ChemComm

IYC 2011
International Year of CHEMISTRY

This article is part of the

Supramolecular Chemistry web-based thematic issue

celebrating the International Year of Chemistry 2011

Guest editors: Professors Philip Gale, Jonathan Sessler and Jonathan Steed

All articles in this issue will be gathered together online at www.rsc.org/chemcomm/supra.

ChemComm

Dynamic Article Links

Cite this: *Chem. Commun.*, 2011, **47**, 2841–2843

www.rsc.org/chemcomm

COMMUNICATION

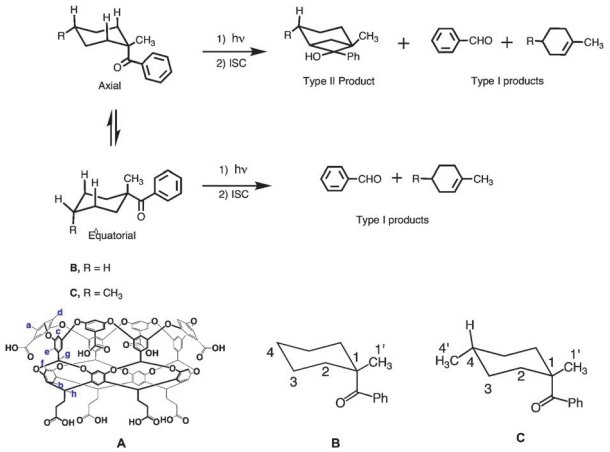
Restricted rotation due to the lack of free space within a capsule translates into product selectivity: photochemistry of cyclohexyl phenyl ketones within a water-soluble organic capsule†‡

Revathy Kulasekharan, Rajib Choudhury, Rajeev Prabhakar and V. Ramamurthy*

Received 2nd December 2010, Accepted 6th January 2011
DOI: 10.1039/c0cc05337f

The rotational mobility of organic guest molecules when included within a confined capsule is restricted and this feature could be translated into product selectivity as established with the photochemical behavior of cyclohexyl phenyl ketones.

The adoption of a high-energy conformation by a piperidine derivative within the confined space of a bimolecular capsule of a deep cavity cavitand commonly known as octa acid (**A** in Scheme 1) has recently been demonstrated.[1] This prompted us to investigate the photochemical behavior of cyclohexyl phenyl ketones which have been established to show conformer dependent photochemistry.[2–4] The Norrish type II reaction that occurs in these compounds is dependent on the placement of the γ-hydrogen in relation to the excited carbonyl chromophore that is part of the phenylacyl group. On the other hand, the Norrish type I reaction is independent of the conformational location (axial or equatorial) of the phenylacyl group. Thus, when the phenylacyl group is in the axial position and the γ-hydrogen within reach of the carbonyl chromophore both Norrish type II and type I reactions occur.[5] Norrish type I reaction alone takes place when the group is in the equatorial position (Scheme 1). It is worth noting that the rotational effect of the α-bond on type I reactions is yet to be fully understood.[6,7] Especially when the α-bond is substituted with the phenyl group the nature of the lowest excited state may vary with the overlap of the aromatic π-bond and C=O π-bond. It should be noted that rotation of the carbonyl group away from the γ-hydrogen, even when the group is axially located would forbid the type II reaction. In the ground state cyclohexyl phenyl ketone equilibrates between two conformers in which the phenylacyl group is either in the axial or the equatorial position (Scheme 1). However the reactive triplet states of the two conformers react before their equilibration and lead to Norrish type I and type II products. This phenomenon established by Lewis *et al.*,[2–4] as well as our recent observation with a piperidine derivative suggested that derivatives of cyclohexyl phenyl ketones, *viz.* 1-methylcyclohexyl phenyl ketone (**B**) and *cis*-4-methyl-1-methylcyclohexyl phenyl ketone (**C**) (Scheme 1), are ideal systems to test the feasibility of the photoproduct control through manipulation of the distribution of the conformer by encapsulation of the ketone within a molecular container. We show below that photoproducts' distributions from **B**@$\mathbf{A}_2$ and **C**@$\mathbf{A}_2$ (one molecule of **B** or **C**, respectively, included within a capsule made up of two molecules of **A**)[8] in water are different from **B** and **C** in acetonitrile. ^{1}H-NMR experiments and molecular dynamic (MD) simulations carried out to gain an insight into the structure of **B** and **C** within the capsule helped us understand their distinctly different behavior within the capsule and in acetonitrile.



Scheme 1 Reaction manifold for the photochemistry of guests **B** and **C**. Structures of host and guests used for the study.

Complexation of guests **B** or **C** with **A** (host) in water was achieved by stirring the host and the guest in the borate buffer for a few minutes that resulted in a clear solution and confirmed by the large upfield shift of the guest and changes in the host ^{1}H NMR signals.[9] Fig. 1 provides the ^{1}H NMR spectra of the free host, and **B** or **C** in the presence of two equivalents of **A**. Note that signals due to most cyclohexyl ring hydrogens of **B** and **C** appear close to or below δ 0 ppm in the presence of **A**. Most importantly, in the case of **C**, the 4-methyl signal (marked 4′ in Fig. 1) appears at δ −3.1 ppm, *i.e.*, 4.0 ppm upfield shifted with respect to $CDCl_3$. To ascertain the guest–host ratio (G : H) ^{1}H

Department of Chemistry, University of Miami, Coral Gables, FL 33124, USA. E-mail: murthy1@miami.edu; Tel: +1 305 284 1534
† Electronic supplementary information (ESI) available: 1D and 2D ^{1}H NMR spectra of **B**@$\mathbf{A}_2$ and **C**@$\mathbf{A}_2$ and structures related to MD simulations, experimental section. See DOI: 10.1039/c0cc05337f
‡ This article is part of a ChemComm 'Supramolecular Chemistry' web-based themed issue marking the International Year of Chemistry 2011.

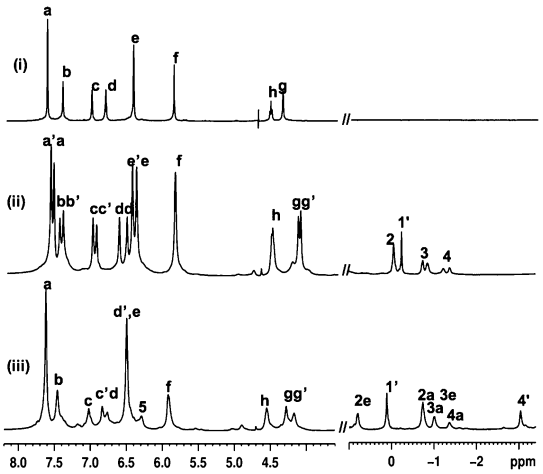


Fig. 1 ^{1}H NMR (500 MHz, D_2O) spectra (i) **A** (1 mM in 10 mM borate buffer), (ii) **B**@$\mathbf{A}_2$ ([B] = 0.5 mM, [**A**] = 1 mM in 10 mM borate buffer) and (iii) **C**@$\mathbf{A}_2$ ([**C**] = 0.5 mM, [**A**] = 1 mM in 10 mM borate buffer). Aromatic resonances of the host **A** are represented by labels a–h and bound guest resonances are labeled 1–4.

NMR titration experiments were performed by slow addition of ketones **B** or **C** to a buffered (10 mM sodium tetraborate) solution of host **A**. The spectra presented in Fig. S1 and S2 (ESI†) suggest a 1 : 2 complex. Consistent with this suggestion, addition of more than 0.5 equiv. of the guest showed signals due to the free ketone in water and there were no changes in the spectrum of the complex. The measured diffusion constants for the complexes by DOSY NMR[10] (Fig. S3 and S4 in ESI†) are consistent with that expected for a 1 : 2 capsular assembly.[11] The absence of exchange between the free and encapsulated ketones inferred from the independence of the chemical shift of the included guest protons at any stage of titration suggests that the capsule remains intact in the NMR time scale, much longer than the excited state lifetime. The observed chemical shifts of the guest and NOESY data provide an indication of the orientation of the guest within the capsule. The large upfield shift for the 4-methyl in **C** is consistent with the structure in which **C** is anchored at the narrower end of the capsule through the 4-methyl group. The appearance of 1-CH_3 (marked 1′ in Fig. 1 and Fig. S5 in ESI†) close to δ 0 ppm ($\sim$1.5 ppm upfield shifted with respect to $CDCl_3$) in **B**@$\mathbf{A}_2$ and **C**@$\mathbf{A}_2$ suggests it to be located close to the middle region of the respective capsule. The appearance of two independent signals for several of the chemically equivalent hydrogens of the two halves of the capsule (Fig. 1) revealed the lack of tumbling of the guest molecule within the capsule.[9] Had the guest molecule been tumbling freely the top and bottom halves of the capsule would have been magnetically equivalent to exhibit a single signal for otherwise chemically equivalent hydrogens. Based on the above NMR data we visualize the two ketones to be held rigidly within the capsule made of two molecules of **A**. The 2D-NOESY data provided in ESI† (Fig. S7 and S10) are consistent with the structure shown for the two complexes in Fig. 2.

We substituted the smaller *cis*-4-methyl-1-methylcyclohexyl phenyl ketone (**C**) that would fit within the capsule for the larger *cis*-4-*tert*-butyl-1-methylcyclohexyl phenyl ketone used by Lewis *et al.*[4] to establish the ground state conformational

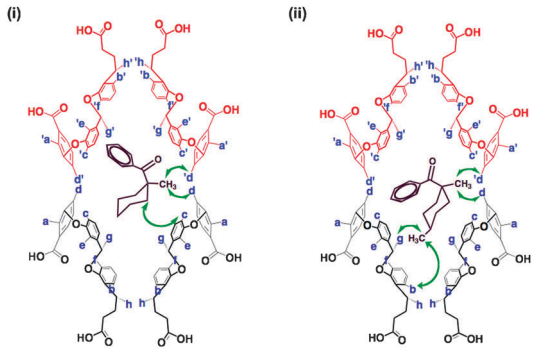


Fig. 2 Orientation of guests within the capsuleplex derived from 2D NOESY studies. (i) **B**@$\mathbf{A}_2$ and (ii) **C**@$\mathbf{A}_2$.

effects on the photochemistry of aryl alkyl ketones. Similar to the latter ketone, **C** upon irradiation in acetonitrile gave the cyclobutanol product exclusively (Scheme 1). Surprisingly, irradiation of **C**@$\mathbf{A}_2$ in the borate buffer resulted in benzaldehyde and 1-methylcyclohexene only, products of Norrish type I reaction without any trace of cyclobutanol as evidenced by ^{1}H NMR and GC. These observations extended to ketone **B** as well. As reported earlier, irradiation of **B** in acetonitrile resulted in cyclobutanol and benzaldehyde (and 1-methylcyclohexene) in the ratio 4 : 1. However, irradiation of **B**@$\mathbf{A}_2$ in the borate buffer gave only Norrish type I products, benzaldehyde and 1-methylcyclohexene. No Norrish type II products were detected. The photochemical behavior of ketones **B** and **C** is thus distinctly different within the capsule.

To probe the possibility that the anomalous behavior could be due to different conformers preference of these ketones in acetonitrile and within the capsule, we performed ^{1}H DQF COSY NMR analysis[10] of **C** in $CDCl_3$ and as capsular complex with **A** in water. In ^{1}H DQF COSY NMR correlation spectrum relatively large coupling constant between pairs of protons is reflected as strong cross peaks; strong cross peaks in a cyclohexyl ring system signify pairs of vicinal hydrogens with diaxial geometry and/or geminal hydrogens; vicinal hydrogens in a gauche relationship, *i.e.*, axial–equatorial or diequatorial pairs in a cyclohexane ring would display either weak or no cross peaks.[12] The ^{1}H DQF COSY NMR partial correlation spectrum of **C** in $CDCl_3$ is provided in Fig. 3i. As illustrated in the figure, the signal at 0.92 ppm for hydrogen 3a shows two cross peaks, a strong one with a signal at 1.25 ppm (hydrogen 2a) and a weak one with a signal at 2.5 ppm (hydrogen 2e) indicating it to be axially located, only position where both large (diaxial, 2a) and small (axial/equatorial, hydrogen 2e) coupling constants can be observed. Hydrogen 3a shows an additional strong cross peak with a signal at 1.3 ppm for the hydrogen 4a suggesting it to be a diaxial coupling. On this basis, we assign hydrogen 4a to be axial and in turn, the 4-methyl to be equatorial. Since the synthetic procedure yielded the *cis*-4-methyl-1-methylcyclohexyl phenyl ketone, the phenylacyl group must be in the axial position. Its axial positioning is consistent with the quantitative formation of the cyclobutanol product. Similar analysis of the ^{1}H DQF COSY NMR spectrum of **C**@$\mathbf{A}_2$ revealed that the conformation of **C** within the capsule is the same as in $CDCl_3$ solution (Fig. 3ii). It was puzzling that

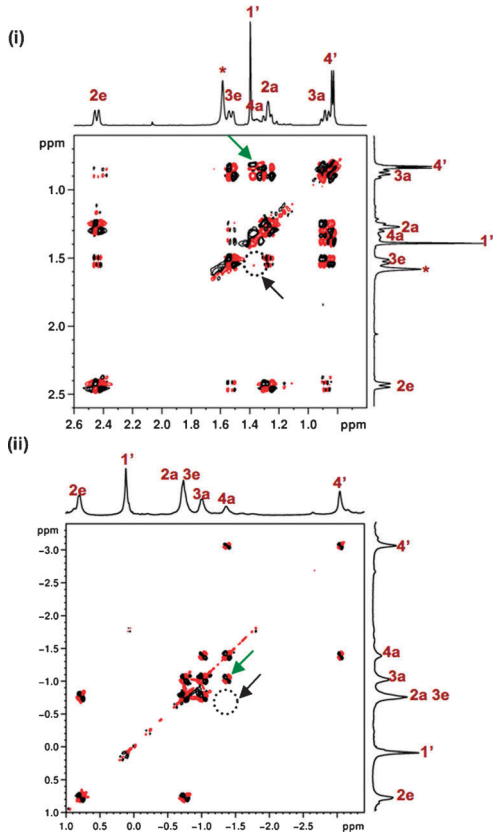


Fig. 3 Partial ^{1}H DQF COSY NMR (500 MHz) spectra of (i) **C** in $CDCl_3$, (ii) **C**@$\mathbf{A}_2$. ([**C**] = 2.5 mM and [**A**] = 5 mM in 50 mM borate buffer in D_2O). (* Peak is the residual water signal). Green arrow shows the correlation between proton 4a and 3a. Dotted circle with an arrow shows the absence of correlation between 4a and 3e.

ketone **C** with the same conformation both inside and outside the capsule yielded different products.

We next turned our attention to explore the rotational restriction of the axial phenylacyl group through 40 ns molecular dynamics (MD) simulations in aqueous solution. These simulations were performed using the OPLS-AA force field[13,14] utilizing the GROMACS program.[15,16] The details of these simulations are provided in ESI.† The root-mean-square-deviation (rmsd) of the MD trajectories indicate that both **B**@$\mathbf{A}_2$ and **C**@$\mathbf{A}_2$ complexes are well equilibrated (Fig. S11 in ESI†), which justify the time scale used for these simulations. The most representative structures of these complexes derived from the MD simulations are shown in Fig. 4. Initial structures used for MD simulations are provided in Fig. S12 and S13 in ESI.† These structures reveal the reason for the lack of Norrish type II reaction despite the presence of the phenylacyl group in the axial position. The carbonyl group in these structures is clearly turned away from the γ-hydrogens and the tight encapsulation most likely prevents rotation of the phenylacyl group within the lifetime of the triplet state to face the γ-hydrogens.[17]

We initiated the investigation with the postulate that one might be able to control the photoproducts' distributions in cyclohexyl phenyl ketones by locking the guest molecule in a high-energy conformation within a tight capsule. Although we achieved our goal of controlling the products' distribution, structural and photochemical studies revealed that the control

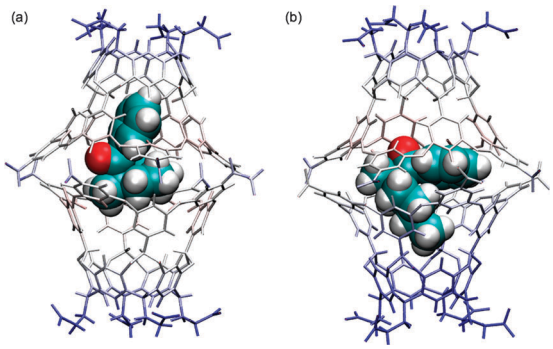


Fig. 4 Orientation of the carbonyl group in (a) **B**@$\mathbf{A}_2$ and (b) **C**@$\mathbf{A}_2$ from molecular dynamics calculations (GROMACS, OPLS-AA forcefield).

has its origin not on the conformational control but on rotational restriction of the reactive part of the molecule[18,19] within the nanoscopic reaction cavity of octa acid. In examples discussed here the lack of free space within a well-defined reaction cavity reduced the rotational mobility, which is translated into product selectivity.[20] Unexpected observations made with the two ketones capable of undergoing classic Norrish type I and II reactions have brought out yet another facet of control on molecular motions in confined spaces thus opening new opportunities for manipulating photoreactions in confined spaces.

VR is grateful to the National Science Foundation, USA, for generous financial support (CHE-0848017). The authors thank A. Barman for help with MD simulations.

Notes and references

1 M. Porel, N. Jayaraj, S. Raghothama and V. Ramamurthy, *Org. Lett.*, 2010, **12**, 4544–4547.
2 F. D. Lewis and R. W. Johnson, *J. Am. Chem. Soc.*, 1972, **94**, 8914–8916.
3 F. D. Lewis and R. W. Johnson, *Tetrahedron Lett.*, 1973, 2557–2560.
4 F. D. Lewis, R. W. Johnson and D. E. Johnson, *J. Am. Chem. Soc.*, 1974, **96**, 6090–6099.
5 N. J. Turro, V. Ramamurthy and J. C. Scaiano, *Modern Molecular Photochemistry of Organic Molecules*, University Science Books, Sausalito, CA, 2010.
6 M. Lipson, T. Noh, C. E. Doubleday, J. M. Zaleski and N. J. Turro, *J. Phys. Chem.*, 1994, **98**, 8844–8850.
7 M. Spichty, N. J. Turro, G. Rist, J. L. Birban, K. Dietliker, J. P. Wolf and G. Gescheidt, *J. Photochem. Photobiol., A*, 2001, **142**, 209–213.
8 C. L. D. Gibb and B. C. Gibb, *J. Am. Chem. Soc.*, 2004, **126**, 11408–11409.
9 R. Kulasekharan, N. Jayaraj, M. Porel, R. Choudhury, A. K. Sundaresan, A. Parthasarathy, F. Ottaviani, S. Jockusch, N. J. Turro and V. Ramamurthy, *Langmuir*, 2010, **26**, 6943–6953.
10 H. Gunther, *NMR Spectroscopy*, John Wiley, Chichester, 1992.
11 N. Jayaraj, Y. Zhao, A. Parthasarathy, M. Porel, R. S. H. Liu and V. Ramamurthy, *Langmuir*, 2009, **25**, 10575–10586.
12 I. Columbus and S. E. Biali, *J. Org. Chem.*, 1993, **58**, 7029–7035.
13 W. L. Jorgensen and J. Tirado-Rives, *J. Am. Chem. Soc.*, 1988, **110**, 1657–1666.
14 G. A. Kaminski, R. A. Friesner, J. Tirado-Rives and W. L. Jorgensen, *J. Phys. Chem. B*, 2001, **105**, 6474–6487.
15 E. Lindahl, B. Hess and D. van der Spoel, *J. Mol. Model.*, 2001, **7**, 306–317.
16 D. V. D. Spoel, E. Lindahl, B. Hess, G. Groenhof, A. E. Mark and H. J. C. Berendsen, *J. Comput. Chem.*, 2005, **26**, 1701–1718.
17 W. Xia, J. R. Scheffer, M. Botoshansky and M. Kaftory, *Org. Lett.*, 2005, **7**, 1315–1318.
18 P. J. Wagner, *Acc. Chem. Res.*, 1983, **16**, 461–467.
19 P. J. Wagner and C.-P. Chen, *J. Am. Chem. Soc.*, 1976, **98**, 239–241.
20 R. G. Weiss, V. Ramamurthy and G. S. Hammond, *Acc. Chem. Res.*, 1993, **26**, 530–536.