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H-abstraction prevails over α-cleavage in the solution and solid state photochemistry of *cis*-2,6-di(1-cyclohexenyl)cyclohexanone☆

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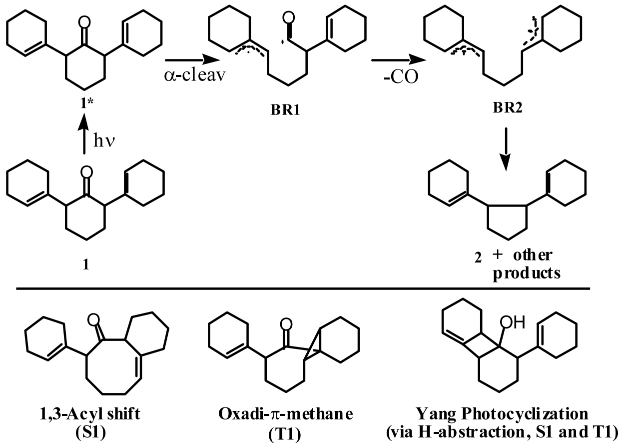
Abstract—The photochemistry of *cis*-2,6-di(1-cyclohexenyl)cyclohexanone was studied in solution and in crystals to determine its photoreactivity and chemoselectivity. Although 1,3-acyl shifts and the oxadi-π-methane rearrangement products are possible for the β,γ-unsaturated chromophore, an efficient intramolecular abstraction of an allylic γ-hydrogen and small amounts of α-cleavage and decarbonylation were observed. The mechanism of the Norrish type-II reaction and the selectivity of product formation were analyzed in terms of structural information obtained by X-ray diffraction analysis.

Based on thermochemical arguments involving excitation and bond dissociation energies, we recently proposed that ketones with α-substituents having radical-stabilizing energies (RSE) greater than ca. 12 kcal/mol are likely to undergo sequential α-cleavage (Norrish type-I)[1] and decarbonylation reactions to form radical pairs and biradicals, even while in the solid state.[2,3] In agreement with this hypothesis, we have reported reactions of crystalline ketones with aryl,[4,5] carbonyl,[6] cyano,[7] and ketal[8] substituents at their α-carbons. In general, radical pairs and biradicals formed in this manner react by stereospecific combination to make a new sigma bond between the former α-carbons in what could become a useful method to generate bonds between sterically hindered centers. In this letter, we report the solution and solid state photochemistry of *cis*-2,6-di(1-cyclohexenyl)cyclohexanone **1** as a model system to explore the effect of α-vinyl groups (Scheme 1).

With RSE of ca. 15–18 kcal/mol,[9] the α-vinyl groups are expected to facilitate α-cleavage and decarbonylation reactions to form allyl-stabilized biradical intermediates **BR1** and **BR2** (Scheme 1). However, β,γ-unsaturated ketones[10] are also known to undergo efficient 1,3-acyl shifts, oxadi-π-methane rearrangement, and the Yang photocyclization by a γ-hydrogen abstraction (Schemes 1 and 2).[11,12] Given the potentially rich photochemistry of **1**, it was of interest to determine the relative contributions of these pathways in solution, and whether they can be modified when reactions occur in the solid state.

cis-2,6-Di(1-cyclohexenyl)cyclohexanone (**1**) was chosen as a model system for its simple preparation by base catalyzed condensation of cyclohexanone, and for its known crystallinity (mp = 79°C).[13] Photochemical experiments were carried out with 8 mM N_2-purged benzene solutions with the Pyrex filtered output of a



Scheme 1.

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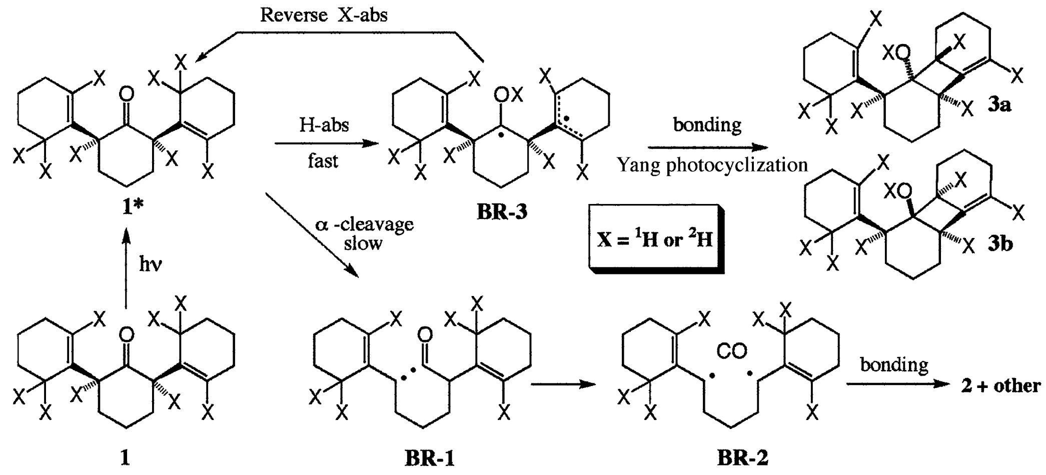

Scheme 2.

medium pressure Hg lamp (λ>300 nm). The product ratio was constant as a function of conversion and complete disappearance of the reactant was observed within 40 min of irradiation. GC MS analyses of the crude reaction mixture showed the formation of three minor products in <10% yield with a mass that corresponds to the loss of carbon monoxide (M^+–28), and two major products isomeric with the starting material (M^+=258 amu) in a 4:1 ratio and a ca. 90% yield (Scheme 2). The MS of the major products had a prominent M^+–18 amu peak, corresponding to the loss of H_2O. These compounds were later identified as cyclobutanols **3a** and **3b** (Scheme 2).[14,15] Regarding the multiplicity of the reaction, solution experiments in the presence of isoprene as a triplet quencher had no effect on the product ratio or photolysis times, suggesting that reaction occurs from the singlet excited state, or from a very short-lived triplet. Triplet-sensitized irradiations using acetone with λ>300 nm, or with xanthone at λ>350 nm, led to complex product mixtures which did not include **3a** or **3b**. Based on these results, we propose that reactions occur from the singlet n,π* excited state of **1**. Needle-shaped crystals from methanol were reactive but required longer reaction times (up to 48 h). Solid state reactions carried out to less than ca. 10% conversion at 300 K yielded cyclobutanol **3b** with >90% selectivity. However, increasing conversion led to rapid degradation of the crystal lattice, which resulted in lower reaction control (Fig. 1).

If one assumes that γ-hydrogen abstraction (type-II) and α-cleavage (type-I) occur from the same excited state, the results would imply that the former reaction is about ten times as fast as the latter. It seemed to us that a primary isotope effect could slow down the rate of H-transfer in favor of the desired α-cleavage.[16] With that in mind, the deuterated analogue **1-d_8** (Scheme 1, X=D) was prepared with cyclohexanone-d_4 in greater than 96% isotopic purity. Remarkably, the results obtained with **1-d_8** were nearly identical to those with **1**, indicating that there is no isotope effect at the branching point where the chemoselectivity of the reaction is decided.[17]

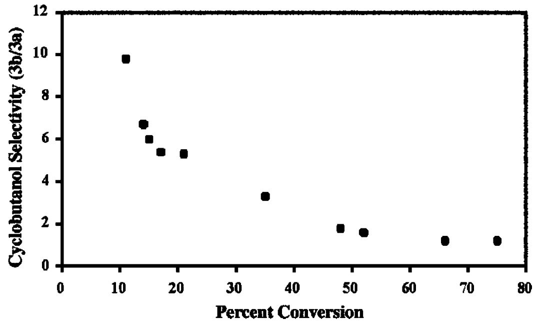

Figure 1. Changes in the ratio of cyclobutanols **3b**/**3a** in the solid state at 298 K as a function of conversion.

The structures of the two cyclobutanols were assigned from their spectral data, including the expected OH bands in their IR spectra at 3448 for **3a** and at 3479 and 3555 cm^{-1} for **3b**. The stereochemistry of the newly formed carbinol and methine carbons was assigned from heteronuclear one- (HMQC) and multiple-bond-correlations (HMBC), as well as NOESY[18] spectra acquired at 500 and 600 MHz (which are described in the supplementary information section). While the configurations of the new hydroxyl and methine groups were determined to be *trans* in both cases, the hydroxyl group is on the same face as the methine hydrogens of the cyclohexanol ring in **3a**, and on the opposite face in **3b** (Scheme 2 and Fig. 2).

A substantial preference for hydrogen abstraction over α-cleavage is indicative of conformations where the cyclohexenyl group allylic hydrogens are close to the carbonyl n-orbital.[19] While this requirement may be satisfied by conformational motions within the lifetime of the excited state in solution, this arrangement must be pre-organized in the crystal for the reaction to occur in the solid state. The X-ray structure of **1**[20] confirmed this expectation, which gave us an opportunity to analyze solid state reaction geometry. As illustrated in Figure 2, ketone **1** is characterized by a chair conformation with the two cyclohexenyl groups adopting equatorial positions. One of the two cyclohexenyl groups

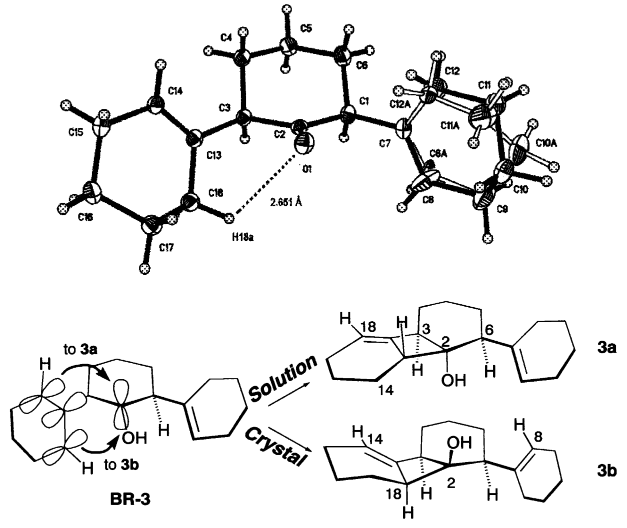

Figure 2. (Top) X-Ray crystal structure of **1** (ORTEP diagram). (Bottom) Orbital diagram illustrating the proposed least motion pathway for the formation of cyclobutanol **3b**. Please see text for details.

has its double bond (C7=C8) *syn* to the carbonyl in a disordered half-chair conformation while the other (C13=C14) is *anti*. The allylic γ-hydrogen H18a is only 2.651 Å from the carbonyl oxygen, which is below the optimum of 2.7 Å suggested by Scheffer.[19] Since the reaction occurs in the singlet excited state, return to the ground state ketone may occur by a well-known avoided crossing mechanism,[21] or by reverse H-transfer from the ketyl to the allyl radical in BR-3, thus explaining the apparent inefficiency of the solid sate reaction. It is well known that the rate constant of cyclobutanol formation from singlet 1,4-biradicals in solution is determined by conformational motions which bring the two radical centers together, and a simple model assuming least motion trajectories helps explain the stereochemistry observed in a reasonable manner (Fig. 2). By this model, a hydrogen is abstracted from C18, the resulting allyl radical delocalizes over C14–18, and product formation is determined by rotation of cyclohexenyl group (allyl radical) along the C3–C13 bond. The formation of **3a** in solution is consistent with bond-formation between C14 and C2, which pushes the hydroxyl group towards the same face of the tricyclic system as the methine hydrogens at C1 and C3. The observed reversal of the stereochemistry in the solid state suggests that both hydrogen abstraction and sigma-bond formation occur at C18 by a topochemically allowed, least motion pathway.[22]

In conclusion, our results suggest that abstraction of allylic hydrogens in β,γ-unsaturated ketones may be more efficient than α-cleavage and decarbonylation, particularly when it is favored by the conformation of the substrate. Although decarbonylation in the case of **1** accounts for a small percentage of the reaction mixture (ca. 10%), analogous compounds lacking allylic hydrogens are expected to decarbonylate efficiently in the solid state. Experiments in progress to test this hypothesis will be reported in due course.

Supplementary Information: Detailed stereochemical assignment of **3a** and **3b** based on ^{1}H and ^{13}C NMR including HMBC, HMQC and NOESY correlations. Crystallographic data for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Center.

Acknowledgements

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15. Cyclobutanol **3a**: ^{1}H NMR ($CDCl_3$) δ 5.52 (s, 1H), 5.45 (d, 1H, $J=2.7$), 3.01 (m, 1H), 2.52 (t, 1H, $J=9.4$), 7.07 (m, 2H) 2.2–1.0 (m, 21H); ^{13}C NMR ($CDCl_3$) δ 142.41, 138.23, 123.78, 114.59, 76.28, 52.29, 51.29, 43.71, 29.69, 29.56, 27.32, 26.66, 25.29, 24.60, 23.55, 23.39, 23.08, 22.41, 21.00, 20.53; IR (CCl_4) ν/cm^{-1} 3448 (m), 2929 (s), 2856 (s), 1700 (w), 1447 (m), 1106 (w), 1047 (w), 1106(w), 1048 (m), 1018(w), 894 (w), 768 (w). HREI MS m/z calcd for $C_{18}H_{26}O$ $[M]^+$ 258.1984, obsd 258.1964; Cyclobutanol **3b**: ^{1}H NMR ($CDCl_3$) δ 5.42 (s, 1H), 5.35 (s, 1H), 2.77 (m, 1H), 2.60 (m, 1H), 2.18 (m, 1H) 2.2–1.0 (m, 20H); ^{13}C NMR ($CDCl_3$) δ 143.13, 138.10, 120.96, 111.63, 74.06, 55.94, 53.41, 52.44, 51.93, 29.69, 29.09, 26.03, 25.25, 24.30, 23.06, 22.58, 21.19, 20.93, 20.57; IR (CCl_4) ν/cm^{-1} 3555 (s), 3479 (s), 3048 (m), 1702 (w), 1448 (s), 1311 (w), 1257 (w), 1182 (w), 1050 (m), 1018 (w), 846 (w), 768 (w). HREI MS m/z calcd for $C_{18}H_{26}O$ $[M]^+$ 258.1984, obsd 258.1984
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20. **1**: $C_{18}H_{26}O$, MW = 258.40, triclinic, space group $P\bar{1}$, $a=5.3051(9)$ Å, $b=10.4576(18)$ Å, $c=14.010(2)$ Å, $\alpha=91.614(3)°$, $\beta=100.733(3)°$, $\gamma=103.339(3)°$, $V=741.0(2)$ Å^3, $Z=2$, $\rho_{\mathrm{calcd}}=1.158$ Mg/m^3, $F(000)=1104$, $\lambda=0.71073$ Å, $T=100(2)$ K, crystal size 0.40×0.30×0.25 mm^3. Of the 4761 reflections collected ($2.01 \leq \theta \leq 28.27°$), 3298 [$R_{\mathrm{int}}=0.0155$] were independent reflections; max/min residual electron density 483 and −400 e nm^{-3}, $R_1=0.0485$ [$I>2\sigma(I)$] and wR_2 (all data) = 0.1377.
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