Structural Elucidation of a Photocycloaddition Dimer of Cyclohexenone

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Intermolecular photocycloaddition of 2-cyclohexenone has been explored by several research groups.¹ Interest in this particular photochemical reaction is based partially on the similarity between the cyclohexenone cycloaddition and the photodimerization of thymidine groups. The thymidine photodimer has been implicated in skin cancer² and DNA photodimerization is a significant event in biological systems.

Positive identification of the cyclohexenone dimers with their spectroscopic data has not been published, however; so comparison with the photoproducts of thymidine or related structures has not been possible. Recently, we have been able to separate and analyze the four detectable photodimers of cyclohexenone.³ Although two of the photodimers have been assigned structures in the literature^{1a}, no positive identifying features (*i.e.* spectral data) of the assignment have been published. Our results provide conclusive data for identification of one of the major dimers.

This paper describes our approach for identifying *cis,trans*-3,12-dioxotricyclo[6.4.0.0^{2,7}]dodecane. We have used several analytical tools to determine the structure of this isomer, including X-ray crystallography and NMR techniques. Most importantly, this work includes the necessary spectral data for future comparisons of 2+2 photodimers.

Lanthanide shift reagents (LSRs) were introduced by Hinckley in 1969.⁴ These reagents are effective in differentiating between NMR signals of similar chemical shift and have become a dependable tool in identifying the structure of a variety of molecules.⁵ The paramagnetic effects of the shift reagent result in significant increases in chemical shifts based on the distance between the nuclei being observed and the lanthanide. Since this tool requires a Lewis acid-base interaction, we reasoned that the cyclohexenone dimer with a head-to-head orientation would be a good bidentate agent. This tight binding was expected to provide a reliable data set which would allow differentiation between the several possible 2+2 head-to-head isomers (see Fig. 1).

Results and Discussion

Irradiation of neat cyclohexenone gave sufficient material for chromatographic separation. The two major products are one head-to-tail and one head-to-head isomers. The head-to-head isomer can be cleanly separated (>99% pure by GC) from the other isomers. In the process of working with this compound we were fortunate to obtain satisfactory crystals for X-ray crystallography. The X-ray data⁶ established the structure as has been assigned (compound A, Fig. 1). Prior to obtaining the crystal data, we carried out the analysis detailed below.

Proton and carbon NMR, in addition to the 2-D COSY and HETCOR data, is sufficient to rule out the unsymmetrical head-to-head isomers shown in Fig. 1 (D and E). The ¹³C NMR has only 6 peaks and there are only 8 types of hydrogens in the proton spectrum. Carbon NMR data of the unknown isomer provided evidence of C-1/C-2 and C-7/C-8 due to their CH nature. Each of the other carbons are CH₂ groups (except for the carbonyl carbon) as shown by DEPT experiment. The C-1/C-2 carbons are shifted downfield by the carbonyl group as expected. Their hydrogens (assigned by HETCOR) are a two hydrogen doublet.⁷ Although this clear coupling of the C-1/C-2 hydrogens

Fig. 1 The possible head-to-head isomers from photodimerization of 2-cyclohexenone.

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Table 1 Calculated distances for each proton from the lanthanide (Å)

	H _a	H _b	H _c	H _d	Proton H _e	H _f	H _g	H _h
Isomer A	3.12	5.33	5.05	4.93	6.63	5.85	6.34	6.75
Isomer B	4.74	6.47	3.82	3.56	5.84	5.92	6.27	6.86

Table 2 Experimental results for each proton from LSR study

	H _a	H _b	H _c	H _d	Proton H _e	H _f	H _g	H _h
Slope	4.540	1.975	2.496	2.192	0.902	1.362	1.041	1.038
Distance (Å) scaled to H _e	3.87	5.11	4.72	4.93	6.63	5.78	6.32	6.33

(H_a) with the C-7/C-8 hydrogens (H_b) precludes the unsymmetrical isomers, it does not distinguish between the *cis,trans* or *cis,cis* isomer (Fig. 1, **A** or **B**, respectively) or the more strained isomers **C** and **F**.

Mild treatment of the unknown isomer with base resulted in no epimerization. This observation, coupled with semiempirical calculations⁸ on the isomers **A**–**F**, led us to discount the isomers **C** and **F**. In addition, the relatively small coupling constant for the H_a hydrogen (7.5 Hz) suggested that the coupling was to a *cis* H_b (as in **A** or **B**) rather than a *trans* H_b (as in **C** or **F**).

Isomer **A** has C₂ symmetry and is a chiral molecule whereas **B** has a plane of symmetry and is achiral. We attempted evaluation with chiral HPLC to determine the correct structure of our unknown isomer. This logic would tell us that the unknown isomer is **A** if two equal peaks were detected from chiral HPLC. If one peak was observed, then the conclusion would be less certain. Unfortunately, the chromophore was not sufficiently strong to allow conclusive interpretation of the HPLC data.

At this point we opted to employ a shift reagent. Our modeling indicated that the LSR should impact the C-1/C-2 hydrogens (H_a) more than the C-4/C-11 hydrogens (H_c or H_d) in the *cis,trans* isomer and C-4/C-11 hydrogens would be closer than the C-1/C-2 hydrogens in the *cis,cis* isomer. Molecular modeling⁸ was carried out with geometry optimization at the AM1 level for the carbon framework followed by Sybyl molecular mechanics for the introduced lanthanide. The calculated distances are summarized in Table 1 for the two head-to-head isomers of interest.

Addition of the shift reagent tris-2,2,6,6-tetramethyl-3,5-heptane-4,6-dionatoeuropium (Eu(thd)₃) in incremental amounts gave the linear change in proton chemical shifts. The slope of the change (indicated in Table 2) is inversely proportional to the cube of the distance (*r*³) between the lanthanide and the proton.⁹ It is apparent from the LSR data that the unknown isomer has the *cis,trans* structure **A**. In addition, we were able to approximate the distances for the other proton signals and we have made assignments of the individual pro-

Fig. 2 Proton assignments for photodimer **A**.

tons with a high level of confidence.

In the original proton NMR of compound **A**, the region between 1.46 and 2.04 ppm is difficult to interpret or assign. At a molar ratio of Eu(thd)₃ to photodimer of 0.6 the signals are resolved on a 300 MHz instrument. We were able to run a COSY experiment at that point which lead us to the proton assignments shown in Fig. 2.

The predicted distances for the protons shown in Fig. 2 (and listed in Table 1) from the lanthanide based on the minimization of isomer **A** are in the following order (closest to furthest): H_a>H_d>H_c>H_b>H_f>H_g>H_e>H_h. The order for isomer **B** (also from Table 1) is: H_d>H_c>H_a>H_e>H_f>H_g>H_b>H_h. The order that we obtained from the LSR study (from Table 2) is: H_a>H_c>H_d>H_b>H_f>H_g>H_h>H_e. It is obvious that isomer **A** is a better fit with the experimental data and thus we have concluded that the correct identity for the compound is *cis,trans*-3,12-dioxotricyclo[6.4.0.0^{2,7}]dodecane.

In this paper we have been able to confirm the identity of the major head-to-head photodimer obtained from irradiation of 2-cyclohexenone. We have provided a full spectroscopic identification of that compound. Further progress in this area will be reported shortly.

Experimental

Reagent grade CDCl₃ was used as the NMR solvent. Eu(thd)₃ was pre-dried at 110°C, *in vacuo*, with P₂O₅ for 24 h. An initial spectrum of the unknown photodimer (10.7 mg/1.5 ml CDCl₃) was obtained.

Additional spectra were taken after addition of 3 – 6 mg of Eu(thd)₃ until a molar ratio of 1.33 was reached. The data for the chemical shifts as a function of added shift reagent were plotted to obtain the slopes given in Table 2.

The spectral data for *cis,trans*-3,12-dioxotricyclo[6.4.0.0^{2,7}]dodecane are: ¹H NMR (500 MHz, CDCl₃) δ 3.12 (2H, d, *J*=7.5 Hz, *H_a*), 2.83 (2H, m, *H_b*), 2.40 (2H, dddd, *J*=15.0, 4.5, 4.5, 1 Hz, *H_c*), 2.26 (2H, ddd, *J*=15.0, 12.0, 5.0 Hz, *H_d*), 1.98 (2H, m, *H_e*), 1.88 (2H, qt, *J*=13.0, 4.0 Hz, *H_f*), 1.70 (2H, dddd, *J*=15.0, 14.5, 6.0, 5.0 Hz, *H_g*), 1.55 (2H, bdt, *J*=15.0, 3.5 Hz, *H_h*); ¹³C NMR (75 MHz, CDCl₃) δ 213.3 (s), 47.6 (d), 41.1 (t), 40.1 (d), 25.0 (t), 22.8 (t); IR (KBr) 2950, 1722 cm⁻¹; high resolution MS (M+H⁺) for C₁₂H₁₇O₂ *m/z* calc. 192.1229, obs. 193.1232; m.p. 77 – 78°C.

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