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Correlation between pressure and steric interactions in organic reactions

Gérard Jenner*

Laboratoire de Piézochimie Organique (UMR 7123), Institut de Chimie, Université Louis Pasteur, 1 rue Blaise Pascal, 67008 Strasbourg, France

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1. Introduction

Amid numerous parameters, the rate of a chemical reaction may be influenced by structural changes of the reagents through polar, resonance and steric effects. Steric hindrance is a wide concept encompassing the effect of bulkiness of reactants and the steric accessibility of reaction centres on reagent approach. As a very general rule, steric effects decrease rate constants, although there are some examples illustrating an opposite effect.[1] Conceptually, it is common practice to distinguish between primary steric effects (steric hindrance to the approach of reagents, steric hindrance to solvation…) and secondary steric effects (moderation of a polar or a resonance effect by non-bonded compression).[2] The quantitative treatment of the kinetic rate constant k of a reaction relates basically to two main parameters: the resonance and field effect and the steric effect. It is a well-known fact that k obeys linear free energy relationships.[3] It is not the aim of this paper to review the relationships (Taft–Hammett, Grunwald–Winstein…) governing sterically congested reactions. We examine here the effect of an external factor on such reactions.

Steric effects are intimately related to volume effects. Accordingly, the velocity of hindered versus unhindered reactions can be affected differently by pressure. Intermolecular distances decrease under pressure, leading to an increase in the potential energy. The molecules try to adjust to the new situation by taking a more crowded conformation

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* Tel.: +33 3 90 24 16; fax: +33 79 03 90 24 17 39;
e-mail: jenner@chimie.u-strasbg.fr

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which occupies a smaller volume.[4] Every reaction is described by two profiles: the well-known energy diagram which in the transition state theory shows the successive transition states and intermediates and the volume profile which is less evident to determine as it requires the determination of the individual volumes, virtual as for transition states and real as for intermediates.[5] The components of the volume profile are measurable only via high-pressure kinetics. A particularly instructive profile determined in this way has been recently pictured in the Baeyer–Villiger (B–V) oxidation of aliphatic ketones showing two transition states with one intermediate (Fig. 1).[6] Sterically hindered B–V reactions are reported at the end of this review.

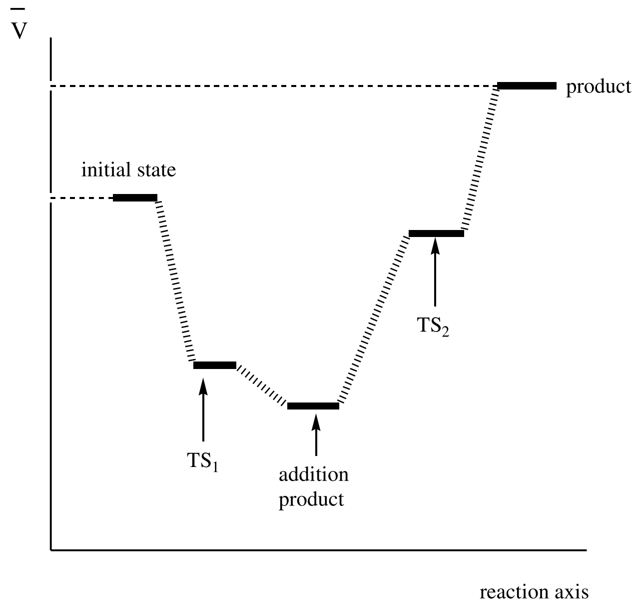
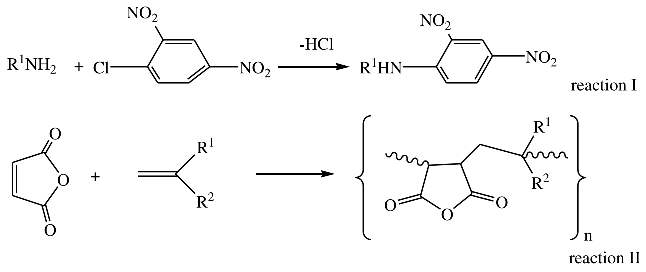


Figure 1. Volume profile of the Baeyer–Villiger reaction.

The influence of pressure on reaction rates was already considered towards the end of the nineteenth century.[7] Some fifty years later, Perrin et al. observed that reactions involving bulky reagents were accelerated by pressure more than their unhindered analogs.[8] Later, two groups examined the pressure effect in Menshutkin reactions of α-methyl substituted pyridines[9,10] and both confirmed Perrin's result, although these were differently rationalized. Gonikberg suggested a preferred more compact spatial arrangement of bulky molecules within the transition state under the influence of pressure,[10] whereas the other authors interpreted the phenomenon via Hammond postulate, according to which the less endothermic activated complex involves less volume contraction and, therefore, should occur earlier. Conversely, a more congested hindered reaction will be shifted to the final product with a late transition state. This view was proposed for the first time by Brower in his study of the pressure effect on aromatic nucleophilic substitutions.[11] In our first review detailing the pressure effect on strained transition states, we reported a correlation between steric hindrance and the activation volume ΔV^*.[12] The purpose of the present paper is to report the recent synthetic advances in the subject and its interpretation based on the activation volume.[13]

2. Correlation between pressure and steric hindrance

We begin with two examples, a nucleophilic aromatic substitution (reaction I in Scheme 1)[14] and the radical copolymerisation of maleic anhydride with *gem*-substituted alkenes (reaction II in Scheme 1)[15] (Table 1). Under similar pressure conditions, the rate constant ratio in both reactions increases when the reaction centres are substituted by more compressive groups.



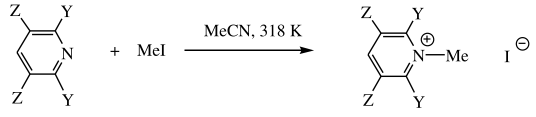
Scheme 1.

Table 1. Effect of steric bulk on rate constant ratios k_P:$k_{0.1}$ in reactions I and II

Reaction	R^1	R^2	Pressure (MPa)		
			0.1	150	200
I^a	Bu	—	1	—	3.29
	t-Bu	—	1	—	7.52
II^b	Me	Ph	1	4.2	—
	Ph	Ph	1	7.1	—
	Me	*t*-Bu	1	15.1	—

[a] In ethanol at 308 K.
[b] In chloroform at 343.4 K; lauroyl peroxide was the initiator.

As another illustrative example, the pressure effect has been clearly evidenced in the Menshutkin reaction of buttressed pyridines (Scheme 2 and Table 2).[16] Whereas the rate constant under ambient pressure conditions is abysmally decreased with increasing bulk of Z and Y, the most hindered reactions are more accelerated by pressure, meaning more negative activation volumes ΔV^*.



Scheme 2.

Table 2. Menshutkin reactions of methyl iodide with buttressed pyridines

Z	Y	Rate constant ratio^a	ΔV^* (cm^3 mol^{-1})
H	H	1	-28.2 ± 0.2
H	Me	0.0354	-30.8 ± 0.2
t-Bu	Me	0.0036	-32.5 ± 0.5

[a] In acetonitrile at 318 K and 0.1 MPa.

There are numerous other examples reporting this interesting effect. A large pressure-induced rate increase was noticed in the Wittig reaction of ylides with hindered cyclohexanones.[17,18] The Michael addition can be very sensitive to steric hindrance. The reaction is also subjected to electrostriction.[19] Successful sterically hindered