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Toward the Development of a Structurally Novel Class of Chiral Auxiliaries. Conformational Properties of the Aldol Adducts of Oxadiazinones: Observation of Unusual Shielding Effects†

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Asymmetric aldol reactions were conducted with the titanium enolate of N_3-hydrocinnamoyl-3,4,5,6-tetrahydro-2*H*-1,3,4-oxadiazin-2-one to afford aldol adducts **5a**−**j**. The dominant product of the asymmetric aldol reaction was the non-Evans syn adduct as determined by ^{1}H NMR spectroscopy and X-ray crystallography. When evaluating the ^{1}H NMR spectra of adducts **5a**−**j**, a highly shielded signal with an average chemical shift of 0.05 ppm was observed. This signal was readily determined to be the C_5-methyl group of the oxadiazinone. It is presumed that the overall conformation adopted by the aldol adducts in solution places an aromatic ring of the N_3-substituent in close proximity to the C_5-methyl group. An investigation of this conformational preference is conducted employing ^{1}H NMR spectroscopy, X-ray crystallography, and computational methods.

Introduction

The asymmetric aldol addition reaction continues to be a synthetic process of great interest.[1] This is primarily due to the fact that the aldol reaction can be manipulated to generate either syn or anti adducts,[2,3] which are valuable intermediates in the synthesis of many natural products. A great variety of methods have emerged over the last 25 years that are capable of achieving high selectivities for one isomer or another. These methods include the use of stoichiometric chiral auxiliaries and substoichiometric asymmetric catalysts.[4] Catalytic methods are proving to be very effective, but chiral auxiliaries still remain as a viable means for obtaining chiral, nonracemic aldol adducts. We have recently reported on the application of a (1*R*,2*S*)-ephedrine-based 3,4,5,6-tetrahydro-2*H*-1,3,4-oxadiazin-2-one (oxadiazinone) as a chiral auxiliary in the titanium-mediated asymmetric aldol addition reaction (Figure 1).[5]

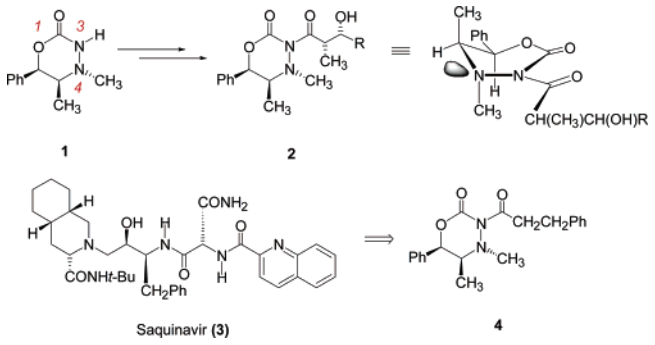

FIGURE 1. Oxadiazinones as chiral auxiliaries.

As evidenced by X-ray crystallography,[5c,6] the ephedrine-based oxadiazinone adopts a twist boat conforma-

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tion wherein the C_5-methyl group and the stereogenic N_4-methyl group are arranged in a 1,2-trans-pseudodiaxial relationship. These two positions work as a stereochemical tandem (intramolecular chiral relay)[7] that directs the outcome of asymmetric induction. The major diastereomer of this asymmetric aldol reaction was determined by ^{1}H NMR spectroscopy and X-ray crystallography to be the non-Evans syn adduct.[5c]

In connection with a program focused on the synthesis of the HIV protease inhibitor saquinavir (**3**),[8] we have acylated the ephedrine-based oxadiazinone (**1**) with hydrocinnamoyl chloride to yield the corresponding N_3-hydrocinnamoyloxadiazinone (**4**) and have conducted a series of test aldol reactions. The chemical yields were fair to very good, and diastereoselectivities were, in general, good for the aromatic aldehydes and poor for the aliphatic aldehydes. More interesting, however, was the fact that all of the aldol adducts exhibited a signal in their respective ^{1}H NMR spectra that appeared near 0 ppm. This was unusual, as we had not observed any chemical shift values near this region in our previous applications of the ephedrine-based oxadiazinone in the aldol reaction.[5] It is believed that this change in the position of the signal in the ^{1}H NMR spectra is due to conformational effects that arise from the unusual conformation adopted by oxadiazinones. Previous work in our labs suggested that oxadiazinones derived from ephedrine and pseudoephedrine adopt a conformation in which the C_2-carbonyl group and the N_3-acyl substituent are arranged in a syn parallel orientation.[9a] In this paper, we examine the conformational aspects of the *syn*-aldol adducts generated from the aldol reaction with the N_3-hydrocinnamoyloxadiazinone (**4**) that most likely give rise to the unexpected chemical shift values by employing ^{1}H NMR spectroscopy, X-ray crystallography, and computational methods.

Results and Discussion

Synthesis. (1*R*,2*S*)-Ephedrine-based oxadiazinone **1** was acylated by reaction with lithium hydride and hydrocinnamoyl chloride in methylene chloride to afford the corresponding N_3-hydrocinnamoyl heterocycle in 90% yield after column chromatography. The acylated oxadiazinone was then treated with 2 equiv of $TiCl_4$ at room temperature for 25 min. The reaction mixture was then cooled to −78 °C, and triethylamine was added. The temperature was allowed to slowly come to 25 °C over a period of 60 min and was then again chilled to −78 °C for the addition of the aldehyde (Scheme 1).

The chemical yield for the 10 aldehyde examples ranged from 38 to 86% (Table 1). The diastereoselectivities of these reactions were, in general, varied (1.4:1.0 to 47:1), favoring the non-Evans syn isomer over the remaining isomers. This stereochemistry was determined by analogy with our previous efforts in the asymmetric aldol reaction with oxadiazinones.[5] In addition, single-crystal X-ray crystallography of aldol adduct **5c** confirmed this stereochemical orientation.

X-ray Crystallography.[10] The asymmetric aldol adduct **5c** was recrystallized to afford crystals suitable for X-ray diffraction studies (Figure 2). With **5c** containing

SCHEME 1. Asymmetric Aldol Reactions with Oxadiazinone 4

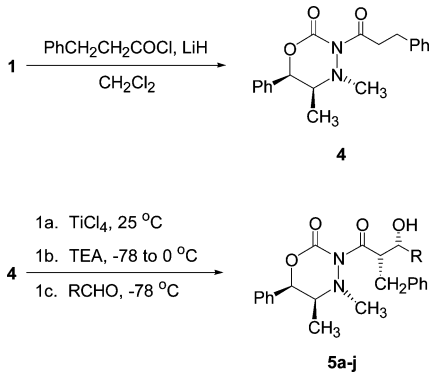
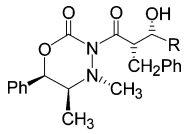


TABLE 1. Asymmetric Aldol Adducts 5a−j



entry	aldehyde	product	dr[a]	% yield[b]
1	$-C_6H_5$	**5a**	47:1	84
2	$-C_6H_3(CH_2O_2)$	**5b**	6:1[c]	68
3	$-p$-C_6H_4Cl	**5c**	21:1	60
4	$-o$-$C_6H_4OCH_3$	**5d**	5:1	46
5	$-p$- $C_6H_4NO_2$	**5e**	22:1	69
6	-1-$C_{10}H_7$	**5f**	13:1	78
7	-2-$C_{10}H_7$	**5g**	13:1	86
8	$-C(CH_3)_3$	**5h**	1.4:1	38
9	$-CH(CH_3)_2$	**5i**	3:1	47
10	$-CH_3$	**5j**	5:1	42

[a] Diastereomeric ratio (dr) was determined either by HPLC or 400 MHz ^{1}H NMR. [b] Isolated yield after column chromatography or recrystallization.

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(10) Please see Supporting Information for details pertaining to the X-ray crystal structure. X-ray structural data has been deposited at the Cambridge Crystallographic Data Center CCDC-221499. Copies of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk; Internet: http://www.ccdc.cam.ac.uk).

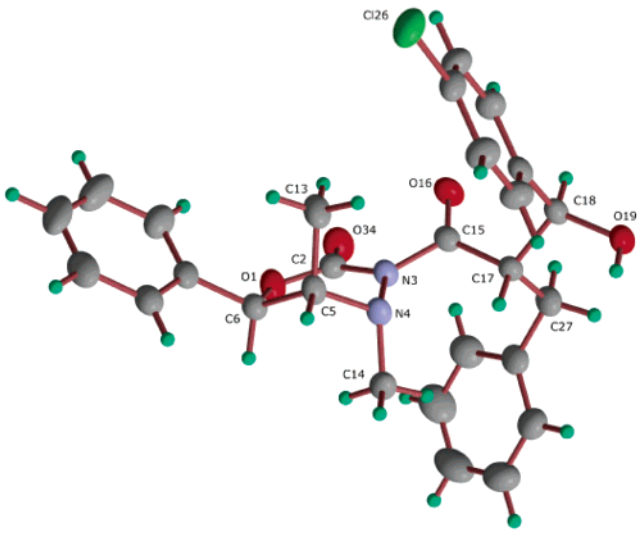


FIGURE 2. RASTEP drawing (50% probability level) of **5c**, with hydrogen atoms drawn arbitrarily small for clarity.

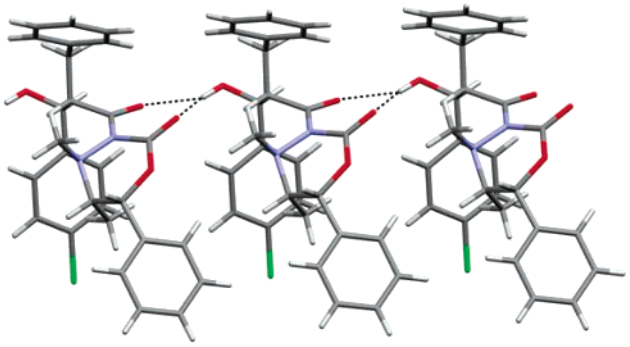
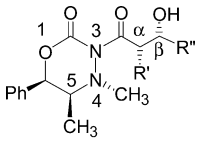


FIGURE 3. Intermolecular hydrogen bonding in the solid state.

a chlorine atom, absolute stereochemical assignment was achieved by refinement of the Flack parameter. Analogous to the related (1*S*,2*S*)-pseudoephedrine-based oxadiazinones,[6,9] the crystallographic analysis revealed that the structure adopted by **5c** is a twist-boat conformation in which the imide carbonyls are arranged with the carbonyls oriented in a syn parallel conformation; however, the steric restraints of the C(15) substituent (i.e., the N_3-acyl substituent) lead to a significant distortion of the imide dicarbonyl from planarity as evidenced by the 30.2(2)° torsion angle for [O(34)−C(2)−C(15)−O(16)]. The conformation adopted by **5c** in the solid state has the terminal *para*-chlorophenyl substituent proximal to the C_5-methyl group and the hydrocinnamoyl substituent (C_{17}−C_{27}Ph) proximal to the N_4-methyl group with respective aryl centroid to C(13) and to C(14) distances equal to 3.622(2) and 3.619(2) Å.

This conformation precludes any intramolecular hydrogen bonding involving the O_{19}-hydrogen atom; however, intermolecular hydrogen bonding exists between the O_{19}-hydrogen atom and the imide dicarbonyl oxygen atoms of the proximal molecule located at $X + 1$, Y, Z as illustrated in Figure 3 and evidenced by the O(19)−O(16)′ 2.851(12), O(16)′−H(19) 2.14(2), O(19)−O(34)′ 3.295(2), and O(34)′−H(19) 2.54(2) Å separations. On the basis of these separations, the O(16)′−H(19) interaction would

TABLE 2. Chemical Shifts of the C_5-Methyl Substituent for Oxadiazinone Adducts 2 and 5a−j



2, 5a-j

entry	adduct	α-substituent R′	β-substituent R″	δ, ppm[a] (C_5-methyl)
1	**2**	$-CH_3$	$-C_6H_5$	0.82
2	**5a**	$-CH_2C_6H_5$	$-C_6H_5$	0.04
3	**5b**	$-CH_2C_6H_5$	$-C_6H_3(CH_2O_2)$	0.05
4	**5c**	$-CH_2C_6H_5$	$-p$-C_6H_4Cl	0.03
5	**5d**	$-CH_2C_6H_5$	$-o$-$C_6H_4OCH_3$	0.08
6	**5e**	$-CH_2C_6H_5$	$-p$- $C_6H_4NO_2$	0.04
7	**5f**	$-CH_2C_6H_5$	-1-$C_{10}H_7$	0.02
8	**5g**	$-CH_2C_6H_5$	-2-$C_{10}H_7$	0.05
9	**5h**	$-CH_2C_6H_5$	$-C(CH_3)_3$	0.02
10	**5i**	$-CH_2C_6H_5$	$-CH(CH_3)_2$	0.11
11	**5j**	$-CH_2C_6H_5$	$-CH_3$	0.09

[a] All chemical shifts measurements were recorded in $CDCl_3$ using a 400 MHz NMR spectrometer.

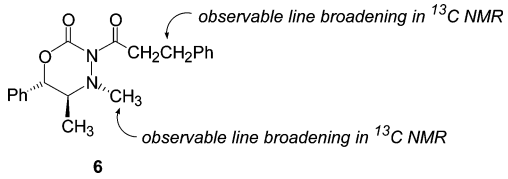


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FIGURE 4. Proximity effects in a (1*S*,2*S*)-pseudoephedrine-derived oxadiazinone.

appear to be the dominant hydrogen bonding interaction in the solid state.

^{1}H NMR Spectroscopy. Interestingly, the ^{1}H NMR spectra of adducts **5a**−**j** also revealed structural information pertaining to the N_3-substituent and its spatial relationship to the oxadiazinone. All of the ^{1}H NMR spectra have a signal near an average value of 0.05 ppm, and this signal was determined to be the C_5-methyl group of the oxadiazinone (Table 2). In contrast, the average chemical shift for the C_5-methyl group in a variety of related oxadiazinone aldol adducts is 0.85 ppm (e.g., oxadiazinone **2**).[5] It is believed that the aromatic ring of the N_3-substituent is folded in toward the heterocycle and has a shielding effect on the C_5-methyl group. The X-ray crystal structure (Figure 2) suggests that it is the terminal aromatic ring of the N_3-substituent. The origins of this conformational preference are not well understood. It is speculated that this is the result of the unique conformational preference of (1*R*,2*S*)-ephedrine- and (1*S*,2*S*)-pseudoephedrine-based N_3-substituted oxadiazinones.[6,9] In fact, the conformational arrangement of the related (1*S*,2*S*)-pseudoephedrine-based *N*$_3$-hydrocinnamoyloxadiazinone (**6**) shows a similar orientation of the imide carbonyls as that of oxadiazinone **5c** depicted in Figure 4.[9b] However, the proximity effects in the pseudoephedrine system are manifested by observable line broadening rather than shielding effects.

NOE Experiments. X-ray crystallography suggested that the terminal aromatic ring was responsible for the chemical shift change, but this work was limited to the solid state and did not address issues of solvation that

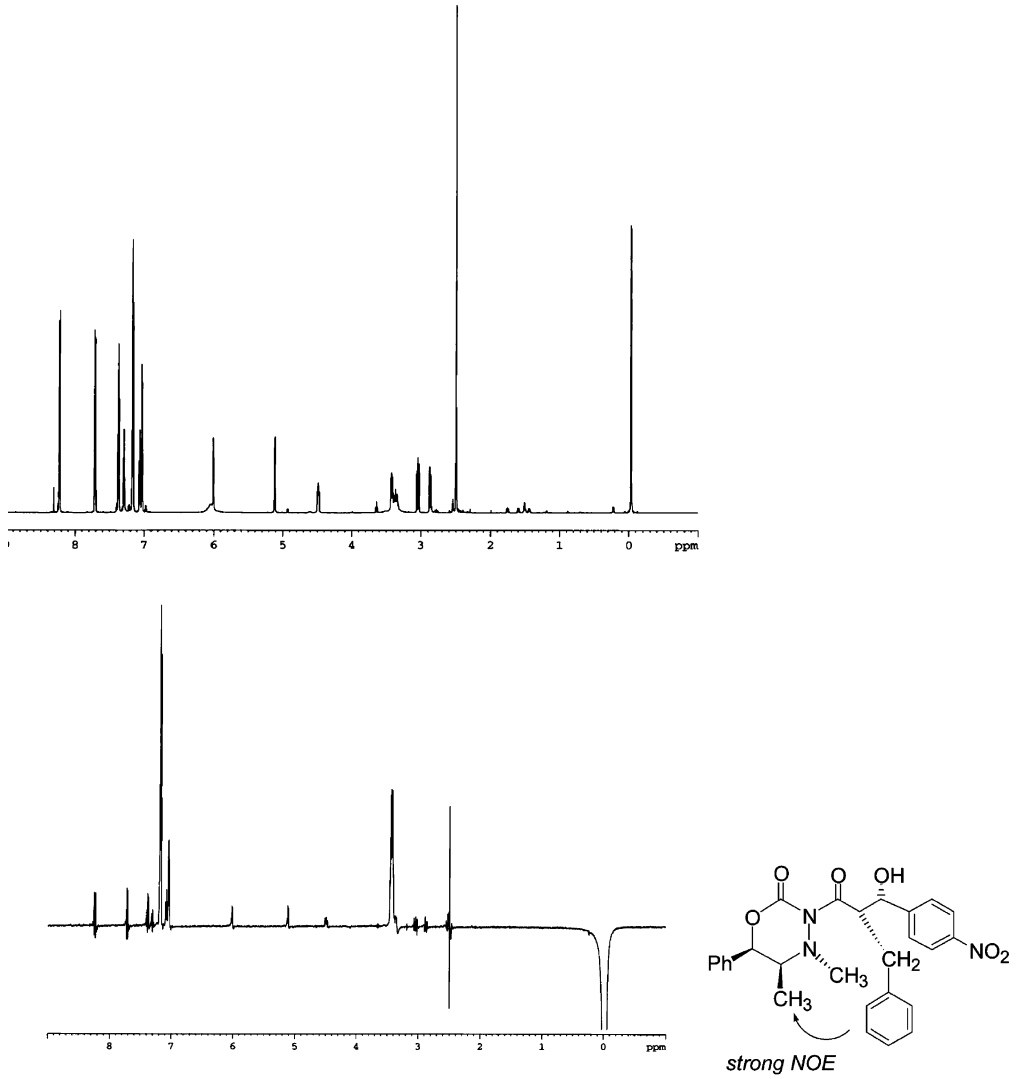


FIGURE 5. NMR spectrum of oxadiazinone **5e**. (a) 700 MHz ^{1}H NMR spectrum of **5e** in DMSO-d_6. (b) 500 MHz ^{1}H NMR NOEDIFF spectrum of **5e** in DMSO-d_6.

would be relevant in solution. To more fully probe the nature of the observed shielding effect in solution, a series of NOE difference experiments were conducted to demonstrate the proximity of the terminal aromatic ring of the N_3-substituent to the C_5-methyl group. In this regard, oxadiazinone aldol adduct **5e** was subjected to the NOE experiment (Figure 5). Interestingly, a strong, positive NOE effect was observed between the protons of the C_5-methyl group and the protons of the aromatic moiety of the N_3-hydrocinnamoyl fragment. This was in stark contrast to what was observed in the solid-state X-ray crystal structure wherein the terminal aromatic ring was proximal to the C_5-methyl group.

Oxadiazinone **5h** was also investigated by NOE. This oxadiazinone was selected because it does not have a terminal aromatic ring; rather, a *tert*-butyl group is at this position. Again, a positive NOE effect was observed for the C_5-methyl group and the N_3-hydrocinnamoyl aromatic ring (Figure 6). This collected body of evidence, along with the observed chemical shifts of adducts **5a**−**d**,**f**,**g**,**i**,**j** ($\delta_{avg} \approx 0.05$ ppm) suggests that the substituents in question (C_5-methyl/N_3-hydrocinnamoyl aromatic) are proximal to one another. Interestingly, this conformation requires that the arrangement of the N_3-hydrocinnamoyl and aryl substituent must be reversed in solution, relative to the solid-state X-ray crystal structure (Figure 2). This is feasible given the generalized packing of the known acylated ephedrine- and pseudoephedrine-based oxadiazinones and the ability of H_{19} to hydrogen bond to the imide dicarbonyls.[5c,6,9a]

To further support the NOE difference experiments, a related oxadiazinone was prepared to demonstrate the impact of the hydrocinnamoyl moiety on the C_5-methyl group (Scheme 2). Thus, ephedrine-based oxadiazinone **1** was acylated with cyclohexanepropanoyl chloride to afford the acylated heterocycle **7** in 78% yield. This product was then treated with titanium tetrachloride, triethylamine, and benzaldehyde to afford the aldol adduct **8** in 40% yield and a diastereomeric ratio of 4:1 favoring the syn diastereomer as determined by ^{1}H NMR spectroscopy. As predicted, the chemical shift of the C_5-methyl group returned to its characteristic value of 0.85 ppm. This further supported the fact that the aromatic

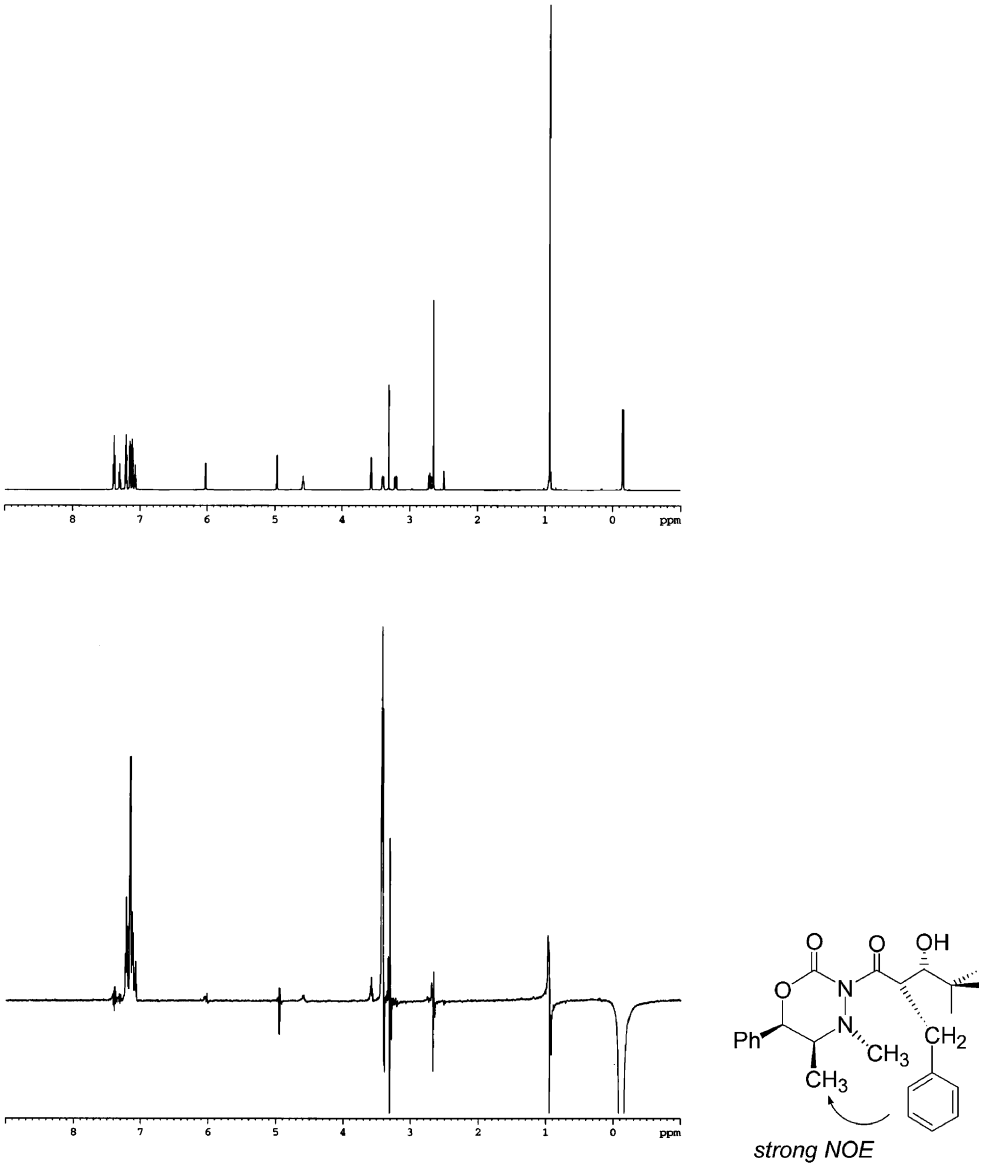
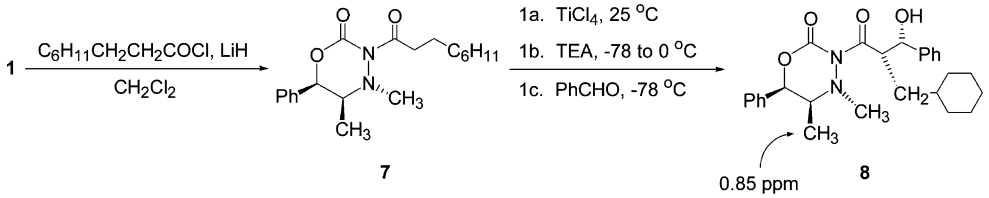


FIGURE 6. NMR spectrum of oxadiazinone **5h**. (a) 700 MHz ^{1}H NMR spectrum of **5h** in DMSO-d_6. (b) 500 MHz ^{1}H NMR NOEDIFF spectrum of **5h** DMSO-d_6.

SCHEME 2. Oxadiazinone Aldol Adduct 8



moiety of the hydrocinnamoyl group is responsible for the observed change in chemical shift.

Computational Studies. The objectives of the computational studies are to search for conformations of oxadiazinone **5a** that exhibit unusual ^{1}H NMR chemical shifts of the C_5-methyl protons and to characterize the structural origins of these unusual chemical shifts. A conformation search employing the AM1 semiempirical molecular orbital method was carried out to locate low-energy conformations of oxadiazinone **5a**. The conformation search was performed using the Spartan5.1 and Spartan02 software packages.[11] Because we were interested in the positioning of the aromatic rings of the N_3-substituent and their effect on the ^{1}H NMR chemical shift of the C_5-methyl group, a systematic conformation search was employed in which initial structures were generated by variation of the dihedral angles responsible for positioning of the aromatic ring of the N_3-hydrocinnamoyl unit and the aromatic ring at the terminus of the N_3-

(11) *Spartan 5.1* and *Spartan 02*; Wavefunction, Inc.: Irvine, CA, 2002.

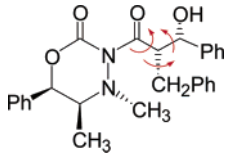


FIGURE 7. Conformational analysis of oxadiazinone **5a**.

substituent chain (Figure 7). The geometries of the initial structures obtained in the systematic search were then optimized in the gas phase using the AM1 method. The AM1 semiempirical method was selected because it has been previously shown to produce structures for similar molecular systems in good agreement with X-ray structural data.[9a]

The NMR chemical shifts of the protons of the methyl group attached to the C_5 position were determined for each conformation from single-point energy calculations at the B3LYP/DZVP level of theory using the equilibrium geometry obtained from the AM1 calculations. The NMR shielding tensors were computed in the gas phase using the Gauge Invariant Atomic Orbital technique as implemented in the PQS ab initio software package.[12]

The conformation search resulted in the determination of 25 conformations of oxadiazinone **5a** with enthalpies of formation within 7.5 kcal/mol (1.8 kJ/mol) of the lowest energy conformation obtained. The two lowest energy conformers are shown in Figure 8. The calculated enthalpies of formation of the 11 lowest conformers within 4 kcal/mol (0.96 kJ/mol) of the lowest energy conformation are listed in Table 3. Also listed in Table 3 are the dihedral angles between the C_2- and N_3-carbonyl groups, as well as the average calculated gas phase ^{1}H NMR chemical shifts of the protons of the C_5-methyl group, measured relative to tetramethylsilane.

Even though the two carbonyl groups (C_2-carbonyl/N_3-carbonyl) were initially aligned to be close to syn parallel in orientation in generating the initial structures for the conformation search (with a dihedral angle of about 26° between the carbonyls), sometimes this orientation changed during the geometry optimization so that in some conformers the carbonyl groups became nearly perpendicular. Overall, dihedral angles between the two carbonyl groups range from 21 to 86° in the 25 conformers that were located. The calculated dihedral angle of 31.8° between the C_2- and N_3-carbonyl groups of conformation 2 of oxadiazinone **5a** is close to the orientation found in the solid-state X-ray crystal structure of oxadiazinone **5c**, 30.2(2)°. It is also interesting to note that conformer 2 of oxadiazinone **5a** is very similar overall to the X-ray crystal structure of oxadiazinone **5c**. For example, in conformation 2 of oxadiazinone **5a**, the terminal aromatic ring of the N_3-substituent is in close contact with the C_5-methyl group, with a distance from the aryl centroid to C(13) (Figure 2) of 3.68 Å. The hydrocinnamoyl substituent of conformation 2 of oxadiazinone **5a** is in close contact with the N_4-methyl group, with a distance from the aryl centroid to C(14) of 3.60 Å. These calculated structural results are quite comparable with respective distances of 3.622(2) and 3.619(2) Å obtained from the X-ray crystal structure of oxadiazinone **5c**.

(12) *PQS*, version 2.5; *Parallel Quantum Solutions*: Fayetteville, Arkansas, 2002.

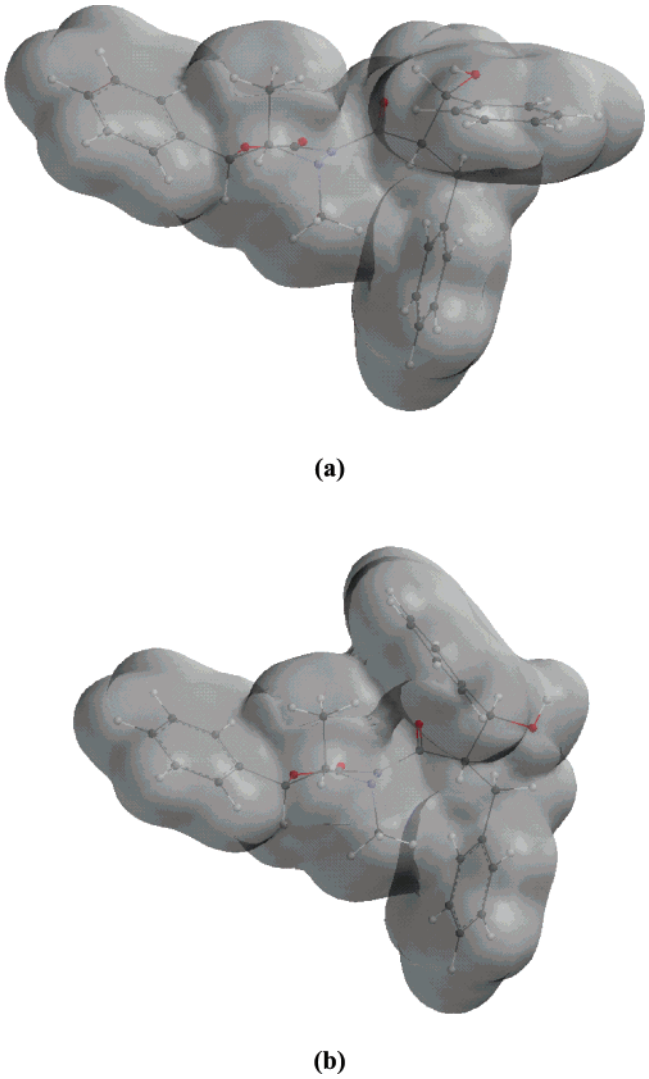


FIGURE 8. Isodensity surfaces of the optimized geometry of (a) conformer 1 and (b) conformer 2 of oxadiazinone **5a** obtained using the AM1 semiempirical method. The isodensity surface is plotted at a value of 0.002.

TABLE 3. Calculated Enthalpies of Formation (kcal/mol),[a] Dihedral Angle between Carbonyl Groups, and Average Chemical Shifts (ppm)[b] of the C_5-Methyl Protons for the 11 Lowest Conformations

conformation	ΔH_f kcal/mol[a] (kJ/mol)	dihedral angle (degrees)	average C_5 methyl chemical shift (ppm)[b]
1	−37.39 (−8.936)	32.0	0.95
2	**−35.79 (−8.554)**	**31.8**	**−0.37**
3	−35.25 (−8.425)	26.3	0.99
4	−35.20 (−8.413)	29.8	1.08
5	−34.81 (−8.320)	37.5	1.03
6	−34.51 (−8.248)	65.6	1.09
7	−34.30 (−8.198)	71.0	1.12
8	**−34.19 (−8.170)**	**48.2**	**0.44**
9	−34.07 (−8.143)	85.7	1.14
10	**−33.86 (−8.093)**	**21.2**	**0.18**
11	−33.45 (−7.995)	82.3	1.19

[a] Enthalpies of formation were computed using the AM1 semiempirical method. [b] Gas-phase chemical shifts in parts per million relative to TMS are reported.

The lowest energy conformation of oxadiazinone **5a** is stabilized by an intramolecular hydrogen bond between

the OH group and the carbonyl group attached to N_3-substituent; the bond distance of this hydrogen bond is 2.19 Å. In fact, 8 of the 11 lowest energy conformations found have an intramolecular hydrogen bond from the OH group to either the carbonyl at the N_3 position or directly to the N_3-nitrogen, and 16 of the total 25 conformers found have an intramolecular hydrogen bond between the OH group and either one of the carbonyl groups or the ring nitrogens. The large amount of intramolecular hydrogen bonding found in the gas-phase conformers of oxadiazinone **5a** is in contrast to the solid-state X-ray crystal structure of oxadiazinone **5c**, which exhibits intermolecular hydrogen bonding. In the solution phase, both these systems would also have the capability to form hydrogen bonds with polar solvent molecules.

The average proton NMR chemical shifts of the protons of the methyl group attached to the C5 position for the compounds exhibiting intramolecular hydrogen bonding are in the expected range, with values from 0.9 to 1.23 ppm depending on the conformer. Of the 11 lowest energy conformers found within 4 kcal/mol (0.96 kJ/mol) of the lowest energy conformation, three (conformers 2, 8, and 10 in Table 3) do not exhibit intramolecular hydrogen bonding. In all three of these conformers, the C_5-methyl group comes into relatively close contact with the terminal aromatic ring of the N_3-substituent. These three low-energy conformers exhibit unusual chemical shifts for the protons of the C_5-methyl group. The chemical shifts of the protons of the C_5-methyl group for these conformers range from −0.37 to 0.44 ppm. These chemical shifts are much lower than those expected for a methyl group and are in accord with the solution-phase NMR studies of the C_5-methyl groups of oxadiazinones **5a**−**j**, which exhibit chemical shifts of close to 0 ppm. The conclusion from the computational studies is that the close contact between the C_5-methyl protons and the terminal aromatic group of the N_3-substituent is responsible for the unusual chemical shifts of the C_5-methyl protons in conformers 2, 8, and 10 of oxadiazinone **5a**.

That the close contact of the terminal aromatic ring of the N_3-substituent is responsible for the unusual chemical shift of the methyl protons attached to C_5-position of oxadiazinone **5a** has been tested by truncating the structure of the molecule by removing the aromatic ring and recalculating the chemical shifts. After truncation, the average chemical shift of the protons of the C_5-methyl group in conformer 2 is 0.81 ppm (compared to −0.37 ppm before truncation). The positioning of the protons of the C_5-methyl group between the aromatic residue at the terminus of the N_3-substituent chain and the benzene ring attached to C_6-position also plays a role in changing the chemical shift. When the aromatic ring at the terminus of the N_3-substituent chain is left in place and the aromatic ring attached to the C_6-position is truncated, the average chemical shift of the C_5-methyl protons in conformer 2 is 0.16 ppm (compared to −0.37 ppm before truncation). This would suggest that both aromatic rings must be present for the full shift to be observed, though the close contact of the aromatic ring at the terminus of the N_3-substituent is most important in causing the unusual chemical shift.

The computational studies also reveal that close contact between the C_5-methyl protons and either the terminal aromatic group of the N_3-substituent or the aromatic ring of the N_3-hydrocinnamoyl unit can lead to unusual chemical shifts for the C_5-methyl protons. The three lowest energy gas-phase conformers of oxadiazinone **5a** (conformers 2, 8, and 10) that exhibit unusual chemical shifts of the C_5-methyl protons involve close contact between the C_5-methyl group and the terminal aromatic group of the N_3-substituent. However, the conformation search also uncovered one conformation in the gas phase, conformer 25, that exhibits an unusual chemical shift of the C_5-methyl protons due to close contact between the C_5-methyl group and the aromatic ring of the N_3-hydrocinnamoyl unit (Figure 9), with a calculated chemical shift of 0.16 ppm. This conformer is 7.4 kcal/mol (1.8 kJ/mol) above the lowest energy conformer in the gas phase, exhibits intramolecular hydrogen bonding between the hydroxyl group and N_4, and has a dihedral angle between the C_2- and N_3-carbonyl positions of 63.4°. Thus, the computational studies indicate that either aromatic ring in proximity to the C_5-methyl group can lead to the unusual chemical shift.

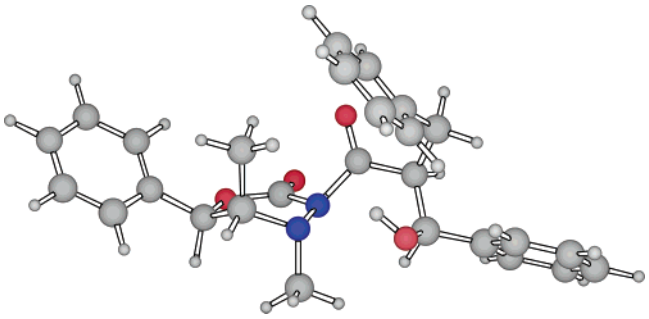


FIGURE 9. Conformer 25 of oxadiazinone **5a**.

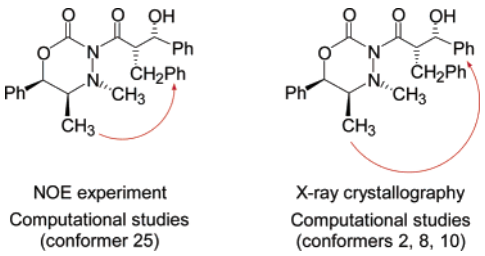


FIGURE 10.

Conformational Analysis Summary. The results of the computational studies suggest that the chemical shift change of the C_5-methyl group is a result of the proximity of either the terminal aromatic group of the N_3-substituent or the aromatic ring of the N_3-hydrocinnamoyl unit in oxadiazinone **5a**. The lowest energy conformers in the gas phase that exhibit this effect correspond to those in which the terminal aromatic group of the N_3-substituent is in close contact with the C_5-methyl group. These results are somewhat at odds with the results obtained from the NOE experiments, which suggest that in solution it is solely the aromatic ring of the N_3-hydrocinnamoyl moiety that is responsible for the change in chemical shift and not the terminal aromatic ring (Figure 10).

In contrast, the results of the computational study are in excellent agreement with the solid state X-ray crystal structure. The reason for the differences among the NOE, X-ray crystallographic, and computational studies is attributed to the impact of solvation effects and hydrogen

bonding on the oxadiazinone conformation. The conformation observed in the solid-state structure is likely attributable to the intermolecular hydrogen bonding interactions (Figure 3). Were the conformation observed in solution to prevail in the solid state, any conventional type of intermolecular hydrogen bonding interactions would be disrupted. While the impact such a conformational change would have on the crystal packing is unclear, nominally it appears the dominant change would be the elimination of conventional hydrogen bonding interactions.

In the computational studies, the gas-phase conformations of oxadiazinone **5a** are quite polar (for example, the dipole moments of conformations 1 and 2 are 6.89 and 6.09 D, respectively) which could lead to strong interactions with polar solvent molecules. In addition, the ability of oxadiazinone **5a** to form both intramolecular hydrogen bonds and explicit hydrogen bonds with the solvent leads to the conclusion that the gas-phase energy ordering of the conformers is not necessarily the same in the solution phase. This is especially likely because the conformers are relatively closely spaced in energy. While calculations employing continuum solvent methods would partially address this issue, the inclusion of explicit solvent molecules in the calculations also would probably be necessary to obtain more reliable energy ordering of the conformers of oxadiazinone **5a**. The lengthy calculations required for a complete solution-phase study of the conformations of oxadiazinone **5a** in the presence of a continuum solvent model and/or explicit solvent molecules were deemed to be outside the scope of the present work. Nevertheless, the present computational studies do provide corroborating evidence that the origin of the unusual chemical shift of the C_5-methyl protons is the close proximity of one of the aromatic groups of the N_3-substituent.

Another explanation of the differences observed among the NOE spectra, X-ray crystallographic data, and computational results could be that while in solution, the C_2- and the N_3-carbonyls are arranged in an antiperiplanar conformation. In this orientation, the aromatic rings of the N_3-substituent effectively change places and would yield the results of the NOE difference experiments. However, this idea is countered by our prior observations that the dominant conformation is the synclinal arrangement.[5c,6,9] The synclinal arrangement of the carbonyls is believed to be the dominant conformation in solution and in the solid state for reasons that were stated earlier. It is more likely that the carbonyls are syn parallel and that the aromatic rings are switched in position.

Conclusion

In summary, we have conducted a series of asymmetric aldol reactions with the titanium enolate of *N*$_3$-hydrocinnamoyl-3,4,5,6-tetrahydro-2*H*-1,3,4-oxadiazin-2-one to afford aldol adducts **5a**−**j**. The dominant product of the asymmetric aldol reaction was the non-Evans syn adduct as determined by ^{1}H NMR spectroscopy and X-ray crystallography. The ^{1}H NMR spectra of aldol adducts **5a**−**j** suggested that the C_5-methyl group of the oxadiazinone ring is highly shielded by an aromatic ring on the N_3-substituent chain. The solution-phase NOE experiments suggest that the aromatic ring of the N_3-hydrocinnamoyl group is responsible for the unusual shielding of the C_5-methyl group. In contrast, X-ray crystallography reveals that in the solid state, the terminal aromatic ring of the N_3-substituent is proximal to the C_5-methyl group. Computational studies reach this same conclusion for the three lowest gas-phase conformations that have unusual chemical shifts of the C_5-methyl protons; however, among the 25 conformations located, one other that has the unusual chemical shift involves close contact between the C_5-methyl group and the aromatic ring of the N_3-hydrocinnamoyl unit (as was observed in the solution-phase NOE studies).

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Supporting Information Available: Experimental details of X-ray crystallography, computational studies, characterization data (400 MHz ^{1}H NMR, 100 MHz ^{13}C NMR) for all new compounds, and 500 MHz ^{1}H NMR spectra (NOE) of **5e** and **5h**. This material is available free of charge via the Internet at http://pubs.acs.org.

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