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Citation	The 22nd International Conference on Raman Spectroscopy (ICORS 2010), Boston, MA., 8-13 August 2010.
Issued Date	2010
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Water Concentration Dependent Photochemistry of Ketoprofen in Neutral Aqueous Solutions

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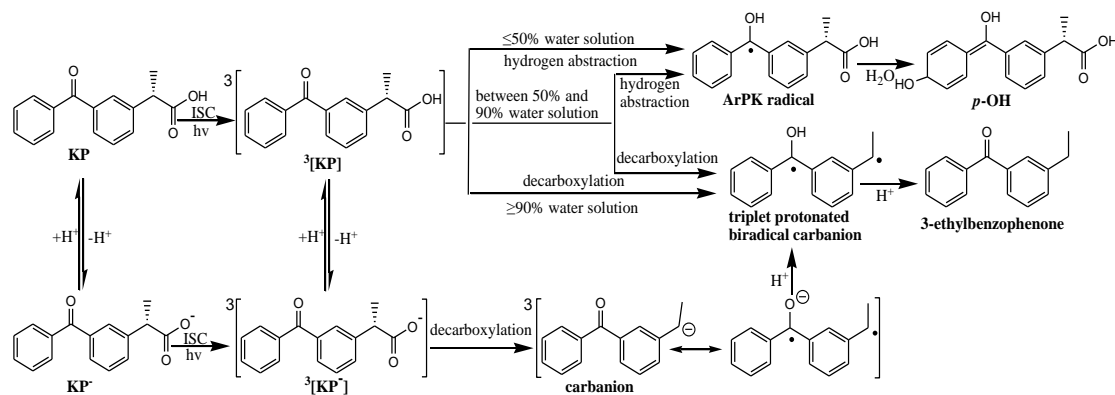
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Ketoprofen (KP) is a nonsteroidal anti-inflammatory drug (NSAID) that is commonly employed to treat moderate acute and chronic painful conditions. However, the use of KP can lead to photosensitivity and phototoxicity because of its specific structure and electronic properties.¹ Many investigations have been done in recent years to study both the phototoxic and photoallergic reactions caused by KP in order to estimate the safety of KP and also to elucidate the mechanism(s) of the photosensitivity reactions when KP is exposed to ultraviolet light.²⁻⁵ These results revealed that the photochemistry of KP in aqueous solution is strongly affected by its acid-base chemistry. The neutral form of ketoprofen that exists in the absence of a base displays typical benzophenone-like photochemistry⁶, while the deprotonated ketoprofen that exists in the presence of a base undergoes an efficient photodecarboxylation process^{6,7} and therefore it appears that the photochemistry of KP is likely determined by the precursors, the neutral form of ³[KP] or the deprotonated ³[KP⁻¹].⁶ In an attempt to determine the nature of the carbanion's precursor, the photochemistry of KP was examined by using transient absorption spectroscopy and quenching experiments in organic solvent-water mixtures.^{2,8} However, it was difficult to clearly distinguish different intermediates that have similar electronic absorption spectra and time-scales in the time-resolved transient absorption experiments because of the spectral overlap of the absorption spectra on similar time scales for the different transient species that could be present in the reactions. In these kinds of reactions, time-resolved vibrational spectroscopy techniques are powerful tools to employ since they can better distinguish the different transient species from each other by their vibrational frequencies that can be utilized as a fingerprint for each species.

In this report, nanosecond time-resolved resonance Raman spectroscopy was employed to study the photochemistry of ketoprofen in neutral aqueous solutions with varying water concentrations.⁹ The rate constants and reaction mechanism of ketoprofen were observed to be greatly dependent on the concentration of the solvent. Scheme 1 shows the proposed mechanism. In neat acetonitrile and solvents with low concentrations of water (such as water:acetonitrile ≤ 1:1, v:v), ketoprofen displays mainly benzophenone-like photochemistry to produce a triplet state that subsequently forms a ketyl radical-like species by a hydrogen abstraction reaction. However, in

solvents with very high concentrations of water (like water:acetonitrile \geq 9:1, v:v), the triplet state ketoprofen is first seen and then experiences a very fast decarboxylation process to produce a triplet protonated biradical carbanion species. For solvents with moderate higher water concentrations (like between 50% and 90% water by volume), the hydrogen abstraction and decarboxylation processes are two competitive pathways with different rate constants so that the triplet state of ketoprofen will simultaneously generate a ketyl radical species and a triplet protonated biradical carbanion species with the population of each species dependent on the water concentration.



SCHEME 1. A schematic diagram of the proposed photochemical mechanism of KP in different water concentration solutions is displayed.

ACKNOWLEDGMENTS

This work was supported by a grant from the Research Grants Council of Hong Kong (HKU 7035/08P), the award of a Croucher Foundation Senior Research Fellowship (2006-07) from the Croucher Foundation and an Outstanding Researcher Award (2006) from the University of Hong Kong to DLP.

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