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TEMPO-Promoted Pauson–Khand Reaction. Single-Electron Activation of Cobalt–Carbonyl Bonds?

Anna Lagunas,[†] Antoni Mairata i Payeras,[†,‡] Ciril Jimeno,[†] and Miquel A. Pericàs*,[†,‡]

*Institute of Chemical Research of Catalonia (ICIQ), Avgda Països Catalans s/n, 43007
Tarragona, Spain, and Departament de Química Orgànica, Universitat de Barcelona,
C/Martí i Franquès 1-11, 08028 Barcelona, Spain*

mapericas@iciq.es

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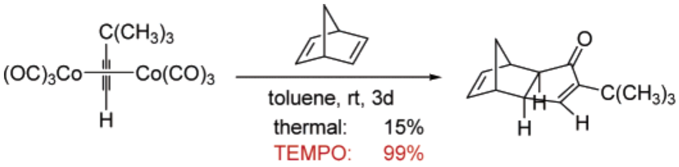
ABSTRACT



The Pauson–Khand reaction is notably accelerated by TEMPO. According to DFT calculations, TEMPO could trigger a radical, low-energy pathway for the reaction by facilitating the decarbonylation of doublet complexes arising either from a CO/nitroxide exchange or from nitroxide addition to a CO ligand.

The Pauson−Khand reaction (PKR) is a powerful method for the construction of cyclopentenones from alkynes, alkenes, and carbon monoxide that receives continued attention.[1] While the initial reaction conditions involved heating the starting alkyne dicobalt hexacarbonyl complex in order to generate free coordination sites that could trigger the reaction, these often harsh reaction conditions were unsuitable for many substrates or complexes. For this reason, several additives have been traditionally used to facilitate CO release from the initial complex. One of the most common approaches uses amine *N*-oxides (typically NMO or TMAO),[2,3] which are believed to oxidize CO ligands to CO_2 (a poor ligand), thus allowing the formation of vacant sites and the subsequent coordination of the reacting olefin.[3]

In connection with previous studies on the effects of ligands bonded to alkyne complexes either to activate them toward PKR or to induce asymmetry leading to enantiocontrol in the reaction,[4] we became interested in investigating the effect of TEMPO (2,2,6,6-tetramethylpiperidine *N*-oxide, free radical)[5] as a radical promoter for PKR. In fact, it is known that TEMPO readily reacts with $Co_2(CO)_8$ by inducing dissociation of the Co−Co bond and initially leading to a (η^2-TEMPO)$Co(CO)_2$ complex without, apparently, oxygen transfer to the lost CO ligands.[6]

[†] ICIQ.

[‡] Universitat de Barcelona.

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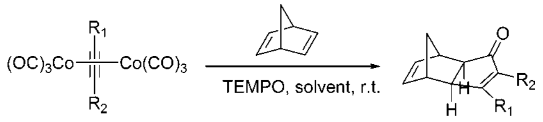
To test this possibility, we carried out the reaction of phenylacetylene with norbornadiene under conditions identical to those used for the *N*-oxide-promoted PKR,[2] but using TEMPO instead as a promoter. Thus, 6 equiv of TEMPO was added at room temperature to a solution of the dicobalt hexacarbonyl complex of the alkyne and a large excess of norbornadiene in dichloromethane. After 3 days, the Pauson–Khand adduct was isolated in 82% yield (Table 1, entry 1). Under identical reaction conditions, except that no TEMPO was used (entry 2), the PK adduct was formed in only 51% yield after 3 days.

Table 1. TEMPO-Promoted Intermolecular PKR with Norbornadiene



entry	R_1	R_2	solvent	TEMPO (equiv)	*t* (days)	yield (%)
1	H	Ph	CH_2Cl_2	6	3	82
2	H	Ph	CH_2Cl_2	0	3	51
3	H	Ph	$PhCH_3$	6	1	78
4	H	Ph	$PhCH_3$	1	3	57
5	H	Ph	$PhCH_3$	0	3	30
6	H	TMS	CH_2Cl_2	6	3	88
7	H	TMS	$PhCH_3$	6	3	61
8	H	TMS	$PhCH_3$	0	3	0
9	H	^{t}Bu	CH_2Cl_2	6	6	32
10	H	^{t}Bu	$PhCH_3$	6	3	99
11	H	^{t}Bu	$PhCH_3$	0	3	15
12	Ph	Ph	$PhCH_3$	6	3	57
13	Ph	Ph	$PhCH_3$	0	3	10
14	H	*n*-Hex	$PhCH_3$	6	3	37
15	H	*n*-Hex	$PhCH_3$	0	3	27

The differences in rate and yield between between the TEMPO-promoted and the purely thermal reaction were more intense in toluene. In this solvent, the PKR of phenylacetylene with norbornadiene led to a 78% yield after 1 day at room temperature (entry 3), while only a 30% yield of adduct was isolated after 3 days when no TEMPO was used (entry 5). To check whether the reaction could be catalytic in TEMPO, an experiment was performed with only 1 equiv of the nitroxide. Under these circumstances the adduct could be isolated in a 57% yield after 3 days (entry 4).

When sterically more demanding alkynes were used, the beneficial effect of TEMPO was accentuated. Thus, the trimethylsilylacetylene complex reacted cleanly either in CH_2Cl_2 or toluene (entries 6 and 7), but no product was formed at all in the absence of TEMPO (entry 8). A more extreme example of this kind of activation was found in the case of *tert*-butylacetylene: TEMPO dramatically increased its reactivity toward the PKR in toluene, a 99% yield of adduct being achieved after 3 days (entry 10) versus 32% in CH_2Cl_2 after 6 days in entry 9. Without TEMPO (entry 11), the PK adduct was obtained in a scarce 15% yield after 3 days. Even a disubstituted alkyne such as diphenlyacetylene (entries 12 and 13) considerably increased its reactivity when TEMPO was added to the reaction mixture. On the other hand, TEMPO exerted a smaller influence on the PKR of the less heavily substituted 1-octyne (entries 14 and 15).

While these experiments clearly demonstrate that TEMPO acts as an activator of the PKR, they also show that an excess of the nitroxide must be used in order to obtain a significant rate increase.

Activation by TEMPO could possibly take place by facilitating the nonoxidative decarbonylation of the starting alkyne complex, either through a reversible electron transfer[7] or via an initial CO/TEMPO ligand exchange,[6] as it has been postulated to occur in the Lewis base-catalyzed Pauson–Khand reaction.[8] To test this hypothesis, the effluent gases in a standard experiment were analyzed.[9] While the presence of CO was confirmed,[9a] no CO_2 could be detected.[9b]

To obtain additional insight on the reaction mechanism, theoretical calculations on the different mechanistic possibilities were performed with DFT methodology (B3LYP hybrid functional with the LACVP* basis set) with Spartan'02[10] on a model system (the dicobalt hexacarbonyl complex of acetylene and the dimethylnitroxide radical). First, the direct electron transfer from the cobalt complex to the nitroxyl radical and the opposite electron transfer, from the radical to the complex, were studied. In any case, both the single-electron oxidation or reduction of the $[Co_2(CO)_6(acetylene)]$ complex is characterized by a very high energy cost (+246.7 and +129.2 kcal mol^{-1}, respectively), which makes these processes very unlikely.

Next, the energetics of the CO/dimethylnitroxide ligand exchange and of the decarbonylation of the inital and the exchanged complexes was scrutinized by DFT on the same model system. In this respect, it is important to point out that all the reported theoretical studies on the PKR indicate that the initial dissociative step in the mechanistic sequence is rate-determining.[4d,11]

The paramagnetic (doublet) complexes resulting from the substitution of a CO ligand by dimethylnitroxide at axial and

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[6] (a) Jaitner, P.; Huber, W.; Gieren, A.; Betz, H. *J. Organomet. Chem.* **1986**, *311*, 379. (b) Jaitner, P.; Rieker, C.; Wurst, K. *Chem. Commun.* **1997**, 1245. (c) Jaitner, P.; Veciana, J.; Sporer, C.; Kopacka, H.; Wurst, K.; Ruiz-Molina, D. *Organometallics* **2001**, *20*, 568.

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[8] Sugihara, T.; Yamaguchi, M.; Nishizawa, M. *Chem. Eur. J.* **2001**, *7*, 1589.

[9] (a) Presence of CO was checked with an electrochemical cell CO detector. (b) Presence of CO_2 was checked by attempted precipitation of $BaCO_3$ from an aqueous solution of $Ba(OH)_2$.

[10] (a) *Spartan'02*; Wavefunction, Inc.; Irvine, CA, 2002. (b) Kong, J.; White, C. A.; Krylov A. I.; Sherrill, D.; Adamson, R. D.; Furlani, T. R.; Lee, M. S.; Lee, A. M.; Gwaltney, S. R.; Adams, T. R.; Ochsenfeld, C.; Gilbert, A. T. B.; Kedziora, G. S.; Rassolov, V. A.; Maurice, D. R.; Nair, N.; Shao, Y.; Besley, N. A.; Maslen, P. E.; Dombroski, J. P.; Daschel, H.; Zhang, W.; Korambath, P. P.; Baker, J.; Byrd, E. F. C.; Van Voorhis, T.; Oumi, M.; Hirata, S.; Hsu, C.-P.; Ishikawa, N.; Florian, J.; Warshel, A.; Johnson, B. G.; Gill, P. M. W.; Head-Gordon, M.; Pople, J. A. *J. Comput. Chem.* **2000**, *21*, 1532.

[11] (a) Yamanaka, M.; Nakamura, E. *J. Am. Chem. Soc.* **2001**, *123*, 1703. (b) de Bruin, T. J. M.; Milet, A.; Robert, F.; Gimbert, Y.; Greene, A. E. *J. Am. Chem. Soc.* **2001**, *123*, 7184.

equatorial sites, **Ia(d)** and **Ib(d)**, were first optimized and characterized as minima on the corresponding potential energy hypersurface.[12] In both cases, the substitution is predicted to be considerably endothermic, being, in any case, less costly at the axial site (5.9 vs 13.0 kcal mol^{-1}, Figure 1).

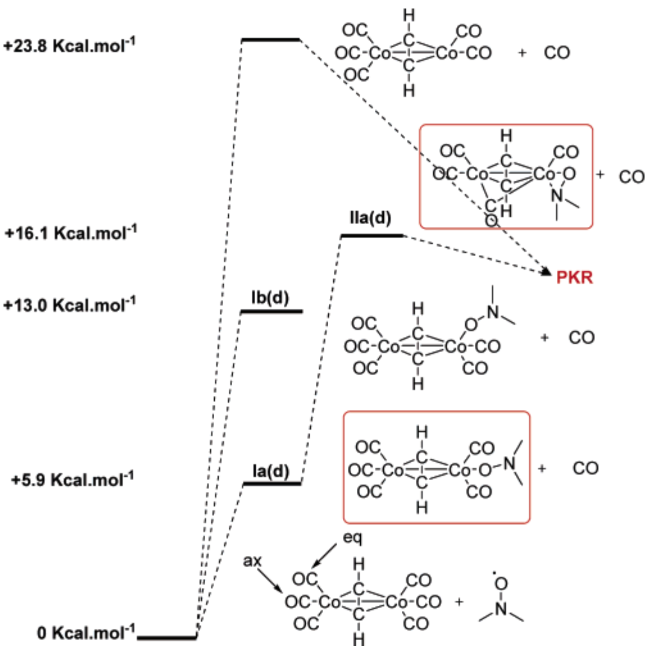

Figure 1. Possible reaction mechanism for the initial steps of the TEMPO-promoted PKR compared with those in the thermal reaction.

Most interestingly, the subsequent decarbonylation of **Ia(d)** involves an energetic cost of only 10.2 kcal mol^{-1} and leads, irrespective of the site from which the CO ligand is suppressed, to a new paramagnetic cobalt complex **IIa(d)**, stabilized through a bridged CO ligand plus a μ-(N−O) bond. This complex, which bears important structural similarities with the initial product arising from the reaction of TEMPO with $Co_2(CO)_8$,[6] would be the active species in a radical-Pauson−Khand mechanistic pathway, progressing toward products by coordination of the reacting olefin.

For comparison purposes, the loss of a CO ligand from the initial dicobalt hexacarbonyl complex was also calculated. The resulting barrier of 23.8 kcal mol^{-1}, which should be associated to the purely thermal reaction, is substantially higher than the barrier associated to the nitroxyl-promoted reaction (16.1 kcal mol^{-1}). This decrease in the *activation energy* of the reaction when run with nitroxide activation could account for the observed increase in reactivity. On the other hand, the presumably low concentration in the reaction medium of nitroxide-substituted species such as **Ia(d)**, resulting from the unfavorable energetics of the ligand substitution step, would account for the need of up to 6 equiv of TEMPO to drive the PKR at a reasonable rate.[13]

A closer look at the nitroxyl−dicobalt complexes shows that the decrease in the enthalpy of CO dissociation can be associated to longer Co−CO bonds. Thus, complex **Ia(d)** exhibits a Co−CO_{ax} bond length of 1.86 Å (1.78 Å in the starting complex), and this is probably related to the increased length of the Co−Co bond (2.77 vs 2.46 Å [2.50 Å in **IIa(d)**]). These findings, together with the significant amount of spin density located at the unsubstituted cobalt (see Figure 2), are consistent with a partial break of the Co−Co bond as a consequence of the CO/nitroxide substitution. They also suggest that the carbonyl ligand actually released is the one placed in an axial position on the $Co(CO)_3$ moiety in complex **Ia(d)**. Thus, the single electron provided by the nitroxide appears to be responsible for the activation of Co−CO bonds in the alkyne complex.

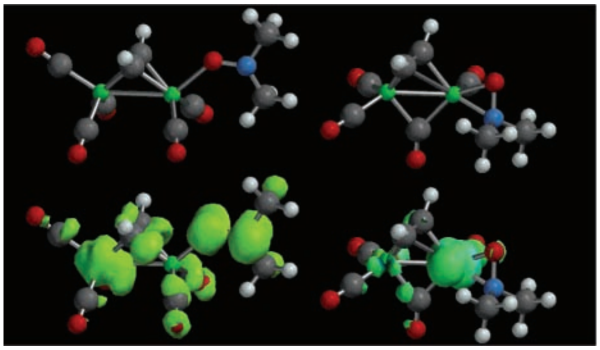

Figure 2. Optimized structures (top) and spin densities (bottom) of complexes **Ia(d)** (left) and **IIa(d)** (right).

For this activation to occur, however, an initial dissociation in the starting dicobalt hexacarbonyl complex should take place. Although this requirement also exists for the Lewis base-catalyzed PKR,[8] we wanted to investigate an alternative reaction pathway involving the attack of the nitroxyl radical to a carbonyl ligand. This reaction mode, similar to the initial attack of amine oxides to metal carbonyl complexes,[3] would not require any previous CO dissociation.

When the interaction of dimethylnitroxide and the dicobalt hexacarbonyl complex of acetylene was studied, a transition state, **TS(SM-III)**, connecting the separated reactants and the dicobalt−nitroxocarbonyl complex **III(d)**, was located. This transition state (see Figure 3) lies only 9.5 kcal mol^{-1} above the starting materials; accordingly, **III(d)** should be easily formed at room temperature or below. The spin density of transition state **TS(SM-III)** closely resembles that of complex **Ia(d)**. In both cases, a significant amount of spin density appears to have been transferred from the organic radical to the cobalt complex.

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(12) Nitroxide-substituted species (doublets) were calculated at the UHF level. ZPE correction was applied to all stationary points.

(13) All attempts to detect metal paramagnetic species by low-temperature EPR have been unsuccessful, and this can be attributed to the large excess of nitroxyl radical present in the reaction media and to the expected low concentration of doublet species such as **I**.

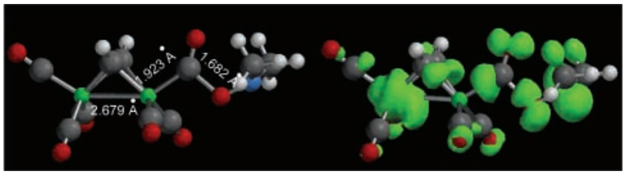

Figure 3. Structure of transition state **TS(SM-III)** (left) and its spin density distribution (right).

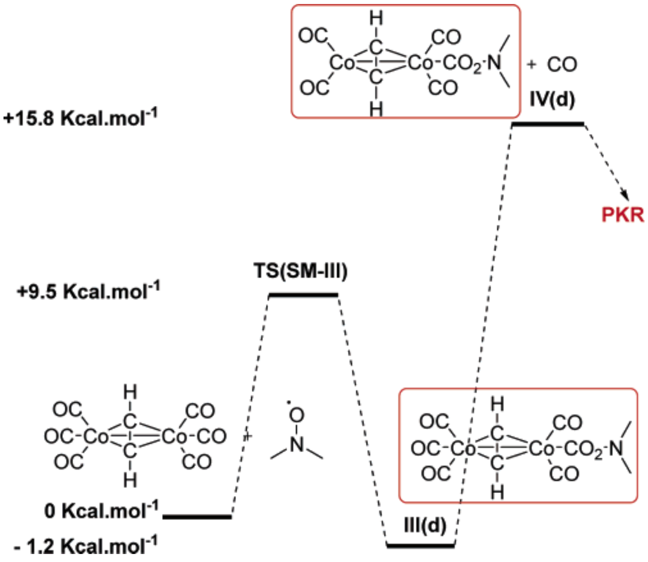

Figure 4. Alternative mechanism for the TEMPO-promoted PKR involving nitroxyl addition to a CO ligand of the starting complex.

Geometry relaxation in **TS(SM-III)** leads to **III(d)** (Figure 4), which is 1.2 kcal mol^{-1} lower in energy then its constituent fragments. Its geometrical characteristics are very similar to those of **Ia**, key bonds [Co—Co 2.69 Å, Co—CO 1.81—1.87 Å] being considerably longer than in the initial complex. Moreover, spin density transfer from the nitroxyl to the distal cobalt atom appears to be already complete at that stage (Figure 5).

Contrary to what is assumed for the *N*-oxide-mediated decarbonylation of metal carbonyl complexes,[3] **III(d)** did not show any tendency toward fragmentation with CO_2 extrusion. Alternatively, its decarbonylation led to a new, single complex, **IV(d)**, independently of the CO ligand lost. As in the case of **Ia(d)**, the decarbonylation of **III(d)** is greatly facilitated with respect to the closed-shell reference system, and the entalphy change for the two-step dissociation is only 15.8 kcal mol^{-1} above the starting materials, so that **IV(d)** could also be the active species in a radical-Pauson—Khand mechanism [compare with **IIa(d)**]. We have represented in Figure 5 the structures and spin density distributions of **III(d)** and **IV(d).**

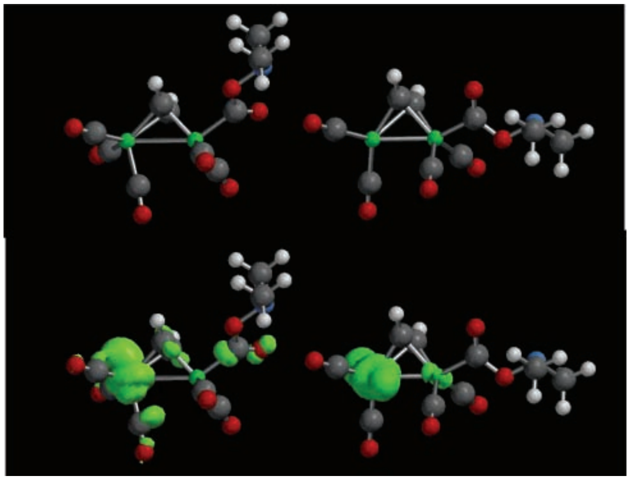

Figure 5. Optimized structures (top), and spin density distributions (bottom) of complexes **III(d)** (left) and **IV(d)** (right).

Thus, the two studied interaction modes between Co_2-$(CO)_6$(acetylene) and dimethylnitroxide [as a model for TEMPO] tend to indicate that the decarbonylation of a radical complex (formed either through a substitution or through an addition process) should be easier than that of the initial, closed-shell species.

In conclusion, we have found that TEMPO is an efficient and mild promoter of the intermolecular Pauson—Khand reaction, especially when sterically demanding acetylenes are involved in the reaction. Moreover, DFT calculations on a realistic model system indicate that paramagnetic cobalt complexes resulting from CO/nitroxide substitution or nitroxide addition to CO readily decarbonylate, thus providing a low-energy, radical pathway for the Pauson—Khand reaction. Further research aimed at expanding the scope of this kind of activation is underway and will be reported in due course.

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Supporting Information Available: Experimental procedures, energies, and atomic coordinates for compounds **Ia(d)**, **Ib(d)**, **IIa(d), III(d)**, **IV(d)**, and **TS(SM-III)**. This material is available free of charge via the Internet at http://pubs.acs.org.

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