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Tetrahedron Letters 46 (2005) 1141–1144

Tetrahedron Letters

Molecular mechanics-assisted crystal engineering of solid state photoreactions: application to the Yang photocyclization of α-1-norbornylacetophenone derivatives

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Received 3 September 2004; revised 15 December 2004; accepted 17 December 2004
Available online 11 January 2005

Abstract—Based on molecular mechanics, Yang photocyclization of α-1-norbornylacetophenone derivatives in the crystalline state was engineered through methylation adjacent to the carbonyl group, thus changing the conformation in the crystal and leading to enhanced diastereo- and enantioselectivity.

With their beautiful three-dimensional structure in which the constituent molecules are locked in specific shapes and intermolecular orientations, crystals provide ideal (and green) environments for carrying out chemistry.[1] Why, then, are crystals not used more widely as organic reaction media? One reason is that crystal packing is extremely difficult to predict, let alone control, the result being that, more often than not, nature fails to provide us with packing arrangements appropriate for the type of chemistry we are seeking to achieve. This is the conundrum addressed by the field of crystal engineering—how to prepare crystals that will undergo specific chemical transformations or physical processes.[2]

The problem is simplified for unimolecular reactions controlled by molecular conformation, since specific intermolecular packing arrangements are generally not required. An example is the Norrish/Yang type II reaction,[3] whose success in the crystalline state depends on a conformation favorable for the initial γ-hydrogen atom abstraction. Recent work from our research group has firmly established the geometric requirements for such abstractions.[4,5] The most critical parameter is *d*, the distance between the carbonyl oxygen and the γ-hydrogen, which should be in the range 2.7 ± 0.2 Å.[6]

With this guideline in mind, and recalling that organic molecules generally crystallize in or near their minimum energy conformations, it is a simple matter to use molecular mechanics to make predictions concerning the probable success of hypothetical type II reactions in crystals. In this way, molecular mechanics serves as a basis for crystal engineering. In the present communication, we report an example of how molecular mechanics-based crystal engineering can be used to increase the enantioselectivity of a type II Yang photocyclization reaction in the solid state.

The compounds selected for study were derivatives of the α-1-norbornylacetophenone system **1/2** (Scheme 1). One question we wished to answer was whether hydrogen abstraction would take place on the one-carbon or the two-carbon bridge. The main goal of our work, however, was to carry out the Yang photocyclization of these compounds *enantioselectively*, since the expected cyclobutanol photoproducts **3–6** are chiral.[7] There has been much recent interest in finding efficient methods of asymmetric induction in photochemical reactions,[8] a field that is still undeveloped compared to the subject of asymmetric synthesis in the ground state.

Keywords: Crystal engineering; Solid state photochemistry; Asymmetric induction; Yang photocyclization; X-ray crystallography; Ionic chiral auxiliaries.

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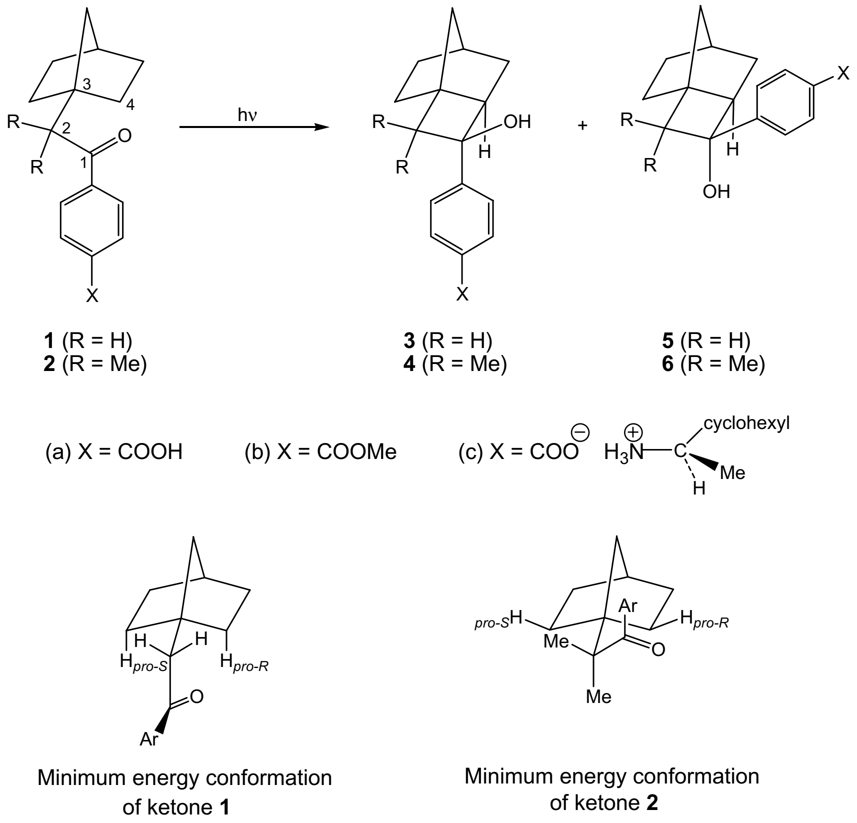
0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.12.090



1 (R = H)
2 (R = Me)

3 (R = H)
4 (R = Me)

5 (R = H)
6 (R = Me)

(a) X = COOH (b) X = COOMe (c) X = $COO^{\ominus}$ $H_3\overset{\oplus}{N}$—C

Minimum energy conformation of ketone **1**

Minimum energy conformation of ketone **2**

Scheme 1. Photochemistry of α-1-norbornylacetophenone derivatives.

Molecular mechanics calculations indicate that ketone **1** (X = H) has a C_S-symmetric minimum energy conformation (Scheme 1) in which the ketone oxygen is equidistant (d = 2.59 Å) from the enantiotopic *pro-R* and *pro-S endo* hydrogens on the two-carbon bridges and much further (d = 4.80 Å) from the γ-hydrogens on the one-carbon bridge.[9] Such a conformation is poorly suited for high levels of asymmetric induction, since this requires selective abstraction of $H^{endo}_{pro\text{-}S}$ over $H^{endo}_{pro\text{-}R}$ or vice versa. In seeking ways to achieve discrimination between the *pro-R* and *pro-S* γ-hydrogens, ketone **2** (X = H) was investigated by molecular mechanics. This showed that placing two methyl groups next to the carbonyl group should have the desired effect, since the minimum energy conformation of the methylated analogue (Scheme 1) situates the ketone oxygen much closer to $H^{exo}_{pro\text{-}R}$ than $H^{exo}_{pro\text{-}S}$ (2.59 vs 5.07 Å).[10] Overall, therefore, molecular mechanics predicts that derivatives of ketone **2** have a much better chance of giving high levels of asymmetric induction than those from ketone **1**. The experimental results presented below show that this analysis is correct.

Even though molecular mechanics predicts that derivatives of ketone **2** will have a minimum energy chiral conformation favoring abstraction of one enantiotopic γ-hydrogen over the other, crystalline samples will normally contain equal amounts of both conformational enantiomers, so that no net asymmetric induction will be observed.[11] How, then, can this be achieved? The answer is to introduce a second element of chirality to the system in the form of a temporary, enantiomerically pure chiral auxiliary. This causes the conformational enantiomers to become diastereomers, and one diastereomer will generally crystallize out to the exclusion of the other.[12] Irradiation of such crystals ‘fixes’ the temporary conformational chirality in the form of permanent molecular chirality, and removal of the chiral auxiliary completes the process, leaving the reaction product in enantiomerically enriched form.

The asymmetric induction studies were carried out using the solid state ionic chiral auxiliary approach in which the reactant is equipped with a carboxylic acid substituent to which an optically pure ammonium ion (the ionic chiral auxiliary) can be attached by means of a salt bridge.[13] This necessitated the synthesis of the *p*-carboxylic acid derivatives **1a** and **2a**, which was accomplished via a straightforward sequence of reactions. Initial photochemical studies on keto-esters **1b**/**2b** for the purpose of product isolation and identification were conducted in acetonitrile. This led to the formation of racemic cyclobutanols **3b**/**5b** (ratio 47:53) and **4b**/**6b** (ratio 36:64). The photoproducts were separated by column chromatography and their structures assigned on the basis of their spectroscopic data, particularly their NOE difference and 2D NMR spectra.[14] In the case of photoproduct **4b**, the structural assignment was confirmed by X-ray crystallography.[15] No other photoproducts, such as those formed by hydrogen abstraction from the one-carbon bridge, were formed in significant amounts.

A variety of salts of keto-acids **1a** and **2a** was prepared by treating them with a random selection of commercially available, optically pure amines. The salts were purified by recrystallization and irradiated in the solid state. The photolysis procedure consisted of crushing ca. 5 mg of each salt between two Pyrex microscope slides, taping the plates together, sealing the resulting sandwiches under nitrogen in polyethylene bags, and irradiating the ensembles to varying degrees of conversion with the output from a water-cooled 450 W medium pressure mercury lamp. Following photolysis, the salts were dissolved in methanol, concentrated in vacuo, and treated with ethereal diazomethane to form the corresponding methyl esters **3b**–**6b**. The photolysis mixtures were then analyzed for extent of conversion by GC and for enantiomeric excess by chiral HPLC.

As predicted by the molecular mechanics calculations, there was a clear difference in solid state photochemical behavior between the salts of methylated keto-acid **1a** on the one hand and the salts of non-methylated keto-acid **2a** on the other. As a general rule, the former reacted to give mainly a single cyclobutanol diastereomer (**6b**) in good to excellent enantiomeric excess, even at high conversions. In contrast, the latter reacted to afford a mixture of cyclobutanol diastereomers **3b** (minor) and **5b** (major), each of which was formed in relatively low ee (generally <50%). In the interests of brevity and avoiding undue speculation, the following discussion deals with the two salts whose crystal structures were successfully determined: the non-methylated (*R*)-(−)-1-cyclohexylethylamine salt **1c** and its dimethyl analogue, **2c**.[15] Table 1 summarizes the solid state photochemical results for each compound. The fact that these salts have the same counterion eliminates structural differences in the ionic chiral auxiliary as a factor contributing to the solid state reactivity differences.

Figure 1 shows the crystal structures of the anionic portion of the two salts discussed above. For non-methylated salt **1c**, the conformation in the solid state is very similar to the C_S-symmetric minimum energy conformation predicted by molecular mechanics. The $C{=}O\cdots H^{endo}_{pro\text{-}R}$ and $C{=}O\cdots H^{endo}_{pro\text{-}S}$ abstraction distances, while not identical, are quite similar at 2.58 and 2.71 Å, respectively, a finding that is consistent with the relatively low enantioselectivity observed. Crystal melting was ruled out as a possible source of low ee in this case by the finding that the ee was not significantly improved by the use of low conversions and low photolysis temperatures.

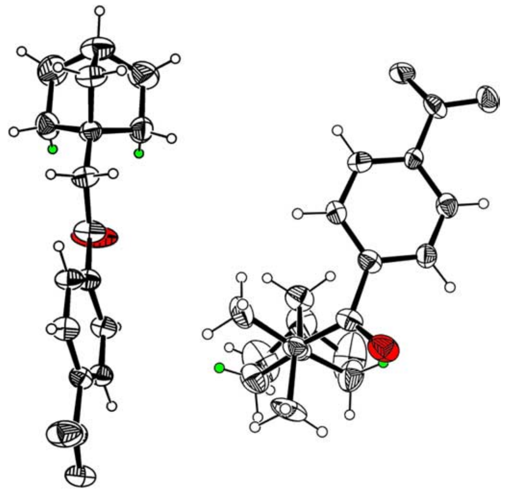


Figure 1. Molecular conformation of the anionic portion of salts **1c** (left) and **2c** (right) (red = ketone oxygen; green = γ-hydrogen).

Table 1. Asymmetric induction in the solid state photochemistry of salts **1c** and **2c**

Salt	Conversion (%)	Product ratio	Enantiomeric excess (%)[a,b]
1c	46	**3b**:**5b** = 46:54	**3b** = 42 (−) **5b** = 33 (+)
2c	100	**4b**:**6b** = 4:96	**6b** = 99 (−)

[a] The symbols (+) and (−) refer to the sign of rotation of the major enantiomer at the sodium D line (absolute configuration unknown).

[b] The ee of photoproduct **4b** could not be determined accurately owing to lack of material and poor HPLC resolution.

The solid state conformation of methylated salt **2c** also conforms closely to the minimum energy conformation predicted by molecular mechanics and is quite different from that of its non-methylated analogue **1c**. The difference in abstraction distances for salt **2c** is large (2.96 vs 5.08 Å), and as a result, the closer hydrogen atom is abstracted preferentially, leading to a high enantiomeric excess (99%).

The X-ray crystal structures also provide a clue as to why methylated salt **2c** gives mainly (96%) of one cyclobutanol diastereomer, whereas non-methylated salt **1c** affords a 46:54 mixture of diastereomers. This is most likely related to the fact that salt **2c** has a conformation that is particularly well suited for formation of cyclobutanol **6c**. Following hydrogen abstraction, the p-orbital on the *re* face of C_1 points directly at the *exo* lobe of the p-orbital on C_4, thus allowing a direct least motion, topochemically allowed closure with retention of configuration at C_1.[16] The alternative inversion pathway leading to cyclobutanol **4c** requires a large amplitude rotation about the C_1–C_2 bond in order to align the *si* face of C_1 with C_4, and this pathway is not only topochemically disfavored, but requires a sterically demanding rotation about the hindered C_1–C_2 bond as well. In contrast, hydrogen abstraction in salt **1c** produces a biradical that is not particularly well arranged for closure to either cyclobutanol, and owing to the lack of methyl substitution at C_2, rotation about the C_1–C_2 and C_2–C_3 bonds is relatively unrestricted, thus allowing formation of roughly equal amounts of diastereomers **3c** and **5c**.

To summarize, molecular mechanics has been shown to provide information useful for the crystal engineering of a diastereo- and enantioselective Yang photocyclization reaction. Current efforts in our laboratory are directed toward applying this concept to other unimolecular solid state photochemical processes.

Acknowledgements

Financial support by the Natural Sciences and Engineering Research Council of Canada is gratefully acknowledged.

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6. Successful abstractions at distances somewhat above and below these limits have occasionally been observed.[4,5] The angle ω, which measures the deviation of the γ-hydrogen atom from the mean plane of the carbonyl group, is also an important parameter. Because hydrogen abstraction involves the n-orbital on oxygen, the ideal value of ω is 0°. Wagner and co-workers have provided evidence that the rate of type II hydrogen atom abstraction is proportional to $\cos^2\omega$. As a result, significant variations in ω are possible without shutting down abstraction. See Wagner, P. J.; Zhou, B. *Tetrahedron Lett.* **1989**, *30*, 5389.
7. Scheme 1 shows only the cyclobutanols resulting from hydrogen abstraction on the two-carbon bridge. It should also be noted that type II cleavage in these systems is forbidden, since it would generate an anti-Bredt olefin.
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9. The molecular mechanics calculations were performed using the HyperChem/ChemPlus software package (versions 5.11/2.0).
10. All other γ-hydrogen atoms in this conformation have d values greater than 3.60 Å.
11. An exception to this rule is found in the case of achiral compounds that crystallize spontaneously in chiral space groups. In such rare but well documented situations, the molecules in the crystal generally adopt homochiral conformations, and chemical reactions of crystals of this type are capable of leading to high levels of asymmetric induction. For a discussion, see: Caswell, L.; Garcia-Garibay, M.; Scheffer, J. R.; Trotter, J. *J. Chem. Ed.* **1993**, *70*, 785.
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14. Diastereomers **3b** and **5b** were differentiated by the presence in **3b** (and the lack in **5b**) of an NOE interaction between the methine hydrogen on the four-membered ring and the *ortho* hydrogens on the aromatic ring; diastereomers **4b** and **6b** were differentiated similarly.
15. Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 248953 (salt **1c**), CCDC 248954 (salt **2c**) and CCDC 248955 (photoproduct **4b**). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44(0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).
16. 1,4-Hydroxybiradical ring closure involving retention of configuration at the hydroxyl-bearing carbon has been noted previously and appears to be a general feature of Yang photocyclization reactions conducted in the crystalline state. See, for example, (a) Gudmundsdottir, A. D.; Lewis, T. J.; Randall, L. H.; Rettig, S. J.; Scheffer, J. R.; Trotter, J.; Wu, C.-H. *J. Am. Chem. Soc.* **1996**, *118*, 6167; (b) Leibovitch, M.; Olovvson, G.; Scheffer, J. R.; Trotter, J. *J. Am. Chem. Soc.* **1998**, *120*, 12755.