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Origins of Selectivity in Conjugate Additions of Alkenylphosphonates to Lithiated Bislactim Ethers: A Semiempirical Study

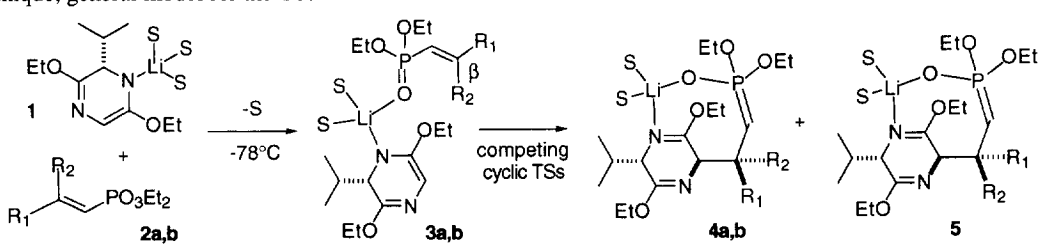
Vicente Ojea, María Ruiz, Juan Vilar and José Mª Quintela*

Departamento de Química Fundamental e Industrial, Facultade de Ciencias, Universidade da Coruña. Campus A Zapateira, A Coruña 15071. Spain

Abstract: The stereoselective conjugate additions of alkenyl and butadienylphosphonates to lithiated bislactim ethers have been studied at the semiempirical level. In the gas phase, an initial lithium-phosphoryl coordination to form a disolvated chelate complex without energy barrier is followed by the rate-determining reorganization through competitive eight-membered cyclic transition structures. A *compact vs. relaxed* transition state model reproduces the sense and degree of the experimental stereoselection. Copyright © 1996 Elsevier Science Ltd

2-Amino-4-phosphonobutanoic acid (AP4) derivatives have become interesting compounds due to their selective affinity to excitatory amino acid receptors in the central nervous system [1] and their isosterism with biologically significant phosphorylated amino acids [2]. Thus, we have recently developed a new stereoselective approach to AP4 derivatives by using a highly face-selective Michael addition of alkenylphosphonates to a chiral glycine enolate in the key step of the synthesis.[3] The stereochemical outcome of this reaction was found to be dependent on the configuration of the acceptor, as was previously observed with other conjugate additions to stereodefined enolates. In this manner, the addition of lithiated bislactim ethers to *E* or *Z* alkenylphosphonates leads to *anti* or *syn* adducts with a higher diastereomeric excess than that observed in corresponding additions to 2-alkenoates[4]. In pursuance of extending the applicability of alkenylphosphonates and related compounds in asymmetric synthesis, we describe herein a theoretical study of the possible reaction pathway associated with these stereoselective additions of lithiated Schöllkopf's bislactim ethers to alkenyl and butadienylphosphonates.

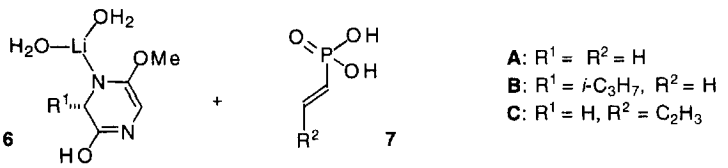
By analogy with the Zimmermann-Traxler model for aldol additions, Heathcock and Oare have suggested that the stereochemical course of enolate Michael additions to α,β-unsaturated carbonyl compounds can be rationalized assuming the participation of cyclic, rate-determining transition structures (TSs).[5] Bernardi *et al.* have studied this hypothesis by *ab initio* methods, and have verified that eight-membered TSs account for the experimental results.[6] Based on these precedents, the reaction between the lithium enolate **1** and the alkenylphosphonates **2a,b** should involve an initial phosphoryl-lithium coordination to form the stable chelate complexes **3a,b** (see Scheme 1). Subsequently, reorganization of these intermediates through competing eight-membered TSs would initially afford the phosphonate carbanions **4a,b** and **5**. According to such a model, the diastereoselective formation of **4a,b** would be determined by the energy difference between the possible cyclic TSs resulting from the enolate attack (*anti* to the isopropyl group) to each of the prochiral faces at the β-carbon of the alkenylphosphonate. As the stereochemical outcome of the addition to *E* and *Z* alkenylphosphonates complement each other, the reaction must always take place on the same side of the alkene moiety (*Si* and *Re* faces of the β-carbon in **2a** and **2b**, respectively), and thus, both processes could be rationalized considering a unique, general model for the TSs.



Scheme 1

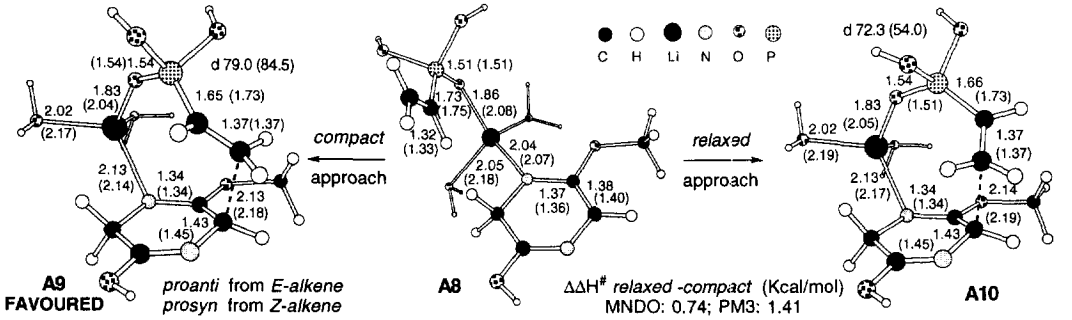
As application of *ab initio* methods to a problem of this size would be prohibitive in terms of computational effort, in this exploratory scanning of the reaction possibilities we have used both MNDO and PM3 semiempirical methods.[7] MNDO has proven to be reliable for studying large organolithium compounds, in spite of its well known shortcomings,[8] while PM3, although tested on relative few systems, appears to improve calculation of hypervalent molecules and also to be particularly suited for mechanistic studies on lithium amides and phosphonates [9]. In order to speed up the calculations without compromising the reliability of the data generated, we have chosen the simpler prototypes **A-C(6+7)**, as minimal molecular models sustaining the intrinsic potentialities of the real systems (see figure 1). Enolates were considered to react as monomers, assumed complete dissociaton of the possible oligomeric clusters in strong donor solvent.[10] Thus, water molecules were used to mimic the ethereal solvent coordinated to lithium.

Figure 1



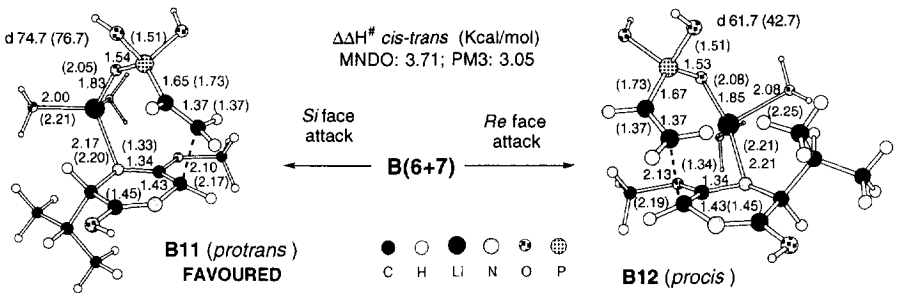
In the gas phase[11] for case **A**, the first step of the addition corresponds to the formation of a stable chelate complex without energy barrier. Thus, approaching the phosphoryl oxygen to the lithium atom of the disolvated monomeric enolate results in a continuous stabilization of the system, to give the disolvated chelate **A8** as the first stationary point (see scheme 2).[13] Low energy conformations with either s-*cis* or s-*trans* configuration on the alkenylphosphonate were accesible for this adduct,[14] and thus, both of them were taken into consideration for the TSs location. To define the potencial energy profile for the rearrangement, the distance between the α-carbon of enolate and the β-carbon of alkenylphosphonate was used as the reaction coordinate, and was held constant between 1.8 and 2.8 Å, while the remaining parameters were optimized. Full optimization of the geometries with maximum energy with respect to the formation of the CC bond resulted in only two different TSs, **A9** and **A10**, consequence of the enolate addition on each of the faces of the acceptor double bond. Both geometries show a synclinal conformation on the acceptor moiety,[15] with a high CCPO torsional angle (*ca.* 75°), suggesting an effective stabilization of the forming phosphonate carbanion by negative hyperconjugation ($n_C-\sigma^*_{P=O}$ interaction).[9b,16] Thus, the two competing TSs clearly differ in the sense of the synclinal arrangement around the forming CC bond. The lower energy structure **A9** (CCCC dihedral *ca.* +60°), resembles the *compact* approach proposed by Sevin in enamine Michael additions,[17] while **A10** (CCCC dihedral *ca.* -30°), with a *relaxed* acceptor/pirazine interaction, is related to the sterically disfavoured models considered by Heactcock in the additions to enones.[5] Although the TSs calculated at MNDO and PM3 levels were found to be very similar, the PM3 structures show a better correlation with previous theoretical calculations and experimental determinations for related lithium amides and phosphonate carbanioms.[9] PM3 method clearly improves the bonding/binding lithium-heteroatom interactions, giving rise to a tighter chelation that may explain the higher difference between the activation energies for the competing TSs. As the sense of the π-face selectivity observed in the additions to stereogenic alkenylphosphonates can only be rationalized by evoking a *compact* approach involving the most stable TS **A9**, the proposed semiempirical model adequately accounts for the experimental trend. Moreover, assuming a Boltzmann distribution at the reaction temperature, the difference of activation free energy between the competing *compact* and *relaxed* TSs is in agreement with the observed diastereomeric excess.[18]

Scheme 2. PM3 optimized structures for the chelate complex and the *compact* and *relaxed* TSs of case **A**.
(distances in Ångstroms; d, dihedral CCPO in degrees; MNDO values in parentheses)



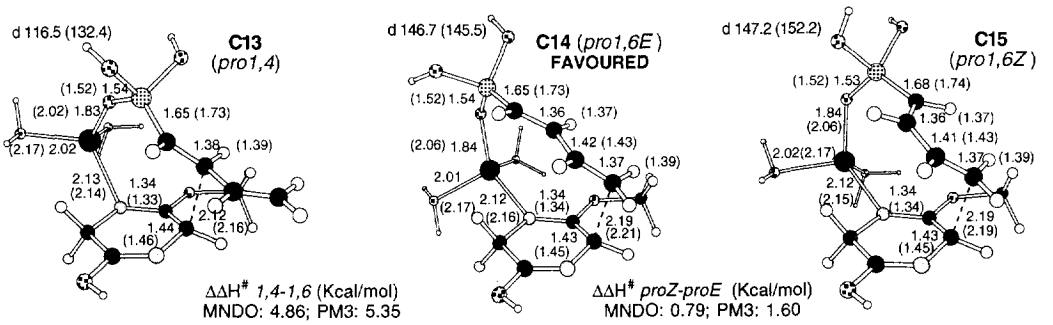
Based on the results obtained for case **A**, we decided to check the applicability of the TS model to the simulation of substituted systems. For case **B**, with a substituted enolate, the reorganization of the corresponding chelate complex by approaching the β-acceptor to the *Re* and *Si* faces of the enolate (reproducing the *anti* and *syn* attack with respect to the isopropyl group), led to the location of the *protrans*-**B11** and *procis*-**B12** structures as the most favorable TSs (see scheme 3). Thus, the introduction of the isopropyl group into the bislactim prototype does not alter significantly either the geometrical features or the activation energies characteristic of the *compact vs. relaxed* TS model.[18,19] The energy gap between the optimized diastereomeric TSs **B11** and **B12** ($\Delta\Delta H^{\#} > 3.0$ Kcal/mol) conveniently correlates with the exceptionally high face-selectivity showed by the lithiated bislactim ethers in Michael additions.

Scheme 3. PM3 optimized structures for the *protrans* and *procis* TSs of case **B**.
(distances in Ångstroms; d, dihedral CCPO in degrees; MNDO values in parentheses)



The modelling of case **C**, which introduces as new feature the vinyl substituent on the acceptor, allows the sensitivity of the TS model upon a substitution on the alkenylphosphonate to be checked, and also more insight on the origins of the high regioselection in the conjugated additions to butadienylphosphonates to be gained.[3d] In this case, after the global minima for the chelate complex was found and the energy profiles for all the possible approaches of either the β- and the δ-positions of the butadienylphosphonate moiety to the α-position of the enolate were analyzed, full optimization of the geometries at energy maxima enabled the location of *pro1,4*-**C13**, *pro1,6E*-**C14** and *pro1,6Z*-**C15** (see figure 2) as the most favorable TSs.[20] While **C13** does not introduce new structural characteristics with respect to cases **A** and **B**,[19] both **C14** and **C15** increase C=CNLi dihedral (from 115°, typical of 1,4-addition TSs, to *ca.* 150°) to cope with the larger size of the acceptor. In agreement with the experimental trend, MNDO and PM3 calculations clearly indicate a strong kinetic preference for the 1,6-addition process, and also support the previously proposed *E* configuration in the major 1,6-adduct.[3d,18]

Figure 2. PM3 optimized structures for the *compact pro1,4*, *pro1,6E* and *pro1,6Z* TSs of case **C**.
(distances in Ångstroms; d, dihedral CCNLi in degrees; MNDO values in parentheses)



In conclusion, the semiempirically optimized *compact vs. relaxed* transition state model reproduces both the sense and degree of the experimental stereoselection in the conjugate additions of alkenyl and butadienylphosphonates to lithiated bislactim ethers, and therefore proves to be a useful tool to investigate the possibilities of these Michael additions in asymmetric synthesis.

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10. The X ray structure of a lithiated bislactim derivative was determined as a trisolvated dimmeric aggregate, but cryoscopic experiments have shown an average degree of aggregation of 1.15 for the same compound at low temperature diluted ethereal solutions, see: Seebach, D.; Bauer, W.; Hansen, J.; Laube, T.; Schweizer, W.B.; Dunitz, J.D. *J. Chem. Soc., Chem. Commun.* **1984**, 853.
11. Calculations were performed on a Fujitsu vp2400/10 using MOPAC93 program.[12a] All structures were fully optimized at the restricted Hartree-Fock level of theory with the MNDO and PM3 methods, using the eigenvector following routine (TS keyword for transition state refinement) under the more rigorous criteria of the keyword PRECISE with no constraints. Maxima were characterized as first order transition structures by normal mode analyses, yielding a single imaginary frequency, and their nature verified by internal reaction coordinate calculations to reactants and products. For each stationary point all the gauche-gauche conformations for the H-O-P-O-H moiety were studied. Rotational minima for the water molecules were located by performing a grid (6x6) calculation. All the hydrogen atoms of the hydroxyl groups were found more than 2.6 Å away from any other basic atom for all the reported models. PCModel 5.0[12b] and CS Chem3D Pro[12c] were used as graphical interfaces for preparing, visualizing and comparing geometries.
12. **a.** Steward, J.J.P. MOPAC93, Fujitsu Limited, Tokyo, Japan, 1993. **b.** PCModel version 5, from Serena Software, Bloomington, IN 47402, USA. **c.** CS Chem3D Pro, Cambridge Soft. Corporation, Cambridge, MA 02139, USA.
13. Similar process for a trisolvated enolate proceeds through a trigonal bipyramidal intermediate to afford **A8** and a free water molecule, in a quite less exothermic fashion ($\Delta H°$= –4.46 (MNDO), –8.26 (PM3) Kcal/mol, see ref 18). Some uncertainty about this step remains, resulting from the known tendency of semiempirical methods to overestimate the stabilities of adduct complexes. See Opitz, A.; Koch, R.; Katritzky, A.R.; Fan, W.-Q.; Anders, E. *J. Org. Chem.* **1995**, *60*, 3743.
14. The global minimum for chelates **8a-c** showed a s-trans configuration. Similar stabilization of s-trans conformation by metal coordination was found for unsaturated aldehydes. See Houk et al *J. Am.Chem. Soc.* **1987**, *109*, 14, and Schereiber *Angew. Chem. Internat. Ed. Eng.* **1990**, *29*, 256.
15. These transition structures suggest that the reaction actually takes place by enolate attack on a s-cis oriented alkenylphosphonate, as previously reported by Heathcock for the corresponding additions to enones.[5]
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18. Heats of formation and energy barriers for the PM3 and MNDO optimized structures (Kcal/mol):

	MNDO	PM3					MNDO	PM3			
	$\Delta H°f$	$\Delta H°f$	$n_i(\nu_i)$	$\Delta H^{\#}$	$\Delta\Delta G^{\#}_{195}$		$\Delta H°f$	$\Delta H°f$	$n_i(\nu_i)$	$\Delta H^{\#}$	$\Delta\Delta G^{\#}_{195}$
A(6+7)	-353.32	-358.45	0			**B11**	-347.39	-373.86	1 (-398.1)	13.43	0.00
A8	-363.35	-376.25	0			**B12**	-343.68	-370.81	1 (-378.0)	16.48	3.14
A9	-343.98	-362.32	1 (-389.7)	13.93	0.00	**C13**	-322.42	-343.05	1 (-367.5)	19.53	5.14
A10	-343.24	-360.91	1 (-384.7)	15.34	1.71	**C14**	-327.28	-348.40	1 (-488.0)	12.86	0.00
						C15	-326.49	-346.80	1 (-502.2)	14.53	1.41

19. Comparison of the heavy atom positions (at the PM3 optimized geometries) for couples **B11/A9**, **B*relaxed,proanti***(not shown in Scheme 2)**/A10**, **C13/A9** and **C*relaxed,pro1,4***(not shown in Fig. 2)**/A10** results in a RMS deviation of 0.094, 0.069, 0.057, and 0.076 Å respectively. The *compact* approaches **B11** and **C13** are also favored over the corresponding *relaxed* ones: according to PM3 method, for case **B** $\Delta\Delta H^{\#}$*(relaxed-compact)protrans* = 1.81 Kcal/mol, while for case **C** $\Delta\Delta H^{\#}$*(relaxed-compact)pro1,4* = 1.10 Kcal/mol.
20. The *relaxed* approaches for case **C** yielded in all the cases TSs of higher energy. It should be noted that the energy gap between the located *compact* and *relaxed* TSs for the 1,6-addition processes {$\Delta\Delta H^{\#}$*(relaxed-compact)pro1,6* = 1.48 Kcal/mol (PM3)} indicates a useful level of facial discrimination. In agreement with this computational based prediction, preliminary experiments in this laboratory have revealed the additions of lithiated bislactim ethers to stereogenic 1*E*,3*E*- and 1*Z*,3*E*-butadienylphosphonates as very promising stereoselective processes.

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