



Molecular structures of the photodimers of 5-phenyluracil and 6-phenyluracil

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ABSTRACT

Two new head-to-head cyclobutane photodimers have been obtained in single stereoisomeric form by irradiation of 5-phenyl- and 6-phenyluracils in acetone solution. While the latter substrate gives a *cis-anti-cis* adduct, the former provides, for the first time in a solution phase reaction, a *cis-syn-cis* photodimer as the only product.

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The photodimerization reactions of pyrimidinediones to give substituted cyclobutanes have been of interest for some time, notably due to the detrimental effects these processes can have on DNA.¹ The solution phase photodimerization reactions of uracil and thymine often lack selectivity. Uracil itself is known to give four isomers – the *cis-syn-cis* and *cis-anti-cis* stereoisomers of each of the head-to-head (HH) and head-to-tail (HT) regioisomers – in proportions which depend on the conditions applied and are not easy to control.² Various approaches have been considered in attempts to improve selectivity, including the use of temporary tether³ or recognition-directed supramolecular assistance.⁴ This latter approach serves as a reminder that *cis-syn-cis* pyrimidinedione cyclobutane dimers have been considered as rigid templates for two-site molecular recognition⁵ and as model substrates for mimetics of DNA photolyase activity.⁶ Such applications remain somewhat underdeveloped, perhaps due to the difficulties encountered in the selective synthesis of such dimers. Indeed, surprisingly few C-substituted pyrimidinedione photodimers have been prepared and characterized. In solution, the acetone-sensitized photodimerization of 6-methyluracil gave a mixture of a HH and HT regioisomers, each with a *cis-anti-cis* configuration.⁷ Under similar conditions, 5-fluorouracil photodimerization provided predominantly the HT *cis-anti-cis* adduct.⁸ The same regio- and stereochemical profile was observed for the solution-state photodimers of orotic acid and of its methyl ester.⁹

During a study of the photochemical [2+2] cycloaddition reactions of pyrimidinediones with ethylene, we discovered that

5-phenyluracil (**1**) and 6-phenyluracil (**2**) had a propensity to form self-condensation products, presumed to be photodimers.¹⁰ Herein, we present the unambiguous preparation of these dimers and their molecular structures.

Irradiation of an acetone solution of **1** or **2** (400 W Hg vapor lamp, Pyrex filter, 6 h) provided, after simple work up, photodimers **3** and **4** as white powders in good isolated yields (65% and 74%, respectively) (Fig. 1). The observation of only one set of signals in the ¹H and ¹³C NMR spectra indicated that a single isomer had been obtained in each case.¹¹ However, in order to establish the structure, X-ray analysis was necessary. Single crystals were grown by slow evaporation of a solution in a polar aprotic solvent (DMSO for **3**, DMF for **4**) and diffraction studies revealed that the 5-phenyluracil dimer **3** had a HH *cis-syn-cis* structure, while the 6-phenyluracil dimer **4** had a HH *cis-anti-cis* geometry (Fig. 2).¹²

Compound **3** is the first *cis-syn-cis* uracil photodimer to be obtained as a unique photoadduct without recourse to elaborate structural constraints (intramolecular tethers) or medium effects (frozen matrix, thin film solid state reactions) during the photoreaction, or painstaking separation of photodimer

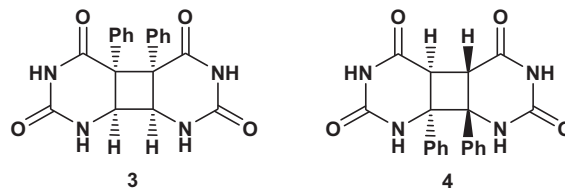


Figure 1. Molecular structures of photodimers **3** and **4**.

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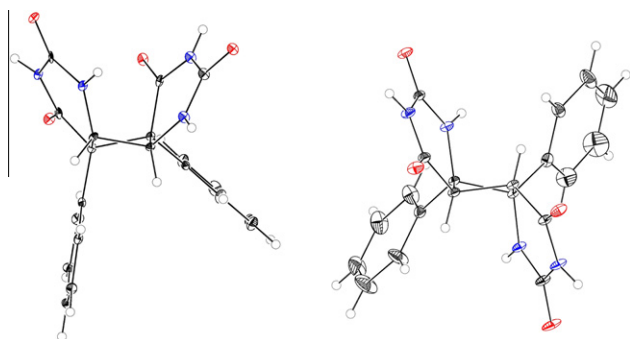


Figure 2. ORTEP plots (30% probability) of the X-ray structures of the photodimers, showing the HH *cis-syn-cis* configuration of **3** (left) and the HH *cis-anti-cis* configuration of **4** (right). Solvent molecules have been removed for clarity.

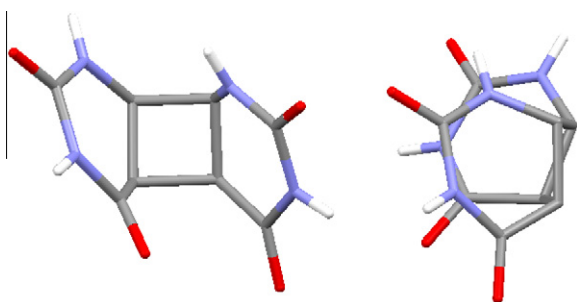


Figure 3. Views of the *cis-syn-cis* structure of compound **3** from above (left) and side-on (right), highlighting the orientation of the heterocyclic systems. Phenyl rings are removed for clarity.

mixtures.¹³ The puckered cyclobutane has a mean torsion angle of 21° and the heterocycles are flattened half-chairs, twisted by about 30° from superposition (Fig. 3, left). This makes for a closer alignment of the hydrogen-bond donor–acceptor pairs N¹–H/C²=O, /C²=O N³–H, and N³–H/C⁴=O of neighboring heterocycles (Fig. 3, right).

The photosensitizing effect of acetone implicates the triplet excited state of **1** or **2**, and formation of the first bond should occur between the non-arylated positions to provide a stabilized biradical intermediate, leading to a HH regioisomer in each case. However it was not clear why one adduct should be *anti* while the other was *syn*. We performed semi-empirical calculations to verify the feasibility of formation of the observed structures.¹⁴ For each substrate **1** and **2** the transition state (TS), biradical intermediate and dimer product energies for both *syn* and *anti* structures were determined (Table 1). For **1**, virtually no difference was apparent between the TS energies of the *syn* and *anti* approaches, although the *syn* biradical was 1.43 kcal mol^{−1} more stable. While the *anti* product is more stable than the *syn*, there is no energy barrier to the formation of the latter. For **2**, even less difference was evident between the energies of the *syn* and *anti* biradicals, with *syn* being favored by only 0.70 kcal mol^{−1} and the *anti* TS being marginally more favorable. Here again, there is no clear-cut argument in favor of either approach mode; the only significant energy difference is the greater stability of the *anti* dimer product. It thus appears that a reaction pathway to either *syn* or *anti* geometry is available, so

Table 1

Calculated energies of different steps in the photodimerization of 5-phenyluracil (**1**) and 6-phenyluracil (**2**)^a

Substrate	Geometry	Transition state ^b	Biradical ^b (<i>T</i> ₁)	Product
1	<i>syn</i>	−4985.53	−5009.91	−5012.61
	<i>anti</i>	−4985.48	−5008.48	−5019.84
	ΔE	0.05	1.43	7.23
2	<i>syn</i>	−4991.53	−5024.53	−5022.08
	<i>anti</i>	−4991.65	−5023.83	−5028.32
	ΔE	0.12	0.70	6.24

^a Total energy is given in kcal mol^{−1}. The lower energy at each step is in bold.

^b The value given is for the most energetically stable approach (transition state) or conformer (biradical).

the origins of the stereoselectivity may lie in self-association effects in the solution, via some kind of stacking phenomenon; such an effect was previously suggested to operate in the photodimerization of tetramethyluracil.¹⁵

In summary, we have prepared and characterized two new pyrimidinedione photodimers. The molecular structure of one of these, compound **3**, is of particular interest being the most-easily synthesized *cis-syn-cis* adduct to date and offering a multiple hydrogen bond donor/acceptor functional group montage. Since the pendant aryl groups may act as chromophores and points of attachment to larger scaffolds, this system may inspire new investigations of cyclobutane photodimers as templates for molecular recognition.

References and notes

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- Compound 3**: White solid, mp >360 °C (DMSO). ¹H NMR (300 MHz DMSO-*d*₆) δ 4.39 (2H, s), 7.21 (10H, m), 7.99 (2H, s), 10.27 (2H, s). ¹³C NMR (75 MHz DMSO-*d*₆) δ 58.2, 54.5, 127.5, 127.8, 128.0, 135.8, 152.4, 169.4. **Compound 4**: White solid, mp 279 °C (DMF). ¹H NMR (300 MHz DMSO-*d*₆) δ 4.19 (2H, s), 7.407.50 (10H, m), 7.87 (2H, s), 10.48 (2H, s). ¹³C NMR (75 MHz DMSO-*d*₆) δ 39.1, 64.8, 127.0, 128.0, 128.4, 137.4, 151.5, 167.7.
- CCDC 916146 and CCDC 916145 contain the crystallographic data for compounds **3** and **4**, respectively. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
- The *cis-syn-cis* uracil photodimer has been characterized: see (a) Adman, E.; Gordon, M. P.; Jensen, L. H. *Chem. Commun.* **1968**, 1019–1020; (b) Adman, E.; Jensen, L. H. *Acta Crystallogr., B.* **1970**, *26*, 1326–1334.
- Semi-empirical calculations were performed with Hyperchem 5.1 using the PM3 method with the Unrestricted Hartree-Fock wave function. The Polak-Ribiere algorithm with conjugate gradient calculations was adopted for geometry optimizations. For the dimerization process, one molecule was considered in the first excited triplet state, and the other was considered in the singlet ground state. Transition states were searched by quadratic synchronous transit algorithm. Radical intermediates were treated in the first triplet state.
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