP/6-311++G(d,p) calculations including the effect of benzene solvent through the PCM-UAHF method render a concerted mechanism without fragmentation as the most favourable one for the Dowd–Beckwith radical ring expansion of the bromomethyl adduct of methyl cyclopentanone-2-carboxylate to yield methyl cyclohexanone-3-carboxylate. The corresponding concerted TS is a bicyclic alcoxy radical.
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Among the methods leading to the synthesis of medium-sized rings the free radical methods for ring expansion play an important role.[1] One of these synthetic strategies is the so-called Dowd–Beckwith reaction,[1–4] which consists in the expansion of the ring of β-keto esters. Particularly, one-carbon ring expansion of β-keto esters is an important procedure with many potential applications.

Two reaction mechanisms have been proposed for one-carbon Dowd–Beckwith ring expansions (see Scheme 1). According to the first one, (A), the formation of the primary radical by addition of a radical-generating reagent is followed by attack on the ketone carbonyl yielding the intermediate cyclopropyloxy radical, which then by cleavage gives the ring expanded product. The second mechanism proposed is a fragmentation mechanism in which ring opening to an α-substituted acrylate is followed by β-addition of the acyl radical to the double bond (B). In the one-carbon ring expansion it is difficult to differentiate between these two mechanistic proposals.
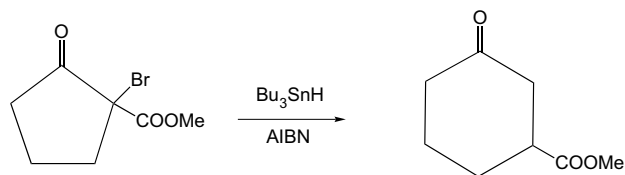
Given that computational chemistry methods are able to supply structural and energetic information on chemical
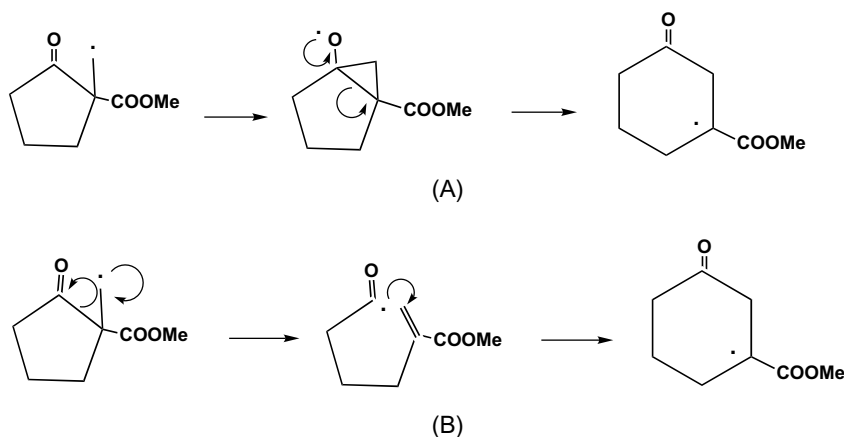
Scheme 1.

Scheme 2.

reaction mechanisms on the molecular level we undertook a theoretical investigation of these two mechanisms for the expansion of the bromomethyl adduct of methyl cyclopentanone-2-carboxylate to yield methyl cyclohexanone-3-carboxylate (see Scheme 2).

Quantum chemical computations were performed using the spin-unrestricted DFT (density functional theory) method UB3LYP,[5] which eliminates the large spin contamination generally encountered with unrestricted Hartree–Fock (UHF) wave functions,[6] and the ROMP2 method with the basis set 6-311++G(d,p). All the critical structures located along the reaction coordinates corresponding to the two above-mentioned mechanisms were optimised and characterised by frequency calculations in the gas phase at the UB3LYP/6-311++G(d,p) theory level. ROMP2/6-311++G(d,p)//UB3LYP/6-311++ G(d,p) single point calculations were also carried out.[7] ΔG values were also evaluated within the ideal gas, rigid rotor and harmonic oscillator approximations.[8] A pressure of 1 atm and 298.15 K of temperature were assumed in the calculations. Solvent effects were taken into account by means of single point UB3LYP/6-311++G(d,p) and ROMP2/6-311++G(d,p) calculations on the gas-phase UB3LYP/6-311++G(d,p) optimised geometries with the PCM (polarisable continuum method) method[9,10] with the UAHF (united atom Hartree–Fock) parameterisation.[11] A value of the relative dielectric constant of 2.247 was used to simulate benzene as the solvent used in the experimental work. All the calculations were performed with the GAUSSIAN98 series of programs.[12]

Figure 1 presents the optimised geometries of the transition states (TS) and the intermediate located. Table 1 collects the relative electronic energies, and Gibbs energies of all the critical structures both in gas phase and in solution.

Figure 2 displays the ROMP2/6-311++G(d,p)//UB3LYP/6-311++G(d,p) Gibbs energy profiles in solution corresponding to the two studied mechanisms.
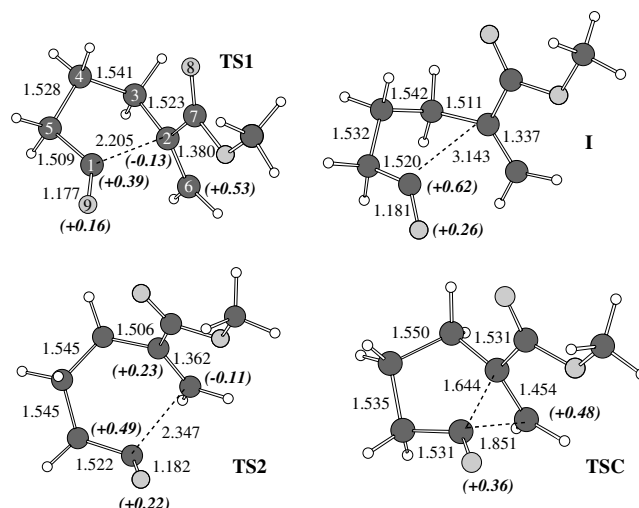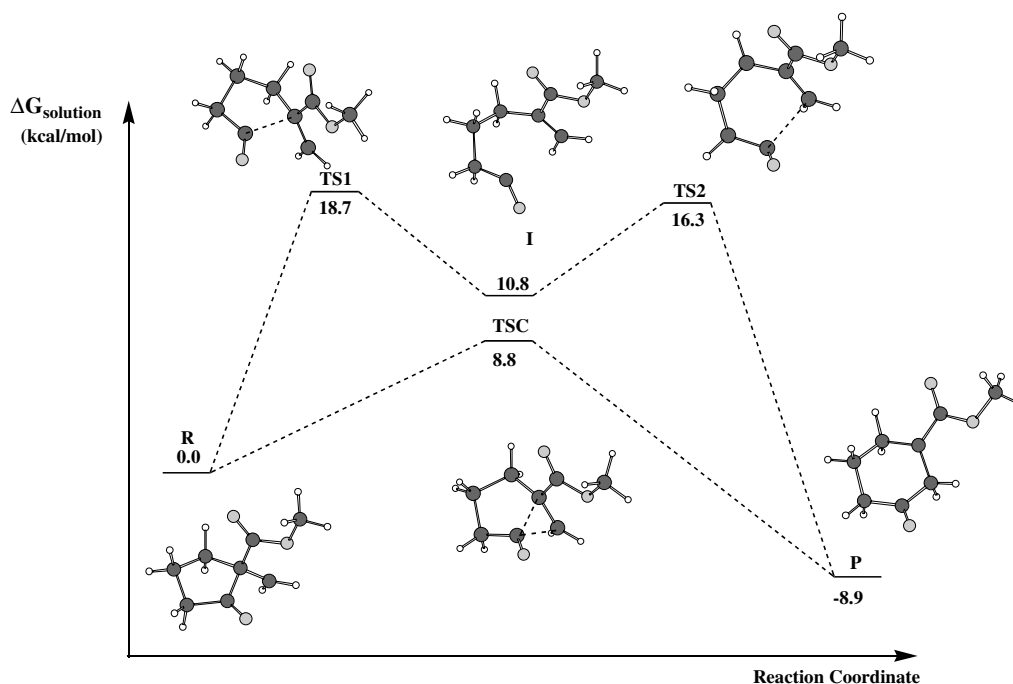

Figure 1. UB3LYP/6-311++G(d,p) optimised geometries for the TSs and the intermediate involved in the mechanisms of the radical expansion reaction of Dowd–Beckwith. Bond lengths are given in Å. In bold and within parentheses the most important NBO atomic spin densities are given.

Table 1S displays the absolute electronic energies, the ZPVE corrections, and the ΔH and $-T\Delta S$ values, and Table 2S collects the cartesian coordinates of all the critical structures located as supplementary material. Unless otherwise stated, we will present in the text the ΔG values in solution.

According to our UB3LYP results the mechanism with fragmentation proceeds in two steps. In the first one the free radical originally formed, **R**, which presents the α unpaired electron localised at C6, evolves through a TS, **TS1**, (11.9 kcal/mol) in which the C–C bond to be broken is considerably elongated presenting a bond length of 2.205 Å. At **TS1** the α spin population is mainly distributed among C6 (total NBO spin density = +0.53), C1 (+0.39), and O9 (+0.16), C2 presenting a certain spin polarisation (−0.13). **TS1** proceeds into an intermediate, **I** (4.4 kcal/mol) in which the α spin population is located mainly at C1 (+0.62) and O9 (+0.26) with practically no spin polarisation. This intermediate evolves through a TS **TS2** (10.1 kcal/mol) in which the new C–C bond to delimitate the final expanded ring is starting to form and presents a bond length of 2.347 Å. At **TS2** the α spin is located mainly at C1 (+0.49), C2 (+0.23) and O9 (+0.22) while C6 is spin polarised (−0.11). The expanded product, **P**, has an

Table 1. Relative UB3LYP/6-311++G(d,p) and ROMP2/6-311++G(d,p)//UB3LYP/6-311++G(d,p) electronic energies including ZPVE correction ($\Delta(E_{\text{elec}}+\text{ZPVE})$), Gibbs free energies in the gas phase ($\Delta G_{\text{gas phase}}$), Gibbs free energies of solvation ($\Delta\Delta G_{\text{solvation}}$), and Gibbs free energies in solution ($\Delta G_{\text{solution}}$), in kcal/mol, for the structures involved in the radical ring expansion of Dowd–Beckwith

Structures	UB3LYP/6-311++G(d, p)				ROMP2/6-311++G(d,p)//UB3LYP/6-311++G(d,p)			
	$\Delta(E_{\text{elec}} + \text{ZPVE})$	$\Delta G_{\text{gas phase}}$	$\Delta\Delta G_{\text{solv.}}$	$\Delta G_{\text{solution}}$	$\Delta(E_{\text{elec}} + \text{ZPVE})$	$\Delta G_{\text{gas phase}}$	$\Delta\Delta G_{\text{solv.}}$	$\Delta G_{\text{solution}}$
R	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
P	−16.5	−16.3	−1.2	−17.5	−9.6	−7.6	−1.3	−8.9
I	4.2	2.9	1.5	4.4	9.4	9.4	1.4	10.8
TS1	10.7	11.1	0.8	11.9	16.6	17.9	0.8	18.7
TS2	9.6	9.6	0.4	10.1	16.1	16.0	0.4	16.3
TSC	10.7	11.6	−0.8	10.8	9.5	9.9	−1.1	8.8

Figure 2. ROMP2 Gibbs energy profiles (kcal/mol) in solution for both the mechanism with fragmentation and the concerted mechanism without fragmentation.

energy of −17.5 kcal/mol. Therefore, the rate determining step is the first one (**TS1**) with a Gibbs energy barrier in solution of 11.9 kcal/mol.

The mechanism without fragmentation is concerted and along it the initial free radical evolves into **P** through a TS, **TSC**, with a Gibbs energy barrier in solution of 10.8 kcal/mol which corresponds to a bicyclic alcoxy radical in agreement with a previous proposal.[2] At **TSC** the C–C bond to be broken is only moderately stretched (1.644 Å) while, simultaneously, the new C–C bond that will close the expanded six-membered product ring is starting to form (1.851 Å). At this concerted TS there is practically no spin polarisation and the α spin population is distributed basically between C6 (+0.48) and O9 (+0.36). Thus the concerted mechanism without fragmentation is the most favourable one by 1.1 kcal/mol. It is interesting to note that in UB3LYP electronic energy including the ZPVE both mechanisms are competitive as they present the same energy barrier (see Table 1). Thermal energy slightly favours **TSC** whereas entropy disfavours it over **TS1** (see Table 1S). However the decisive factor determining the lower Gibbs energy barrier for **TSC** in solution is the interaction with solvent that clearly favours **TSC**, which has the largest dipolar moment in solution, 3.25 D (**TS1** and **TS2** have dipole moments of 1.91 D and 2.51 D, respectively).

ROMP2/6-311++G(d,p)//UB3LYP/6-311++G(d,p) calculations yield **TS1**, **I** and **TS2** about 6–7 kcal/mol less stable than reactants compared to the UB3LYP results and reduce the exothermicity of the process to −8.9 kcal/mol. **TS1** remains the rate determining TS. In contrast, **TSC** becomes stabilised by 2 kcal/mol. The ROMP2 method disfavours clearly the mechanism with fragmentation already in electronic energy and renders

the concerted mechanism, which is also favoured by solvent effects, as the most favourable one by 9.9 kcal/mol in Gibbs free energy in solution (see Table 1).

In summary, PCM(UAHF) calculations in benzene as solvent at the ROMP2/6-311++G(d,p)//UB3LYP/6-311++G(d,p) theory level render a concerted mechanism without fragmentation as the most favourable one by 9.9 kcal/mol for the Dowd–Beckwith radical ring expansion of the bromomethyl adduct of methyl cyclopentanone-2-carboxylate to yield methyl cyclohexanone-3-carboxylate. The corresponding concerted TS is a bicyclic alcoxy radical in agreement with a previous proposal.[2]

Supplementary data

Tables 1S (absolute electronic energies and ZPVE corrections) and 2S (cartesian coordinates of all the critical structures) are available for download. Supplementary data associated with this article can be found, in the on-line version, at doi:10.1016/j.tetlet.2004.09.147.

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