DOI: 10.1002/ejoc.200900906

Merging of E2 and E1cb Reaction Mechanisms: A Combined Theoretical and Experimental Study

Edoardo Mosconi,[a] Filippo De Angelis,*[b] Leonardo Belpassi,[a] Francesco Tarantelli,[a,b] and Sergio Alunni[a][†]

Keywords: E1cb vs. E2 / Elimination / Reaction mechanisms / Density functional calculations

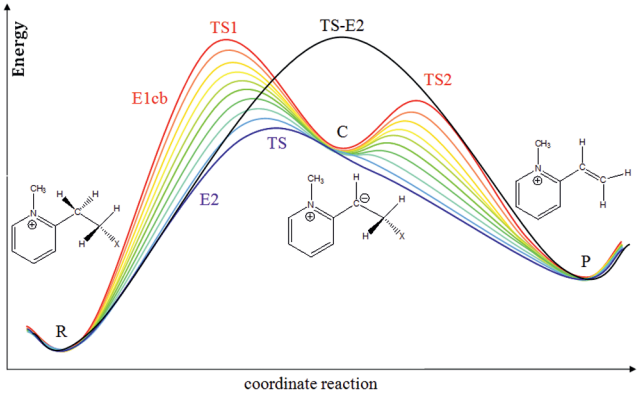
By combining the results of kinetic measurements with DFT calculations we provide a clear-cut evidence of the merging between the E2 and E1cb reaction mechanisms for a large series of leaving groups. Our results solve a long-debated issue in chemical reactivity with profound implications both from a fundamental and biological point of view, thus paving the way to further investigations with different substrates.

Introduction

Base-induced β-eliminations are one of the most fundamental and ubiquitous class of chemical reactions, relevant both as case studies of basic chemical reactivity[1] and for their implications in biochemistry.[2] Various mechanisms can operate[1] depending on the relative timing of C–H and C–X bond breaking, X being the leaving group. If the C–X bond breaking precedes C–H bond breaking, then an intermediate carbocation is formed and the mechanism is of E1 type ($D_N + A_{xh}D_H$).

Systems with significant β-activation (with respect to the leaving group) can instead react via the E1cb ($A_{xh}D_H + D_N$) mechanism, where C–H bond breaking precedes C–X bond breaking; a stable carbanion intermediate is formed (see curve printed in red in Scheme 1). Finally, an E2-concerted mechanism ($A_{xh}D_H\ D_N$) can occur when the C–H and C–X bond breakings take place simultaneously (blue curve in Scheme 1). In this case the reaction proceeds without intermediates on the reaction path.

Being able to distinguish between E1cb and E2 reaction pathways is a daunting task,[3] since the two mechanisms share several common characteristics. On the other hand, which one of the two mechanisms actually prevails may be extremely consequential, e.g., in biological systems, where the E1cb carbanion intermediate might undergo undesired collateral reactions. The nature of the borderline region between the two mechanistic regimes has only recently been explored,[4] suggesting, in specific cases, the lack of discontinuity between E1cb and E2 pathways. These results lend support to the classic "merging" theory considered by More O'Ferrall and Jencks,[1,3] in which the two reaction mechanisms merge into each other, leading to a smooth transition between the E1cb and E2 pathways. The possibility of coexistence of the E2 and E1cb mechanisms has also been considered.[3b] The merging theory requires continuity in both activation free energies and transition state structures. Alternatively, a sharp discontinuity can be envisaged, with the two reactive pathways occurring on unrelated, possibly distant regions of the potential energy surface (see red vs. black curve in Scheme 1).



Scheme 1. Potential energy surfaces for merging of (irreversible) E1cb and E2 reaction mechanisms (red to blue curves) or uncorrelated E1cb and E2 pathways (red and black curves), along with structures of elimination reactant (R), carbanion intermediate (C) and olefin product (P).

Here we investigate the transition from E1cb to E2 reaction mechanisms in systems activated by the pyridine ring, by varying the nature of the leaving group. By combining

[a] Dipartimento di Chimica, Università di Perugia, Via elce di Sotto 8, 06213 Perugia, Italy
[b] Istituto CNR di Scienze e Tecnologie Molecolari (ISTM), c/o Dipartimento di Chimica, Università di Perugia, Via elce di Sotto 8, 06213 Perugia, Italy
Fax: +39-0755855606
E-mail: filippo@thch.unipg.it
[†] Professor Sergio Alunni died on July 17, 2009.
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.200900906.

the results of kinetic measurements with DFT calculations in solution we provide clear-cut evidence of the merging between the two reaction mechanisms. The investigated 1-methyl-2-(2-X-ethyl)pyridinuim substrate is a model for several important biological processes in which a relevant role is played by the stabilization of a carbanion by a protonated or alkylated nitrogen heteroaromatic ring;[2] examples are the biochemistry of the cofactor pyridoxalphosphate, the mechanism of action of thiamine pyrophosphate, the E1cb mechanism involved with the enzyme histidine ammonia lyase.[2]

Results and Discussion

From previously reported[4a] kinetic measurements of H/D exchange in the reaction of 1-methyl-2-(2-X-ethyl)pyridinuim iodide with X = Me, Ph, OEt substrates it was possible to evaluate the k_{OH} rate constants for the deprotonation by OH^- with formation of the related carbanion. Also available[4a] are the second-order rate constant for the OH^--induced elimination reactions with X = F, Cl, OTs, Br. The results are collected in Table 1, and show a steady decrease in the activation free energy in the 20.5–14.8 kcal/mol range on going from Me to Br. With Me, Ph and OEt groups we probe the formation of the carbanion, while with F, Cl, OTs and Br we observe a shift from E1cb (F) to E2 (Cl, Ots and Br) reaction mechanisms, as testified by the deviations of the latter substrates from the Taft equation.[4a]

Table 1. Measured rate constants ($M^{-1}s^{-1}$), activation free energies [kcal/mol] and methyl activating factors (MAFs), along with calculated activation free energies [kcal/mol] and transition state parameters [Å], see text for definition.

	Br	OTs	Cl	F	OEt	Ph	Me
k_{OH}	78.5	81	25.2	10.25	0.38	0.0229	0.0051
MAF(10^6)	0.2[a]	–	1.0[b]	3.8[c]	–	–	–
$\Delta G^{\#}_{exp}$	14.8	14.8	15.5	16.0	17.9	19.6	20.5
$\Delta G^{\#}_{theor}$	13.2	–	18.2	21.1	–	–	–
CH_{ts}	1.282	1.316	1.294	1.289	1.334	1.409	1.357
CX_{ts}	2.066	1.498	1.913	1.481	1.438	1.525	1.538
Δ–/Δ+	0.623	0.769	0.594	0.590	0.880	0.955	0.963
ΔCH_{mw}	0.169	0.205	0.183	0.178	0.222	0.289	0.242
ΔCX_{mw}	0.351	0.350	0.277	0.200	0.095	0.058	0.018
$\Delta-/\Delta+_{mw}$	–0.310	–0.219	–0.161	–0.013	0.438	0.690	0.874

[a] Ref.[4a] the value of $k_{OH} = 5.02 \times 10^{-4}\ M^{-1}s^{-1}$ in OH^-/H_2O, 25 [°C] fort he unmethylated substrate was measured following the formation of 2-vinylpyridine at 290 nm. [b] Ref.[4a,5a] [c] Ref.[5b]

For these systems, an important indication on the carbanion stabilization is the Methyl Activating Factor (MAF), the ratio between the reaction rate for the *N*-methylated and the non-methylated substrates. MAF values are reported in Table 1 for F, Cl and Br leaving groups: the high (ca. 10^6) values are those characteristic of highly activated systems, although only in the F case a stable carbanion was found.

To provide insight into the nature of the transition states of the investigated reactions, we performed DFT calculations in water solution (see Exp. Sect. and Supporting Information).

Our model is reported in Figure 1. The quantum mechanical system is embedded into a Polarizable Continuum Model (PCM) of solvation,[6] to account for residual solute-solvent interactions. Activation free energies have been calculated as previously reported.[4a,7]

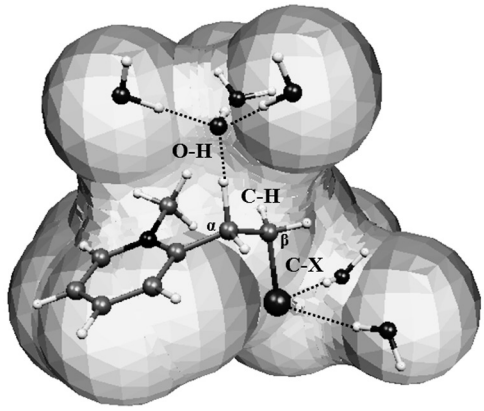


Figure 1. Optimized molecular structure of the transition state for the elimination reaction with the Br leaving group, along with the explicit/implicit solvation model used.

The transition state (TS) geometries are those characteristic of elimination reactions:[4a,7] the solvated OH^- base attacks the proton in alpha to the pyridine, inducing a lengthening of the C_α–H distance (Table 1) in the range 0.17–0.29 Å. Depending on the nature of the leaving group a carbanion is formed or the reaction proceeds to the products by breaking of the C_β–X bond. Comparison of calculated activation free energies with experimental data (Table 1) shows a satisfactory agreement, with maximum deviations within 5 kcal/mol. Here we focus however on structural parameters which are expected to be more accurate than calculated free energies. Considering the mass-weighted (mw) C_α–H and C_β–X variations occurring from the reagent to the TS (ΔCH_{mw} and ΔCX_{mw}, see Supporting Information), we notice that ΔCH_{mw} (ΔCX_{mw}) steadily increases (decreases) on going from Br (E2) to Me (E1cb) substituents. A useful combination of geometrical parameters is the ratio (ΔCH–ΔCX)/(ΔCH+ΔCX), hereafter Δ–/Δ+. This quantity can vary between 1 for pure E1cb (no C_β–X bond variation in the TS), while it is 0 for a synchronous E2 mechanism. In the present case the Δ–/Δ+ values are comprised within 0.623 and 0.963 for Br and Me, respectively, suggesting that even the E2-reacting Br, OTs and Cl substrates have a substantial activation due to pyridine methylation, as confirmed by their high MAF values.

Prompted by these observations, we investigated in detail the reactive potential energy surface for the Br substrate along the C_α–H and C_β–Br distances. The results (Figure 2) show that despite the lack of a stable carbanion, this systems evolves towards the products by a TS which has one almost broken C_α–H bond (1.282 vs. 1.097 Å) and still an intact, albeit elongated, C_β–Br bond (2.066 vs. 1.988 Å, in the reagent and TS, respectively). This TS structure is very

similar to that calculated for the F-substrate (Δ–/Δ+ = 0.590), which however proceeds by an E1cb mechanism through a moderately stable carbanion.

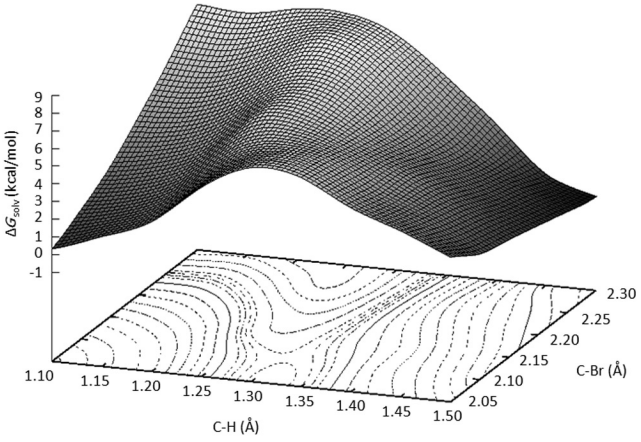


Figure 2. Potential energy surface [kcal/mol] for the elimination reaction in the Br-substituted system as a function of C_α–H and C_β–Br distances [Å]. Total free energies in solution are reported relative to the starting adduct.

To provide a unified representation of our joint theoretical and experimental data, we plot in Figure 3 the experimental activation free energies as a function of the mass-weighted Δ–/Δ+ displacements (Δ–/Δ+$_{mw}$). Further correlations can be outlined between calculated geometrical parameters only (Supporting Information). The resulting data show an almost perfect linear correlation (R^2 = 0.993), suggesting that the investigated systems belong to the same data set. This in turn implies that a merging between E2 and E1cb reaction mechanisms exists, with the activation free energies decreasing as the mechanism and TS structure shift from E1cb to E2. To the best of our knowledge, this represents the first case in which such a behavior has been proved. Interestingly, on the basis of electronegativity considerations one would expect F to activate the reaction more than Br, due to stabilization of the ensuing negative charge developed in the TS. The fact that the opposite is found both theoretically and experimentally, suggests that part of the negative charge developed in the TS is transferred to the leaving group, or, from a different perspective, that the more favorable solvation of Br^- compared to F^- contributes to lower the TS energy. This is confirmed by optimization of the TS structures of the F- and Br-substituted systems, enforcing the C_β–X distance to the value it had in the reagent. By doing so we calculate a higher activation energy (by 1.1 kcal/mol) for the Br-substituted system, confirming the relevant role of the lengthening of the C_β–X bond in decreasing the activation free energies.

The inset of Figure 3 shows the correlation between the experimental activation free energies and ΔCX$_{mw}$. Two distinct slopes are found for the data comprising the Me, Ph, OEt and F and F, Cl, OTs and Br leaving groups, the F case representing the crossing point between the two data

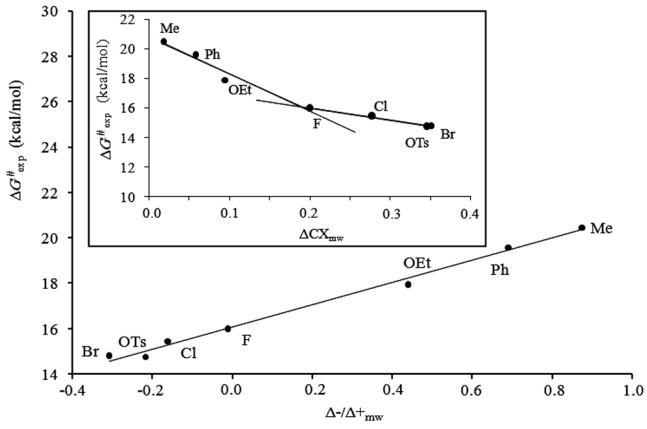


Figure 3. Correlation between the experimental activation free energies and the calculated mass weighted Δ–/Δ+ for various leaving groups. Inset: same but with ΔCX$_{mw}$.

sets. This implies that the F case represents the merging and borderline region between E1cb and E2 reaction mechanisms.

Conclusions

In conclusion, we have investigated the transition between E1cb and E2 reaction mechanisms in systems activated by the pyridine ring, employing a combined experimental and computational approach. A clear-cut evidence of merging between E1cb and E2 mechanisms has been reported and the borderline between the two reaction mechanisms has been highlighted. Our results solve a long-debated issue in chemical reactivity with profound implications both from a fundamental and biological point of view, thus paving the way to further investigations with different substrates. We expect the present findings to be of very general relevance and useful for further studies.

Experimental Section

All calculations have been performed by the Gaussian 03 program.[8] We used the B3LYP exchange-correlation functional, along with a 6-31++G** basis set. The C–PCM solvation model was employed, see Supporting Information for further details.

Supporting Information (see also the footnote on the first page of this article): Computational procedures and correlations.

[1] a) W. H. Saunders Jr., A. F. Cockerill, in: *Mechanism of Elimination Reaction*, Wiley-Interscience, New York, **1973**; b) E. Baciocchi, in: *The Chemistry of Halides, Pseudo Halides and Azides, Supplement D* (Eds: S. Patai, Z. Rappoport), Wiley Chichester, UK, **1983**; c) J. R. Gandler, in: *The Chemistry of Double Bonded Functional Group* (Eds: S. Patai), Wiley Chichester, UK, **1989**; d) W. H. Saunders Jr., *Acc. Chem. Res.* **1976**, *9*, 19; e) C. J. M. Stirling, *Acc. Chem. Res.* **1979**, *12*, 198; f) F. G. Bordwell, *Acc. Chem. Res.* **1972**, *5*, 374; g) W. P. Jencks, *Acc. Chem. Res.* **1980**, *13*, 161; h) R. A. More O'Ferrall, in: *The chemistry of the Carbon-Halogen Bond* (Ed.: S. Patai), part 2, Wiley-Interscience, New York, **1973**.

[2] a) R. H. Abeles, P. A. Frey, W. P. Jencks, *Biochemistry*, Jones and Bartlett Publisher, **1992**; b) D. Voet, J. G. Voet, *Biochemistry*, John Wiley & Sons, New York, **1990**; c) M. Langer, A. Pauling, J. Rétey, *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1464.
[3] a) J. R. Gandler, W. P. Jencks, *J. Am. Chem. Soc.* **1982**, *104*, 1937; b) W. P. Jencks, *Chem. Soc. Rev.* **1981**, *10*, 345; c) F. Larkin, R. A. More O' Ferrall, D. G. Murphy, *Collect. Czech. Chem. Commun.* **1999**, *64*, 1833; d) R. A. More O'Ferrall, F. Larkin, P. Walsh, *J. Chem. Soc. Perkin Trans. 2* **1982**, *12*, 1573; e) R. A. More O'Ferrall, P. J. Warren, *J. Chem. Soc., Chem. Commun.* **1975**, *12*, 483; f) F. Larkin, R. A. More O'Ferrall, *Aust. J. Chem.* **1983**, *36*, 1831.
[4] a) S. Alunni, F. De Angelis, L. Ottavi, M. Papavasileiou, F. Tarantelli, *J. Am. Chem. Soc.* **2005**, *127*, 15151; b) F. De Angelis, S. Alunni, F. Tarantelli, *J. Phys. Chem. B* **2006**, *110*, 11014; c) Z. S. Jia, J. Rudzinski, P. Paneth, A. Thibblin, *J. Org. Chem.* **2002**, *67*, 177; d) ; X. F. Zeng, A. Thibblin, *J. Chem. Soc. Perkin Trans. 2* **2002**, 1352; e) J. R. Mohrig, D. G. Alberg, C. H. Cartwright, M. K. H. Pflum, J. S. Aldrich, J. K. Andesron, S. R. Anderson, R. L. Fimmen, A. K. Snover, *Org. Biomol. Chem.* **2008**, *6*, 1641; f) F. M. Bickelhaupt, *Mass Spectrom. Rev.* **2001**, *20*, 347.
[5] a) S. Alunni, A. Busti, *J. Chem. Soc. Perkin Trans. 2* **2001**, 778; b) S. Alunni, V. Laureti, L. Ottavi, R. Ruzziconi, *J. Org. Chem.* **2003**, *68*, 718.
[6] M. Cossi, N. Rega, G. Scalmani, V. Barone, *Comput. Chem.* **2003**, *24*, 669.
[7] E. Mosconi, F. De Angelis, F. Tarantelli, S. Alunni, A. Sgamellotti, *Chem. Phys. Lett.* **2008**, *460*,100.
[8] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery, Jr., T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, J. A. Pople, *Gaussian 03*, Revision D.02, Gaussian, Inc., Pittsburgh PA **2003**.

Received: August 10, 2009
Published Online: September 25, 2009

