



New insights in the mechanism of the microwave-assisted Pauson–Khand reaction



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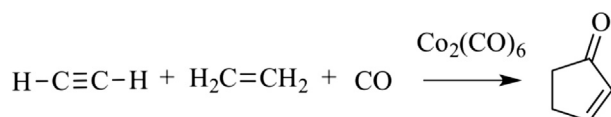
ABSTRACT

A complete analysis of the stereoselectivity observed in the Pauson–Khand reaction has been performed using computational calculations. The differences observed in the stereoselectivity when this reaction is performed either by conventional means or under microwave conditions have also been studied. The mechanisms suggested by Magnus–Schoore and by Gimbert were used as a model in this investigation. The outcomes show that the observed diastereoselectivity is consistent with the mechanism proposed by Gimbert et al. Moreover, the high activation energy of the process could be responsible for the observed improvement under microwave irradiation.

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1. Introduction

The Pauson–Khand reaction (PKR) is a formal [2+2+1] cycloaddition between an alkene, an alkyne and a transition metal carbonyl, usually dicobalt hexacarbonyl, to give cyclopentenone substrates (Scheme 1). The reaction was first discovered in 1971 in its stoichiometric form after an unexpected reaction between an alkyne and norbornadiene in presence of the dicobalt complex.^{1,2}



Scheme 1. Pauson–Khand reaction (PKR) formal [2+2+1] intermolecular cycloaddition.

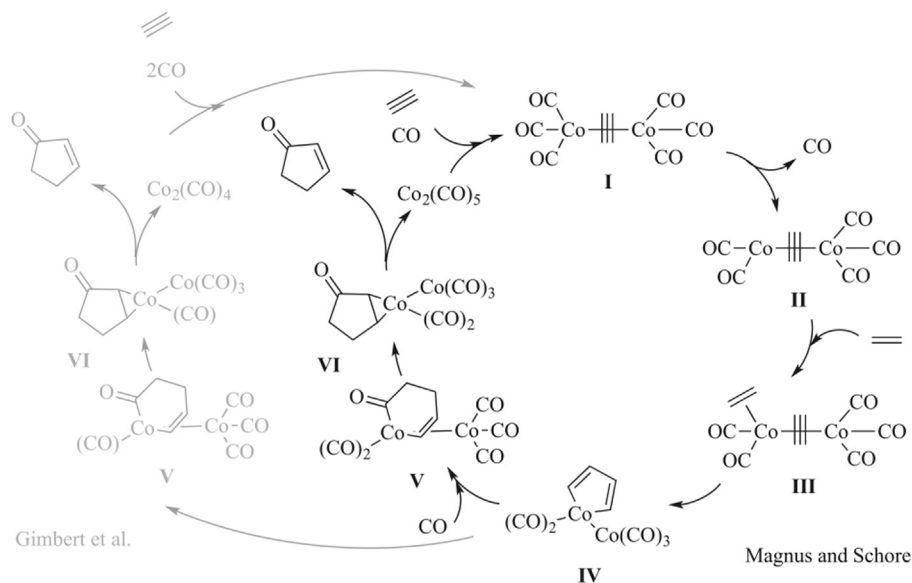
The utility of this reaction is based on the formation of a cyclopentenone moiety in the case of the intermolecular PKR, whereas in the intramolecular PKR a bicyclic pentenone derivative is formed from an acyclic substrate. The reaction was subsequently studied and it was found that the process could also work under catalytic conditions,³ although very high temperature and CO pressure were required. Initially it was thought that the reaction was only

catalysed by cobalt, but in recent years it has been shown that other metals (titanium,⁴ iron,⁵ rhodium,⁶ ruthenium,⁷ palladium,⁸ and others⁹) can mediate the reaction.

The mechanism for the PKR was not known for a long time, mainly because the intermediates were difficult to detect. In 1985 Magnus and Schoore (MS) independently proposed the widely accepted mechanism for this reaction.^{10,11} This mechanism (Scheme 2, black path) served as a working hypothesis in both experimental and computational studies.^{12–15}

When Magnus and Schoore proposed their mechanism, the only complex for which experimental evidence was available was the hexacarbonyldicobalt(μ^2 -alkyne) (complex I in Scheme 2) as this had been isolated experimentally.¹⁶ A few years later, intermediate II was characterized by NMR spectroscopy for complexes with a substituent on the alkyne moiety that coordinates to the vacant site of the cobalt atom.^{17,18} More recently, intermediate III was also identified by X-ray crystallography.¹⁹ Further evidence for the other intermediates was obtained, as it was possible to interrupt the PKR under an O₂ atmosphere. This led to indirect evidence for the metallacycle intermediate IV.²⁰ More recently, Gimbert et al.^{21,22} studied the use of highly sensitive mass spectrometry techniques with ¹³C (Scheme 2, grey path). The results strongly suggest that the incorporation of an additional CO in complex IV does not follow a bimolecular process as proposed in the MS mechanism. Further information about the energy profile, rate- and stereo-determining steps for this reaction was obtained from theoretical calculations by

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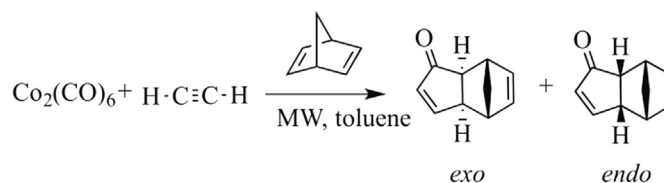


Scheme 2. Possible mechanisms of the Pauson–Khand reaction.

Nakamura¹² and Pericàs,²³ considering the MS mechanism as a low-barrier process, and therefore difficult to control the stereoselectivity of the process.

The synthetic application of this reaction is important as it enables the formation of complex molecules from cheap starting materials in a single step—a fact that has been exploited in the synthesis of complex natural products and analogues.^{24–27} However, the PKR is a difficult reaction to optimise as it can become difficult to treat upon prolonged heating (mostly due to decomposition of the catalyst). The results also depend on the choice of the alkene and alkyne, and purification processes can be troublesome. Modifications^{28–31} that have been made to the standard conditions include microwave irradiation^{32–38} and photochemically induced reactions (in batch and continuous flow conditions).^{39,40}

The first example of the PKR under microwave irradiation was reported by Evans et al.,³² who found that microwave irradiation helps to reduce the long reaction times of the standard PKR reaction and thus avoid catalyst decomposition, which normally occurs at elevated temperature. Their initial results were confirmed by Groth et al.,³³ who found that the cobalt catalyst was significantly affected by the microwave irradiation when the reaction was performed in a completely microwave transparent solvent. They also observed that under microwave irradiation there was no need for high CO pressures. In both cases the best solvent was toluene. Moreover, in the contribution by Evans et al. (Scheme 3), microwave irradiation was found to enhance the *exo:endo* diastereoselectivity obtained in the reaction of the acetylenedicobalthexacarbonyl complex with norbornadiene under microwave irradiation either in toluene (Table 1, entry 1) or dichloroethane (Table 1, entry 2) in comparison with conventional conditions (Table 1, entry 3).



Scheme 3. PKR of acetylene and norbornadiene.

2. Results and discussion

The aim of this theoretical work is to identify reasons for the improvement of the PKR under microwave irradiation in both yield and stereoselectivity. Other experimental studies regarding the link between microwave heating and selectivity are collected elsewhere.^{41,42} On this basis, we considered all previously discussed mechanisms. With this aim in mind, the PES was calculated for the reaction of acetylene and norbornadiene (reactants employed experimentally by Evans and Groth).

According to the principle reported by Shaik and Kozuch,⁴³ only relative Gibbs energies are discussed for all species in the catalytic cycle. They proposed that a computational study of a catalytic cycle generates state energies (the E-representation), whereas experiments lead to rate constants (the k-representation). Since the connection between computational and experiments is not always obvious, we based our approach on transition state theory (TST), where the energetic and kinetic representation terms have been made equivalent. In the energetic description of a cyclic system, the energetic span model⁴³ offers a straightforward method to calculate the TOF of catalytic cycles based on its computed energy profile. In most cases, the TOF is determined by one transition state (TDTS), one intermediate (TDI) and by the reaction energy, ΔG_r . The energy difference between the TDI and the TDTS (with due ΔG_r correction), the so called the energetic span (δE), is the apparent activation energy of the entire catalytic cycle.

The first step of the reaction is known experimentally¹⁶ involving acetylene and the cobalt complex $\text{Co}_2(\text{CO})_6$ to give cobalt complex **1** (Scheme 4). In this step, a molecule of gaseous CO is released in an endothermic process ($10.9 \text{ kcal mol}^{-1}$) to allow coordination of norbornadiene. This results in the thermodynamically

Table 1
Experimental results obtained in the PKR between acetylene and norbornadiene

Entry	Heating mode	Solvent	Temp (°C)	Time (min)	Rdto (%)	<i>Exo:endo</i>
1	MW	Toluene	90	5	72	90:10
2	MW	DCE	90	20	90	95:5
3	CH	Toluene	110	960	70	80:20

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