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The origin of stereoselectivity in cycloaddition reactions promoted by stereoisomers of 8-phenylmenthyl glyoxylate oxime

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ABSTRACT

A structural study of three synthesized stereoisomeric oximes, (−)-8-phenylmenthyl glyoxylate oxime (8-PMGO), (+)-8-phenylneomenthyl glyoxylate oxime (8-PnMGO), and (−)-8-phenylisoneomenthyl glyoxylate oxime (8-PinMGO), was performed by means of variable temperature ^{1}H NMR spectroscopy, X-ray crystallography, and ab initio calculations. It was found that in 8-PMGO a conformation where the phenyl and oxime moieties are stacked is significantly favored, whereas in the other stereoisomers this preference was not so evident. The conformational differences found between the isomers were used to rationalize the outcome of the reaction (simultaneous 1,3-cycloaddition and aza-Diels–Alder reaction) between the referred oximes and cyclopentadiene, in which the stereoselectivity was evaluated and found to be nicely reproduced by a simple conformational analysis. The global results indicate that the stereoselectivity of the studied oximes, a bit higher for 8-PMGO, originates from their particular conformational distribution, in which the phenyl·oxime aromatic interaction plays a decisive role.

1. Introduction

Since the introduction of 8-phenylmenthol as a chiral auxiliary by Corey,[1] there are not many examples of the usage of its stereoisomers.[2] Just recently the other 8-phenylmenthol stereoisomers have been used and proved to have potential as chiral auxiliaries in asymmetric synthesis, particularly in aza-Diels–Alder reactions.[3]

From the time when 8-phenylmenthol started to be used, it exhibited excellent results as chiral auxiliary, leading to high diastereomeric and enantiomeric excesses in asymmetric synthesis,[1,2,4] this essential feature being considered to be related to its structure.[1d,5] In solution, even when it is complexed to Lewis acids, the phenyl group of an acrylate ester of 8-phenylmenthol (as an example) is believed to be positioned so as to allow an attractive interaction between the π double bond of the acryloyl group and the aromatic ring, which is well positioned under the acrylic ester π system at a favorable stacked π–π spacing of approximately 3.5 Å.[1d] As a result of this interaction, the phenyl ring blocks one of the diastereotopic faces of the acrylic ester π system, thus forcing the approach of the reactants from the other side, giving rise to a large diastereomeric excess. Some computational calculations[6] and experimental data[7] seem to sustain this interpretation. In fact, the structures of the compounds obtained from reactions between acrylate esters and dienes (as cyclopentadiene, CPD), in which 8-phenylmenthol is used as chiral auxiliary, as well as the observed diastereoselectivities, are in agreement with the described analysis. Nonetheless, in the cases of aza-Diels–Alder reactions, in which the dienophile is usually an imine, such interpretation is expected to be more complex. Comparatively to acrylates, imines may adopt diverse conformations (e.g., s-cis/s-trans and *E*/*Z* conformations), allowing more possible structures to exist in solution. Moreover, such conformations may be strongly dependent on the reaction conditions as solvent, temperature, presence of a catalyst and on the catalyst itself. Considering this, and also the increase on the application of the other 8-phenylmenthol stereoisomers in asymmetric synthesis, we intended to compare and rationalize the resulting stereoselectivity in cycloaddition reactions when those different stereoisomers are employed as chiral auxiliaries. To do this, (−)-8-phenylmenthyl, (+)-8-phenylneomenthyl, and (−)-8-phenylisoneomenthyl glyoxylate oximes (8-PMGO, 8-PnMGO, and 8-PinMGO, respectively) (Fig. 1) were structurally analyzed in solution, condensed and gas phases; in addition, 8-PMGO and 8-PnMGO were reacted with CPD in order to evaluate their

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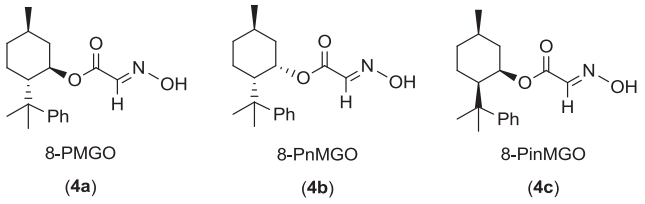


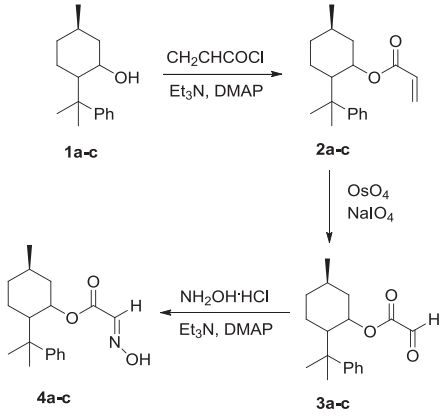
Fig. 1. Structural formulas of the oximes considered in this work, and respective abbreviations.

enantioselectivities by analyzing the obtained cycloadducts (the isoxazolidines being the major products).[8]

2. Results and discussion

2.1. Synthesis

(−)-8-phenylmenthol (**1a**), (+)-8-phenylneomenthol (**1b**), and (−)-8-phenylisoneomenthol (**1c**) were synthesized according to the literature.[3a] The correspondent acrylates (**2a**–**c**) were prepared by treatment with acryloyl chloride in the presence of triethylamine. The oxidative cleavage of the acrylate's double bond by $OsO_4/NaIO_4$ provided the respective glyoxylates (**3a**–**c**).[2,3d] 8-PMGO, 8-PnMGO, and 8-PinMGO (**4a**–**c**, respectively) were synthesized according to a previously reported method,[8] from their respective glyoxylates by treatment with hydroxylamine hydrochloride in the presence of triethylamine and a catalytic amount of DMAP (Scheme 1).



Scheme 1. Procedure adopted for the synthesis of the studied oximes.

2.2. Conformational study

For each oxime, ^{1}H NMR spectra were recorded at several temperatures in $CDCl_3$ and the chemical shifts (δ) of the more significant protons were plotted against *T*. All the values were scaled by considering δ at the lower temperature as zero.

The ^{1}H NMR spectra (see Supplementary data) show that the H_{imine} signal in 8-PMGO (6.79 ppm) has a high upfield shift relative to both 8-PnMGO and 8-PinMGO (δ=7.45 and 7.50 ppm, respectively). This fact suggests the existence of a significant degree of π···π stacking between the phenyl ring and the glyoxylate oxime π system in 8-PMGO, the upfield shift arising from the shielding effect produced by the magnetic anisotropy of the phenyl ring.[9] On the other hand, the chemical shifts of the H_{imine} for the other isomers are similar to those of other aliphatic *E* aldoximes,[10] which suggests that no significant π···π stacking occurs between the phenyl ring and the glyoxylate oxime moiety in both 8-PnMGO and 8-PinMGO.

The effect of the temperature on the ^{1}H NMR spectra was also studied. Signals for characteristic protons of the 8-phenylmenthyl moiety for each of the three oximes [5′-CH_3, 2× 8′-CH_3 (represented as a, b, and c, respectively), and Ph−H_{para}] were monitored, showing negligible changes in the chemical shifts with temperature. Concerning the H_{imine} signals of 8-PnMGO and 8-PinMGO, one can verify that the dependence of their chemical shift with temperature is very small (see Supplementary data). The plot of $\Delta\delta$ against *T* for 8-PMGO is presented in Fig. 2. In this case a significant downfield shift of the imine proton is observed as the temperature increases, which can be due to thermal displacement from the conformation in which the intramolecular π···π stacking exists.

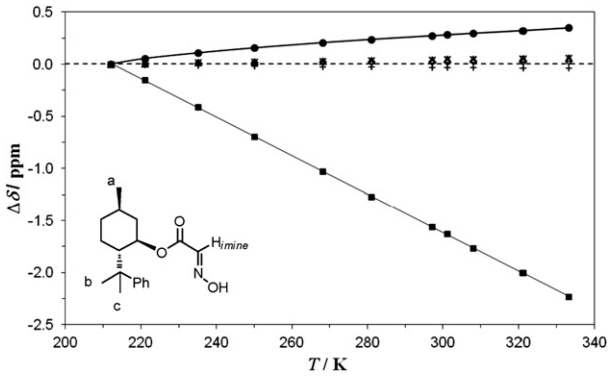


Fig. 2. Temperature dependence of the proton chemical shifts, $\Delta\delta$, in 8-PMGO. Legend: ■ OH; × CH_3 a; Δ CH_3 b; ◇ CH_3 c; + Ph−H_{para}; ● H_{imine}.

NOEs NMR were also performed for the three oximes. Some NOE effect between H_{imine} and the aryl protons in 8-PMGO was observed. On the contrary, for 8-PnMGO and 8-PinMGO, a small NOE signal was observed between H_{imine} and 8′-CH_3 protons while no (or a negligible) NOE signal was detected between H_{imine} and the aryl protons (see Supplementary data for more details).

In summary, the NMR results are consistent with the fact that in 8-PMGO the phenyl ring and the glyoxylate oxime π system establish an intramolecular π···π interaction; however there are no evidences for this same interaction in 8-PnMGO and 8-PinMGO.

In view of these results we carried out an ab initio computational study in order to better understand the conformational behavior of the studied oximes. The torsional potentials about the dihedral angle, ϕ_1, depicted in Fig. 3 for 8-PMGO, 8-PnMGO, and 1-(2-cyclohexylpropan-2-yl)benzene were obtained at the SCS-MP2/cc-pVDZ level of theory.[11] Since there are conformers able to establish intramolecular aromatic interactions, which involve a large fraction of dispersion forces, the use of a method that accounts for correlation energy is mandatory. SCS-MP2/cc-pVDZ has been employed before to yield fairly accurate results on relatively large aromatic systems with intramolecular aromatic

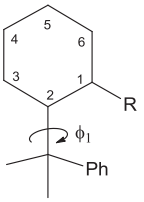


Fig. 3. Schematic representation of the dihedral angle, ϕ_1, considered for the evaluation of the internal rotation profiles in (2-cyclohexylpropan-2-yl)benzene (R=H), 8-PMGO, and 8-PnMGO/8-PinMGO (R=O−C(O)−C(H)=N−OH).