Application of NMR Spectroscopy for the Detection of Equilibrating $E$–$Z$ Diastereomers

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ABSTRACT: Conjugation can lower the energy barrier for unsaturated C–C bond rotations, resulting in a mixture of equilibrating diastereomers at room temperature. Therefore, methods claiming diastereoselective synthesis of conjugated double bonds often require proof that the observed diastereomeric ratio is not because of the diastereomeric equilibration of the product. Variable-temperature (VT) NMR experiments are commonly used to distinguish between the two possibilities. However, the VT technique requires accessories for the NMR spectrometer and more setup time. Here, we show that the rarely used application of 1-D and 2-D nuclear Overhauser effect spectroscopy experiments for the detection of the equilibrating diastereomers is a convenient alternative to the VT technique.

INTRODUCTION

Conjugated double bonds are prone to room temperature $E$–$Z$ interconversion. Therefore, methods reporting the stereo-selective synthesis of conjugated systems need to rule out such an interconversion. What detection techniques do chemists use? They use variable-temperature (VT) NMR, solvent switching, and hydrogen-bonding agents for such a task. Hu et al. showed that 1-D nuclear Overhauser effect spectroscopy (NOESY) experiments are alternatives to these methods for distinguishing between rotamers and nondouble-bonded diastereomers. Here, we show the use of 1-D and 2-D NOESY/exchange spectroscopy (EXSY) to detect equilibrating $E$ and $Z$ diastereomers. Rarely, chemical exchange NMR experiments have been used to observe interconverting diastereomers, but organic chemists have largely not taken advantage of them. Through this paper, we hope to encourage wider usage of this technique. Here, we show the use of preloaded 1-D and 2-D NOESY/EXSY experiments to detect such equilibrating diastereomers. Such a use of these NMR techniques will be helpful in other areas of chemistry as well. For example, apart from traditional organic synthesis, they will be useful in the field of photoswitches. When employed, the techniques will show if $E$–$Z$ isomerization occurs without intervention, and if not, whether it happens only when controlled thermally or photochemically. Potential molecular switches are screened for $E$–$Z$ isomerization, and only those are selected where the diastereomeric interconversion is controlled using light or heat.

The 1-D NOESY/EXSY technique has been used to detect rotameric peptides (Figure 1). These rotamers were detected because they are under a chemical exchange, and the 1-D NOESY technique was used to observe such an equilibrium.

Figure 1. Peptide rotamers identified using the 1-D NOESY technique.

Therefore, we expected to detect equilibrating diastereomers using the 1-D NOESY technique. If the energy barrier between two diastereomers is $>21$ kJ mol$^{-1}$, then two different isomers are detectable at once, while a smaller barrier shows only the average of NMR signals from interchanging isomers. Usually, chemists use VT NMR spectroscopy to observe equilibrating diastereomers. However, for general organic synthesis purposes, qualitative knowledge of diastereomers that are equilibrating at room temperature is sufficient. Qualitative information is ample to show if the product’s diastereomeric ratio is due to room temperature equilibration or a diastereoselective reaction producing two...
products that do not interconvert. Such a qualitative information can be obtained using the 1-D and 2-D NOESY/EXSY experiments.

NMR experiments show separate hydrogen resonances for each isomer if the rate constant of interconverting diastereomers (approximately $10^{-1}$ to $10^{3}$ s$^{-1}$) is within the NMR timescale. Specifically, in a 1-D NOESY/EXSY experiment, if the irradiated proton is under a significant chemical exchange with another proton, the second proton appears as a negative peak because of saturation or inversion transfer. In a 2-D NOESY/EXSY experiment, protons undergoing chemical exchange show the same phase as the diagonal.

Consider the enamino carbonyl structures 1–4 (Figure 2). Enamino carbonyl compounds can exist in these four conformations.

Depending upon the substrate, the room temperature interconversion between $Z$ and $E$ enamino carbonyl compounds happens because of the rotation of the unsaturated C–C bond or isomerization (Figure 3). Electron-withdrawing substituents on R$^1$ or electron-donating substituents on R$^2$ lower the activation energy of this rotational barrier. In simple alkenes, such as 2-butene, the barrier (259 kJ mol$^{-1}$) is too high, and $E$ and $Z$ isomers are isolable at room temperature. In conjugated alkenes, such as enamino carbonyl compounds, this barrier could be low enough (<85 kJ mol$^{-1}$) to cause room temperature $E$–$Z$ interconversions (Figure 3a). Such an interconversion of diastereomers makes it impossible to isolate individual diastereomers at room temperature. The $E$–$Z$ interconversion also occurs because of the proton transfer reaction (Figure 3b).

Irrespective of the cause of $E$–$Z$ interconversion, if characteristic signals due to $E$/$Z$ isomers are identifiable in NMR spectra, then, the $E$–$Z$ equilibrium may be detectable using the NOESY/EXSY techniques. If such an equilibrium exists without any intervention, then, the reaction is not diastereoselective.

### RESULTS AND DISCUSSION

An example is shown below where $E$ and $Z$ enamino carbonyl isomers are under an equilibrium ($E/Z = 2.5:1$) at room temperature (Figure 4). Resonance at 2.65 ppm belongs to

![Figure 2. Conformers of $E$ and $Z$ enamino carbonyl compounds.](image_url)

![Figure 3. Two equilibrating $E$ and $Z$ isomers. (a) $E$–$Z$ interconversion due to rotation. (b) $E$–$Z$ isomerization due to protonation and deprotonation.](image_url)

![Figure 4. Solvent: CDCl$_3$. (a) Two equilibrating conformers ($5$) and ($5'$). (b) Portion of 1-D NOESY spectrum of the mixture of $5$ and $5'$ showing the chemical exchange. (c) Portion of 2-D NOESY spectrum of $5$ and $5'$ showing the chemical exchange.](image_url)
protons present at position a of the E isomer, while the resonance at 3.05 ppm belongs to protons present at position a’ of the Z isomer (please see the Supporting Information for chemical shift assignment details). At room temperature, irradiation of the peak at 2.65 ppm results in a negative peak at 3.05 ppm in the 1-D NOESY spectrum (Figure 4b). The 2-D NOESY/EXSY (Figure 4c) shows this chemical exchange as well, and protons present at 3.05 and 2.65 ppm show the same phase as the diagonal (yellow in color instead of green). Therefore, both 1-D and 2-D NOESY/EXSY experiments show that 5 and 5’ are equilibrating at room temperature. We reported VT-NMR studies of this compound that confirm the chemical exchange. There was no difference in the product E/Z ratio when the 1H NMR was recorded with CDCl3 versus K2CO3-treated CDCl3. Therefore, the equilibrium is suspected to be because of the rotation of the unsaturated C=C bond rather than the acid-catalyzed isomerization.

The NOESY/EXSY method is general in nature and uses the common pulse sequences preinstalled on instruments. Both 1-D and 2-D NOESY/EXSY experiments successfully show E=Z equilibration, even in the presence of other chemical exchanges. For example, 6 and 6’ are in equilibrium (Figure 5). This equilibrium is concentration-dependent (1H NMR spectra in two different concentrations are provided in the Supporting Information), favoring 6’ at lower concentrations and 6 at a higher concentration. We suspect that isomer 6’ is preferred at low concentrations because of intramolecular hydrogen bonding. In contrast, at higher concentrations, 6 is predominant because of intermolecular hydrogen bonding and less steric hindrance than 6’. Similar observations have been reported earlier. Two protons of the major isomer (6) underlined in Figure 5a show a spurious negative peak in exchange spectra, possibly because of spin diffusion. Despite this artifact, it is possible to see the chemical exchange between 6 and 6’, with EXSY cross-peaks linking four pairs of corresponding protons from the two isomers (see the Supporting Information for NOESY/EXSY spectrum). More scans and longer mixing time were needed (see the Supporting Information for the experimental parameters) to see E/Z equilibration in both 1-D and 2-D NOESY/EXSY experiments. In Figure 5, this is shown for the protons marked a (2.10 ppm) and a’ (2.32 ppm). The chemical exchange was confirmed by the VT 1H NMR (see the Supporting Information).

As expected, two non-interconverting diastereomers do not display a negative peak in the 1-D NOESY/EXSY or an exchange cross peak in the 2-D NOESY/EXSY spectrum. An example of a mixture of a cis- and trans-stilbene is given in the Supporting Information. The mixture does not show any chemical exchange between the two diastereomers in the NOESY/EXSY spectra. The two NOESY techniques are well suited to detect even minimal quantities of isomers. We recently reported the synthesis of compound 7 as a single isomer. Both 1H NMR and 13C NMR suggested one diastereomer to be present. However, when we reexamined the data, we noticed that the 1-D NOESY/EXSY spectrum showed a negative peak when one of the protons was irradiated. We also noticed minor peaks in the 1H NMR spectrum (see the Supporting Information for the NMR spectra), which we earlier attributed to minor impurities. Detailed examination of the sample indicated that 7 and 7’ are in equilibrium at room temperature (Figure 6). The stereochemistry of 7 and 7’ is assigned on the basis of 1-D NOESY and by comparing 1H chemical shift values of 7 and 7’ with dibenzyl 2-(1-methylpyrrolidin-2-ylidene)malonate (8) (see the Supporting Information for details). Compound 8 was prepared by the coupling reaction of dibenzyl 2-diazomalonate (9) and 1-methylpyrrolidine-2-thione (10). The equilibrium overwhelmingly favors 7 (7:7’ 17.6:1). Still, many protons of 7’ can be observed, albeit as tiny signals. Figure 6b shows that the irradiation of a results in a negative peak at 3.01 ppm, which belongs to a’ protons. The 2-D NOESY (Figure 6c) also shows this chemical exchange as both a and a’ show a cross peak with the same phase as the diagonal. The VT-NMR studies again confirmed the findings (see the Supporting Information).

One limitation of the method is that when the quantity of one diastereomer is minute, more scans (or a higher concentration) are needed to see the exchanging protons in the 1-D and 2-D NOESY/EXSY spectra (see the 1-D and 2-D
of 7 and 7′ in the Supporting Information). However, the biggest challenge is probably differentiating between unsaturated C−C versus unsaturated C−O rotations (E−Z vs s-cis and s-trans) in tetrasubstituted (e.g., 5 and 5′, and 7 and 7′) enamino carbonyl compounds. Detailed 1-D and 2-D NMR studies are required (see the Supporting Information) to differentiate between the two types of isomers.

### CONCLUSIONS

Organic chemists have continued to mainly rely on the VT technique for observing E−Z equilibration. We have shown that 1-D and 2-D NOESY/EXSY experiments can be used effectively to detect equilibrating diastereomers in enamino carbonyl compounds. We have demonstrated the application of these techniques even when one diastereomer is present in as low of a quantity as 1/17.6 of the major isomer. Exchange experiments can be done at room temperature and so are convenient as they do not require setting up a dry gas supply and chilling method, as for low-temperature work. Furthermore, preinstalled pulse sequences available on NMR instruments are sufficient to observe the chemical exchange. Therefore, organic chemists are expected to find 1-D and 2-D NOESY/EXSY techniques simpler to use. In conjugated systems, these techniques will speed up the process of distinguishing between a diastereoselective method and a method where the diastereomeric ratio is because of the equilibration after the product formation.

### EXPERIMENTAL SECTION

**General Experimental.** ¹H, ¹³C NMR, and all 2D-NMR experiments (except for DQF-COSY) were performed on a Varian Inova 400 MHz instrument with OneNMR probe at the Oklahoma Statewide Shared NMR Facility at Oklahoma State University. The NMR spectra were measured in parts per million (ppm) relative to TMS (0.00 ppm) or the residual solvent signals (CDCl₃ for ¹H NMR δ = 7.26 ppm and ¹³C NMR δ = 77.16 ppm). High-resolution mass spectrometry measurements were conducted on a Thermo Scientific Fusion or Exactive spectrometer operating in a positive ion electrospray mode using an Orbitrap analyzer at a nominal resolution of 120,000. Thin-layer chromatography was performed on 250 μm glass silica gel plates or on 250 μm polyester silica gel plates. Plates were visualized with UV and a basic aqueous potassium permanganate stain or with UV or a basic aqueous potassium permanganate stain alone. Flash chromatography was performed using a sorbent silica gel 60 Å (40–63 μm). Petroleum ether here means the fraction of the mixture that distills in the range 30–60 °C. Anhydrous dichlorehethane and acetone were prepared by distilling them from calcium hydride and onto activated 4 Å molecular sieves. All other reagents were obtained from commercial sources and used without further purification. Unless noted otherwise, all reactions were carried out under an argon atmosphere (argon) with oven-dried glassware. Compounds 5 and 7 were prepared according to literature procedures.

**Synthesis of (E/Z)-1-(Methylamino)pent-1-en-3-one (6).** This procedure is based on a literature report for the preparation of similar compounds. ¹H NMR (CDCl₃): δ (major) 7.14−6.95 (br, m, 1H), 6.74 (br, s, 1H), 4.49 (d, J = 12.4 Hz, 1H), 2.10 (br, s, 1H), 1.72 (q, J = 7.2 Hz, 2H), 0.43 (t, J = 7.2 Hz, 3H); (minor): 9.00 (br, s, 1H), 6.08 (dd, J = 7.6, 12.4 Hz, 1H), 4.32 (d, J = 7.6 Hz, 1H), 2.32 (d, J = 4.8 Hz, 1H), 1.60 (q, J = 7.6 Hz, 2H), 0.41 (t, J = 7.6 Hz, 3H); ¹³C NMR (CDCl₃): δ (major) 197.6, 149.2, 93.7, 32.2, 28.3, 8.6; (minor): 198.9, 153.0, 91.1, 33.7, 33.4, 8.6; HRMS (ESI⁺) m/z (M + H)⁺: calcd for C₆H₁₂NO, 114.0928; measured, 114.0928.

**Synthesis of Dibenzyl 2-(1-methylpyrrolidin-2-ylidene)malonate (8).** The coupling reaction of 9 and (1-methylpyrrolidin-2-thione) 10 is based on the preparation of similar compounds. Thioamide (10, 0.20 mmol, 23.0 mg) was dissolved in dry 1,2-dichloroethane (1.00 mL), and the
solution was transferred to a vial containing 9 (81.0 mg, 0.26 mmol). The mixture was added to a pressure vessel containing 5 mol % (CuOTf)2·Tol. The vials containing 9 and 10 were washed twice with dry 1,2-dichloroethane (0.50 mL), and the contents were transferred to the reaction mixture. The mixture was stirred and heated at 90 °C for 16 h. The solvent was evaporated, and the crude was chromatographed (25% ethyl acetate in petroleum ether) to give pure 8 as a yellow liquid (57 mg, 0.16 mmol, 77%). Rf = 0.1 (30% ethyl acetate in petroleum ether). 1H NMR (400 MHz, CDCl3): δ 7.31–7.27 (m, 10H), 5.15 (s, 4H), 4.49 (d, J = 12.4 Hz, 1H), 3.49 (t, J = 7.2 Hz, 2H), 3.15 (t, J = 7.6 Hz, 2H), 2.77 (s, 3H), 1.94 (tt, J = 7.2, 7.6 Hz, 2H); 13C NMR (100 MHz, CDCl3): δ 167.91, 167.90, 136.9, 128.4, 128.1, 127.8, 85.6, 85.5, 57.4, 37.0, 35.4, 20.6; HRMS (ESI+) m/z (M + H)+: calcd for C22H24NO4, 366.1705; measured, 366.1700.

Dibenzy 2-diazomalonate (9). 90 The procedure is based on the preparation of similar dioxo compounds. 90 Dibenzyl malonate (95%, 299 mg, 1.00 mmol) was dissolved in anhydrous CH2CN (2.00 mL), and the solution was cooled to 0 °C. A solution of p-toluenesulfonyl azide (1.20 mmol) in anhydrous CH2CN (1.00 mL) was added dropwise to the stirred reaction mixture. DBU (98%, 0.23 mL, 1.50 mmol) was stirred for 1 h at 0 °C. The solvent was evaporated, and the crude was purified via a short column (25% ethyl acetate in petroleum ether). The pure product (9) was obtained as a cream-colored liquid (303 mg, 0.98 mmol, 98%). The 1H and 13C NMR spectra matched the earlier reports. 90

ASSOCIATED CONTENT
1 Supporting Information
The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.0c03554.
1-D and 2-D NMR spectra and E/Z assignments of compounds (PDF)

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Notes
The authors declare no competing financial interest.

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