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The Slow Rearrangement of a Sterically Hindered Nitro-Cyclohexadienone and the Absence of Phenol Oxidation by Nitrogen Monoxide

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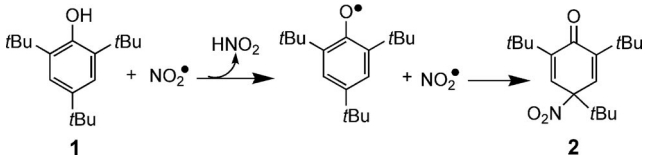
The exposure of 2,4,6-tri-*tert*-butylphenol (**1**) in solution to $NO_2^{\cdot}$ results in the rapid formation of 2,4,6-tri-*tert*-butyl-4-nitro-2,5-cyclohexadienone (**2**), which then undergoes a slow (ca. 3 d) rearrangement in the absence of air. The mechanism that describes this rearrangement is understood for the first time and involves the initial isomerization of **2** to form a (–ONO)-substituted cyclohexadieneone (**6**). The nitrite moiety undergoes bond homolysis releasing $NO^{\cdot}$ while forming an oxyl radical intermediate. An intermolecular, concerted hydrogen abstraction, which proceeds between **6** and this oxyl radical, results in the simultaneous formation of all stable products, some of which have not been previously observed. Furthermore, when **1** is exposed to $NO^{\cdot}$ under anaerobic conditions, no reaction is observed.

Introduction

The importance of phenoxyl radicals and the free radical nitrogen monoxide ($NO^{\cdot}$) in many environmental and biological processes has made these species the subject of many studies. Phenoxyl radicals are commonly used to protect organic materials from oxidative stress and are important in the combustion of aromatic compounds.[1] In biological systems they act as catalysts and are involved in protein redox reactions.[2a–2c] Furthermore, its been shown that these phenoxyl radical species can function as $NO^{\cdot}$ carriers.[2d,2e] With $NO^{\cdot}$ linked to many physiological processes, the reactivity and stability of these coupled species are the subject of continued interest.[2c,2f] For well over a century, the oxidation of sterically hindered phenols by nitrogen oxide free radicals has been explored.[3] Although the literature results for $NO^{\cdot}$ are conflicting,[2d,3f] it is clear that nitrogen dioxide ($NO_2^{\cdot}$) quickly oxidizes phenols.[3c–3f]

In the case of 2,4,6-tri-*tert*-butylphenol (**1**), and other sterically hindered phenols, previous kinetic studies indicate that $NO_2^{\cdot}$ initially extracts a phenolic hydrogen atom, generating a phenoxyl radical which then couples with a second $NO_2^{\cdot}$ to form 2,4,6-tri-*tert*-butyl-4-nitro-2,5-cyclohexadienone (**2**), see Scheme 1.[3c] Further studies have revealed that **2** is not the thermodynamically stable product, but it undergoes significant rearrangement to final products that no longer contain the nitro group (or nitrogen atom) originating from the bound $NO_2^{\cdot}$.[3d,3e] Surprisingly, the mechanism for this reaction is not completely understood, and no experimental results have been obtained confirming any of the postulated intermediates.[3d,3e] We have found that the rearrangement of **2** is remarkably slow under the conditions used allowing for the identification of intermediates and new products not seen in these previous studies.[3] A significant finding, not observed until now, is the release of $NO^{\cdot}$ via bond homolysis.



Scheme 1. Nitrogen dioxide reaction with 2,4,6-tri-*tert*-butylphenol (**1**).

Finally, when the reaction between **1** and $NO^{\cdot}$ was carried out under vacuum conditions, we observed a very different result from those previously published.[2d,3g]

Results and Discussion

When a cyclohexane solution of **1** was allowed to react with a molar excess of $NO_2^{\cdot}$ in a closed evacuated apparatus with an attached NMR tube, a completely anaerobic reaction ensued. After a few minutes, the excess $NO_2^{\cdot}$ and the solvent were removed leaving behind a solid, yellow residue. Deuteriated cyclohexane (C_6D_{12}), needed for the NMR lock, was placed into the apparatus. The resulting yellow solution was poured into the NMR tube which was subsequently sealed from the apparatus. The solution was then monitored, under anarobic conditions, over an extended period of time using NMR techniques.

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The first ^{1}H NMR spectrum, collected after the NMR sample was removed from the apparatus (0.17 h), shows a strong down-field resonance at δ = 7.15 ppm from two equivalent Hs on the cyclohexadienone ring of **2**, Figure 1.

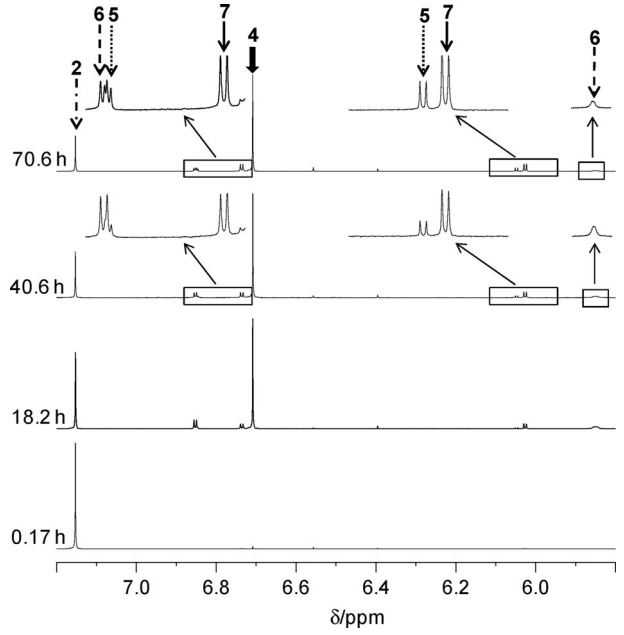


Figure 1. Down-field expansion of the 400-MHz ^{1}H-NMR spectra recorded at various time intervals as the rearrangement of **2** progressed at 298 K. The different arrows (pointing down) mark the ^{1}H resonances for all species found in solution. The expanded regions have been magnified vertically (8×).

There are also two strong proton resonances in the up-field region at δ = 1.26 ppm and δ = 1.04 ppm with a peak integrated ratio of 2:1, respectively, which are from the two different sets of *tert*-butyl groups on **2** (see Supporting Information). The spectrum recorded at 0.17 h shows that **2** is the dominant species in solution, and no NMR peaks due to **1** were observed, Figure 1.[4] A closer look at this spectrum reveals that a small amount of 2,4,6-tri-*tert*-butyl-4-hydroxycyclohexa-2,5-dienone (**3**) (ca. 2%) was also formed in the initial minutes of exposure to $NO_2^{\cdot}$.[5] As the reaction progressed, the yellow solution turned emerald green, and the most notable changes in the NMR spectrum were the decrease in intensity of the peak at δ = 7.15 ppm and the appearance and growth of a new resonance at δ = 6.71 ppm (Figure 1). The growth of this singlet peak also correlates with the growth of two other peaks at δ = 1.24 ppm and δ = 0.988 ppm in the up-field *tert*-butyl signal region that also integrate as 2:1, respectively. This new species must have a structure that is quite similar to that of **2**. If it contains a nitrogen atom from the rearrangement of the nitro group on **2** then ^{15}N isotopic labeling coupled with ^{15}N-NMR would be definitive.

The experiment was repeated with ^{15}N-nitrogen dioxide, and the resulting C_6D_{12} solution was analyzed using ^{15}N-NMR spectroscopy (Figure 2). The resonance at δ = 12 ppm diminishes in intensity while the one at δ = 204 ppm increases in intensity, just as shown in Figure 1. The up-field resonance is that of the nitro group on **2**,[6] and the ^{15}N coupling is also apparent in the ^{1}H NMR spectrum where the resonance at δ = 7.15 ppm is now split into a doublet ($^3J_{1H-15N}$ = 1.08 Hz). The down-field resonance is commonly found in systems that contain an O-bound nitrite (ONO-) substituent;[6] the structure of this compound must be 1,3,5-tri-*tert*-butyl-4-oxocyclohexa-2,5-dienyl nitrite (**4**). The peak at δ = 6.71 ppm in the ^{1}H NMR spectrum remains a singlet; no $^4J_{1H-15N}$ coupling is observed. Although **4** has been postulated as a reactive intermediate by others, it has never been detected until now.[3d,3e] However, in the absence of air (i.e., under vacuum conditions), it appears that **4** is quite stable becoming the dominant species in solution.

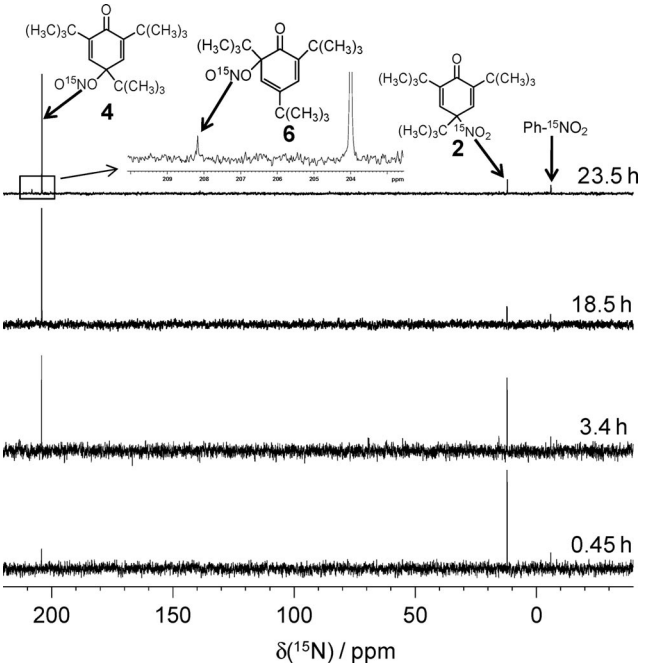
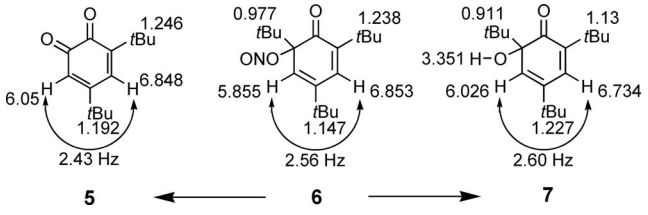


Figure 2. 50.70-MHz ^{15}N-NMR spectra recorded at various time intervals as the rearrangement of **2** progressed at 298 K. The spectrum collected at 23.5 h was collected for a longer time period (10×). ^{15}N-Nitrobenzene (Ph-$^{15}NO_2$) was used to calibrate the ^{15}N-chemical shifts. (Inset) Expansion of the downfield region of the top spectrum that shows the resonance for **6**.

A closer look the ^{1}H NMR spectra (expanded regions in Figure 1) reveals that there are three other cyclohexadienone derivatives in solution that vary in concentration over time.

They are structurally different from **2**, **3** or **4**, because the ring protons are no longer magnetically equivalent. After careful analysis of the ^{1}H NMR spectroscopic data, along with ^{13}C{^{1}H} NMR and 2D heteronuclear (^{1}H-^{13}C HSQC and HMBC) and homonuclear (^{1}H-COSY) spectroscopy, the structures of these three species have been determined, Scheme 2.[7] One of these is 4,6-di-*tert*-butyl-*o*-benzoquinone (**5**) which has been isolated by others,[3d,3e] while the other two have not been previously observed.[8] The presence of 1,3,5-tri-*tert*-butyl-6-oxocyclohexa-2,4-dienyl nitrite (**6**), the asymmetric isomer of **4**, was also con-

firmed in the ^{15}N-NMR spectroscopic data (see inset in Figure 2) having a weak resonance at δ = 208 ppm. The formation of 2,4,6-tri-*tert*-butyl-6-hydroxy-cyclohexa-2,4-dienone (**7**) was quite unexpected, because no other study has detected it in solution or proposed it as a viable product or intermediate.[3d,3e] Lastly, the presence of isobutylene (**8**) was also detected in the ^{1}H NMR spectroscopic data at δ = 4.62 ppm (2 H atoms) and at δ = 1.68 ppm (6 H atoms), see Supporting Information



Scheme 2. The three other derivatives formed from **2** with ^{1}H-chemical shifts (in ppm). $^4J_{HH}$ are below the curved arrows.

To our surprise, when the evacuated NMR tube was opened to air, a brown gas (believed to be $NO_2^{\cdot}$) appeared instantly. Because $NO_2^{\cdot}$ forms when nitrogen monoxide (a colorless gas) and oxygen are mixed, it would seem that NO$^{\cdot}$ is produced during the rearrangement of **2**. In a separate experiment, the gas generated from the rearrangement was condensed into an evacuated IR cell via the vacuum manifold and the FT-IR spectrum obtained. A strong absorption band centered at 1876 cm^{-1} was observed confirming the presence of NO$^{\cdot}$.[9]

With all species in solution now identified, we tracked their change in concentration over the course of the reaction using the ^{1}H NMR peak integrations and the initial concentration of **2**, Figure 3. We see from the plots that **2** *decreases* rapidly while that for **4** *increases* rapidly early on in the rearrangement. After some time, the rate of change for both slows significantly where the former continues to exhibit a steady loss in concentration while the latter remains essentially constant. There is also a rapid production of **6** followed by a steady decay suggesting that this species is a true intermediate. The expanded spectra in Figure 1 clearly show this loss of **6** as seen from the peaks at δ = 5.855 ppm and at δ = 6.853 ppm. Moreover, **7** is also produced quickly at first, but its rate of growth then slows and remains linear. With **5** and **8** we find that they are generated much more slowly, but their rates of growth and concentration are identical throughout the course of the reaction. Furthermore, we find that **3**, produced during the $NO_2^{\cdot}$ exposure, actually *decreases* in concentration initially, after which a slow and steady production occurs. Finally, we see that decreasing the initial concentration of **2** reduces the rate of production of all species as expected.

A proposed mechanism that accounts for all of these observations requires at least three important factors. First, a homolytic bond cleavage of the nitrite moiety is necessary for the formation of NO$^{\cdot}$. Second, hydrogen extraction from a *tert*-butyl group must occur during the formation of **8**, and finally, this hydrogen extraction must coincide with the

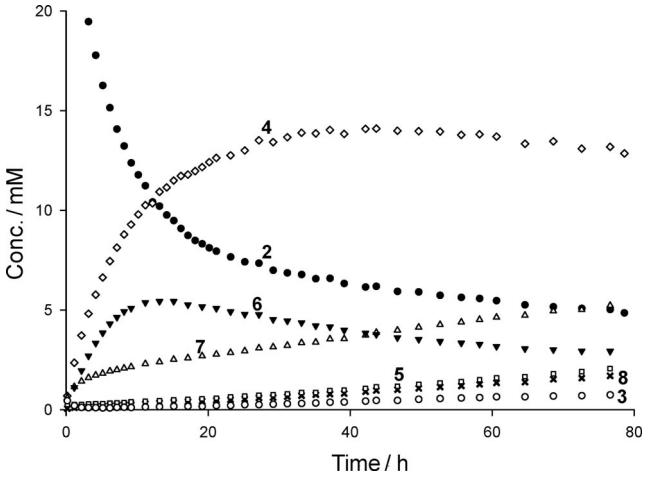
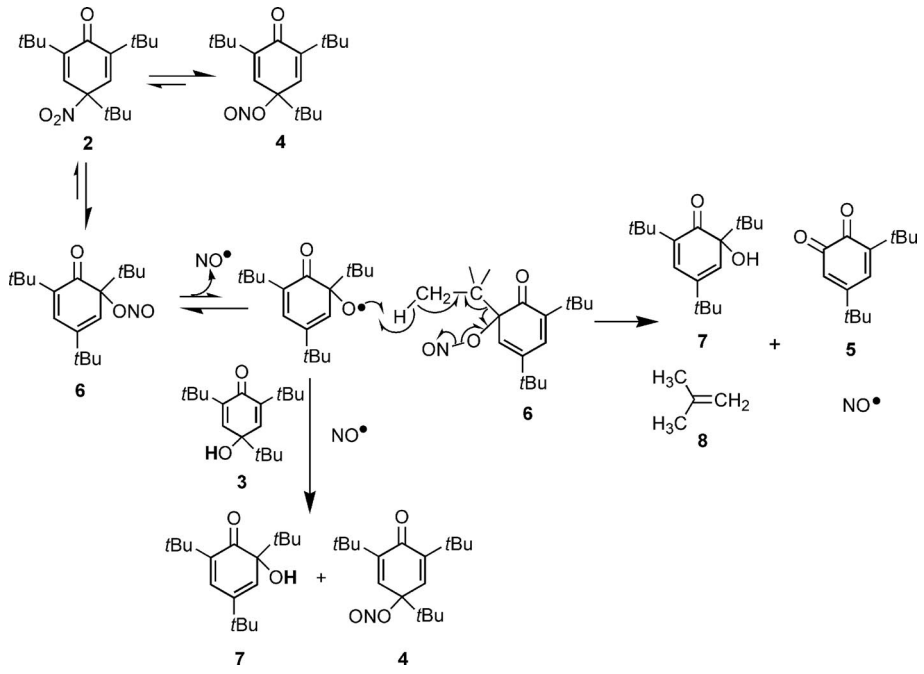


Figure 3. Concentration vs. time plots for all species observed in solution at 298 K in the ^{1}H NMR spectroscopic data. The concentrations were determined from the ^{1}H peak integrations and the initial concentration of **2**. Symbols representing each species are: **2** (●), **3** (○), **4** (◇), **5** (□), **6** (▼), **7** (Δ), **8** (×).

simultaneous production of **5** and **8**. A mechanism that accounts for all of these aspects is presented in Scheme 3.

The equilibrium formation of **4** and **6** are the first steps in the rearrangement of **2**, and it takes many hours for them to accumulate in solution, Figure 3. No further rearrangement of **4** is expected, because it shows little sign of abating and therefore is not very reactive under these conditions. The path by which **2** rearranges to form **4** and **6** could not be determined from these studies. However it has been proposed that **2** dissociates back to $NO_2^{\cdot}$ and a phenoxyl radical (see Scheme 1) before forming the nitrite species.[3b,3d,3e] The buildup of **6** is necessary to drive the reaction forward during which this unstable species undergoes homolysis to form NO$^{\cdot}$ and a 6-oxylcyclohexadienone radical intermediate, Scheme 3. Two reactions then ensue with this radical. The presence of **3** in solution (formed from the initial exposure of **1** to $NO_2^{\cdot}$) provides a hydrogen donor to the oxyl radical generating **7**, as well as more **4**,[10] which would explain the observed loss of **3**. Finally, as the concentration of **6** increases, an intermolecular, concerted hydrogen abstraction between **6** and the oxyl radical proceeds. This results in the simultaneous formation of **5** and **8**, and the production of more NO$^{\cdot}$. These two reaction paths also account for the greater production of **7** relative to that of **5**. We considered a possible intramolecular 1,4-hydrogen abstraction between the -O$^{\cdot}$ moiety and one of the hydrogen on the geminal *tert*-butyl group. However, this would lead to very different products than those observed in the NMR spectroscopic data.

Interestingly, when the solution was analyzed via EPR spectroscopy, no radical was detected. This is explained by the slow progress of this reaction, which suggests that the equilibrium formation of the oxyl radical intermediate must lie far to the left and have a high energy of activation. However, once formed the oxyl radical reacts quickly to generate the observed products. Nitrogen monoxide was also not ob-



Scheme 3. Proposed mechanism for the rearrangement of **2**.

served via EPR, but this is not surprising because EPR spin traps are needed for its detection.[11]

A nearly identical mechanism involving a 4-oxylcyclohexadienone radical intermediate (from the homolysis of **4**) and **6** would explain the formation of **3** observed later in the course of the reaction. However with such a small amount produced, this homolytic cleavage must be less favorable than that for **6**, because the loss of **4** is quite slow.

With the generation of NO˙ during the course of rearrangement, we anticipated that a possible side reaction would take place between NO˙ and the phenoxyl radical intermediate that is expected to form during the equilibrium isomerization between **2**, **4** and **6** (see Scheme 3). Based on Janzen's observations,[2d] we would expect to see nitroso-substituted species (R–N=O, where R is the hindered cyclohexadieneone) in the NMR spectroscopic data. However, we found no evidence for these compounds. These results motivated us to investigate further the reaction between NO˙ and **1** using nearly the same procedures described above. After the C_6D_{12} solution containing **1** was generated in the evacuated apparatus, a molar excess of NO˙ was then added. The apparatus was sealed, and the resulting solution was mixed for 30 min under this NO˙ atmosphere. After this time, an NMR sample was collected while maintaining this NO˙ atmosphere. Remarkably, the ^{1}H NMR spectrum obtained looked *identical* to that of **1**! No reaction between the hindered phenol and NO˙ was apparent (see Supporting Information for NMR spectra). We are currently investigating the exposure of NO˙ to other hindered phenols to see if similar results are obtained.

Conclusions

The pristine experimental conditions used in this work have allowed us to observe the rearrangement of **2** without the potential complications from exposure to air, which was critically important when characterizing all products and intermediates formed. Because radical intermediates and NO˙ are clearly involved in this mechanism, the exposure of this system to the atmosphere (particularly O_2) will completely alter its chemistry and kinetics. Therefore, our method is quite advantageous, because it removes this complication, and can be applied to a host of nitrogen oxide/phenoxyl radical reactions using NMR spectroscopy for analysis. We are currently exploring the role of O_2 in the rearrangement of **2** and how its presence may account for the discrepancy between our results and those of others.[2d,3] These studies are quite valuable for gaining more insight in this important area of phenoxyl and nitrogen oxide radical chemistry, which has considerable biological interest. In particular, NO˙ does not react with tri-*tert*-butylphenol under anaerobic conditions!

Experimental Section

To a glass apparatus was added 1.0 mL of a cyclohexane solution (27.5 mM) containing **1**. A glass-break tube containing 2.0 μL tetramethylsilane (TMS) was also added. The TMS served as a peak integration reference. The apparatus was attached to a vacuum line and evacuated. Next, approximately 0.3 mmol of NO_2˙ gas (a tenfold excess) was released into the manifold and condensed into the apparatus using liquid nitrogen. The apparatus was isolated, using an attached stopcock, warmed to ambient temperature, and the solution was mixed for 3 min. The apparatus was re-attached to the vacuum manifold and the excess NO_2˙ and solvent were pumped away. One milliliter of C_6D_{12} was vacuum distilled into the apparatus which was then isolated via a stopcock on the apparatus. The TMS break tube was broken and the contents well mixed. A portion of the C_6D_{12} solution was transferred to an NMR tube (attached to the apparatus) which was subsequently

sealed, while maintaining vacuum conditions, using a glass torch. For the ^{15}N experiments with $^{15}NO_2^{\cdot}$, ^{15}N-nitrobenzene (Ph-$^{15}NO_2$) was placed in the break tube instead of TMS. The sealed NMR sample was then analyzed over a period of 80 h at 298 K using either a 400 MHz (for ^{1}H NMR experiments) or 500 MHz (for ^{15}N, ^{13}C and 2D experiments) Bruker Avance III NMR spectrometer with a variable temperature, pulsed field gradient probe. The sample was left in the NMR probe and continuously spun at 20 Hz for the duration of the experiment; NMR spectra were obtained at fixed time intervals using an automation routine within the Bruker NMR software.

Supporting Information (see also the footnote on the first page of this article): Experimental details and all 1D and 2D NMR spectroscopic data.

Acknowledgments

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[4] The ^{1}H NMR assignments for **1** in C_6D_{12} are: δ = 7.13 ppm (2 H), δ = 4.78 ppm (1 H), δ = 1.414 ppm (18 H) and δ = 1.268 ppm (9 H) and was not observed in these experiments.

[5] The ^{1}H NMR assignments for **3** are close to those measured by other groups, see reference 3d. The signals of the two equivalent ring hydrogen atoms appear at δ = 6.56 ppm.

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[7] HSQC Heteronuclear Single Quantum Coherence detects H,C correlations via $^1J_{HC}$, HMBC-Heteronuclear Multiple Bond Coherence detects H,C correlations via $^2J_{HC}$ and $^3J_{HC}$. See Supporting Information for complete ^{13}C assignments and 2D spectra.

[8] The broadening of the ^{1}H resonance at δ = 5.855 ppm (**6**) is likely due to rotational motion of the nitrite moiety.

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