

Education Application for picoSpin™

Aldol Condensation



A solid understanding of NMR spectroscopy is a basic learning goal for any student of chemistry. The hands-on approach to learning is the most powerful method for instructors in both classroom settings and in the teaching laboratory. Direct experience with acquiring and processing NMR spectra to determine product purity or to monitor the course of a chemical reaction is extremely valuable, especially for organic chemistry students.

The challenges for teaching lab directors and instructors of organic chemistry in applying modern NMR techniques are manifold:

- Accessing modern high-field research NMR facilities for student instruction.
- Managing complex and technically challenging instrumental operations.
- Funding expensive equipment dedicated solely to teaching.
- Housing oversized instrumentation in existing lab space.
- Developing NMR applications to complement existing lab curricula.
- Allowing students direct access to an expensive instrument.
- Gaining or maintaining American Chemical Society (ACS) or other national accreditation by incorporating NMR into the curriculum.

The picoSpin-45 NMR spectrometer is your key to solving all of these problems. In this Tech Info, we illustrate the use of the picoSpin-45 in teaching through the aldol condensation reaction.

Applications for picoSpin™ Aldol Condensation *continued*

In many undergraduate organic teaching programs, the aldol condensation reaction is the first exposure students have to NMR as an analytical tool. While the technical aspects of executing the aldol reaction are not difficult, the analysis of products is challenging since this is frequently a student's first time using NMR instrumentation, interpreting NMR spectra and evaluating the outcome of their synthetic efforts. Because of the simplicity of its design and ease of use, the aldol condensation lab is a good entry point for applying the picoSpin-45 spectrometer in a teaching laboratory.

Aldol condensation reactions represent an important class of reactions for forming carbon-carbon bonds. In the aldol reaction, two carbonyl compounds are *condensed* to form a β -hydroxyaldehyde or β -hydroxyketone — the aldol product. The classic aldol reaction is a "self-condensation" of the reactant aldehyde or ketone where one molecule adds to another of the same type. An example of a self-condensation aldol reaction is shown in **Figure 1**, using acetaldehyde as the sole reactant. Here, the aldol product, 3-hydroxybutanal, is the result of adding acetaldehyde to another acetaldehyde reactant molecule to form the aldol (aldehyde-alcohol) product.

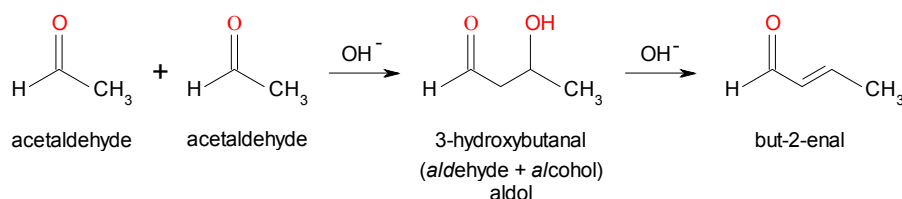


Figure 1. Aldol self-condensation of acetaldehyde

When carried out under base-catalyzed conditions, the aldol reaction proceeds via an enolate ion (**Figure 2**). The resonance stabilized enolate then undergoes nucleophilic addition to the carbonyl carbon of another aldehyde or ketone molecule, forming a new C-C bond and an alkoxide ion (**Figure 3**).

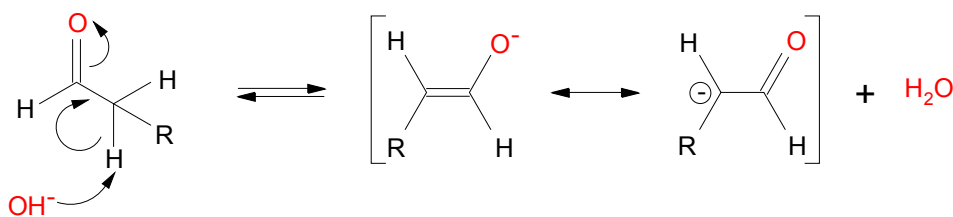


Figure 2. Base-catalyzed production of the enolate ion in the aldol self-condensation reaction (R = H, alkyl, phenyl)

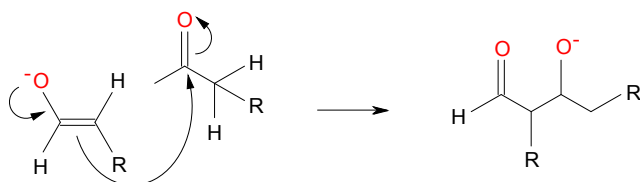


Figure 3. Nucleophilic addition of enolate anion to the carbonyl group (R = H, alkyl, phenyl)

The β -hydroxy aldehyde or ketone is then formed in the next step by reaction with water, and the reaction is finalized by dehydration of the alcohol group in a strong base, resulting in the loss of water and the formation of an α,β -unsaturated product (**Figure 4**).

Applications for picoSpin™ Aldol Condensation *continued*

Similar self-condensation reactions will occur for ketones, as well as derivatized aldehydes and ketones, so long as an enolizable proton at the α carbon position exists.

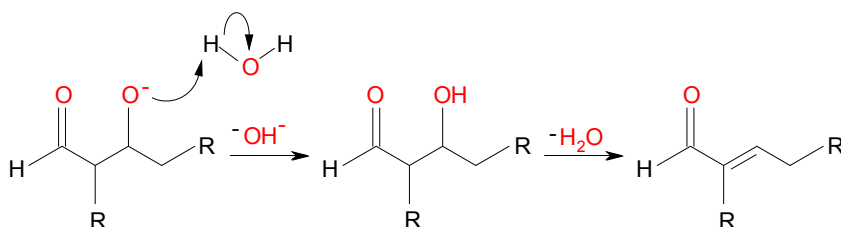


Figure 4. Formation of the aldol product and dehydration to an α,β -unsaturated carbonyl product

Crossed aldol reactions between aldehydes and ketones result in the formation of mixed condensation products. Here, the enolate ion of one compound undergoes nucleophilic addition to the carbonyl carbon of a different compound. Crossed-condensation products are usually undesirable since they result in a mixture of products, and reduce the yield of a desired product. Careful selection of starting materials where only one reactant has an enolizable α hydrogen can minimize the formation of mixtures. This is illustrated in **Figures 5** and **6** where an aromatic aldehyde, benzaldehyde, is substituted for the alkylaldehyde as a reactant.

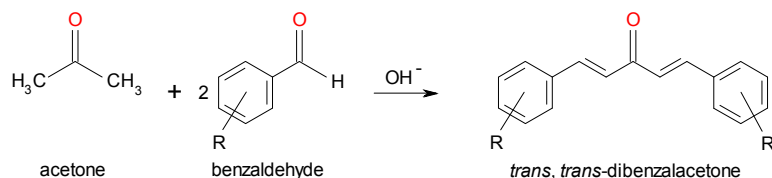


Figure 5. Crossed aldol condensation reaction, producing the α,β -unsaturated ketone dibenzalacetone

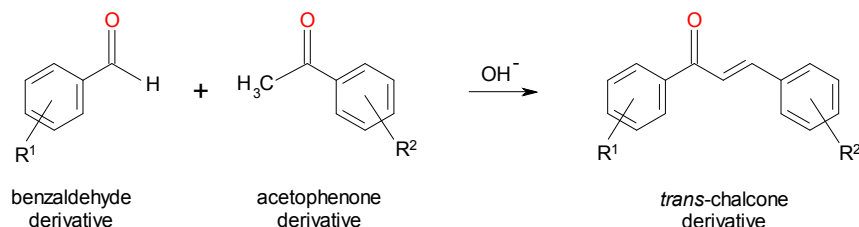


Figure 6. Crossed aldol condensation reaction, producing the α,β -unsaturated ketone chalcone

Derivatives of the parent reactant molecules benzaldehyde and acetophenone can include a variety of R, R¹ and R² functional groups, such as methyl (-CH₃), methoxy (-OCH₃), chloro (-Cl), bromo (-Br), amino (-NH₂), hydroxy (-OH), nitrile (-CN), etc. and in various positions around the phenyl ring. Due to intermolecular hydrogen bonding, the hydroxy group will show temperature, concentration and solvent polarity dependence, which complicates interpretation. Similarly, complications will arise in the spectrum of the amino group due to spin coupling of the proton with the ¹⁴N nucleus. Halogen substitution does not introduce a new peak in a proton NMR spectrum but will affect peak positions and splitting patterns on the aromatic protons. Only the methyl and methoxy groups introduce new, non-overlapping resonance lines in the parent molecule spectrum, which affords straightforward interpretation.

Applications for picoSpin™ Aldol Condensation *continued*

¹H NMR – A Qualitative Lesson

It is easy to identify the prominent peaks in the pre-synthesis ¹H NMR spectra of the reactants in the aldol reactions of **Figures 5** and **6**. Both the aldehyde proton and methyl-ketone protons produce only one resonance line each, thus making them simple to monitor. NMR spectra can be measured on pure samples or using a portion of the premeasured reaction mixture.

The picoSpin-45 NMR spectrometer is ideal for preliminary qualitative analysis of neat samples and mixtures, giving students the opportunity to determine the quality of their starting materials, establish the stoichiometry of their mixture, identify the predominant functional groups which will undergo chemical transformation, and gain valuable hands-on experience using NMR in the lab. Because the picoSpin-45 sample capillary can be quickly flushed and refilled, it can be used repeatedly throughout the course of a 3-4 hour organic chemistry lab experiment. Students can sample their reaction mixture multiple times at various stages throughout their experiment, obtaining NMR spectra as the reaction proceeds and measuring an NMR spectrum of their isolated product. ¹H NMR spectra shown below were taken with a 90-degree pulse angle, 750 ms acquisition time, 6 s recovery delay, and are an average of 16 or 36.

picoSpin-45 spectra of reactants 4-methoxybenzaldehyde and 4-methylbenzaldehyde are shown in **Figures 7** and **8**. The aldehydic proton produces a lone signal due to a lack of neighboring proton. Diamagnetic anisotropy arises from circulating π electrons of the carbonyl (C=O) bond induced along the transverse axis by the applied field, giving rise to strong deshielding of this lone proton. In the spectrum of 4-methoxybenzaldehyde, the aldehyde proton appears as a singlet at 9.90 ppm, while for 4-methylbenzaldehyde this same signal is at 10.08 ppm.

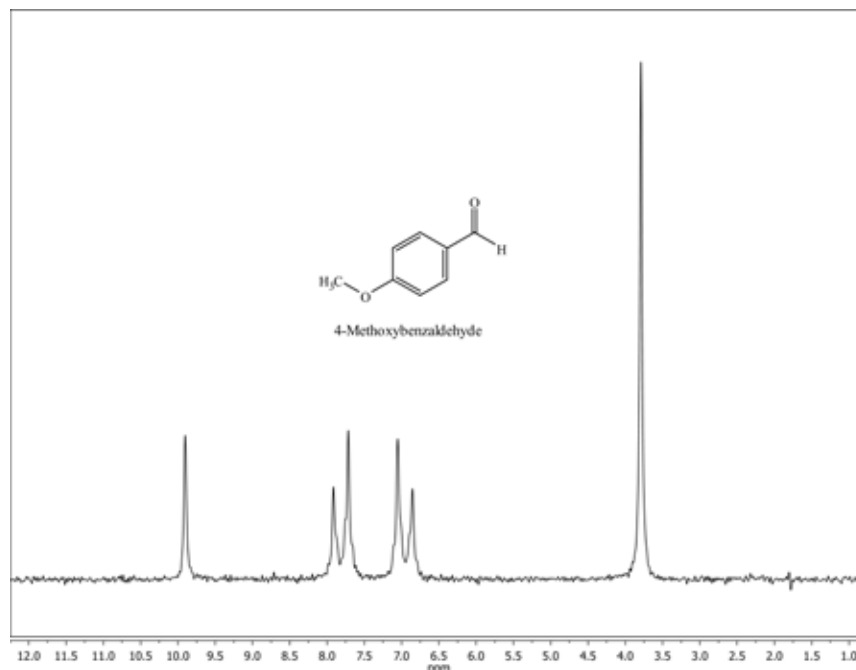


Figure 7. picoSpin-45 NMR Spectrum of 4-Methoxybenzaldehyde (neat, 16 scans).

The protons of the methoxy methyl group experience deshielding due to carbon bonding to an electronegative oxygen atom and shift down field, producing a singlet at 3.79 ppm. There are four aromatic protons that are in

Applications for picoSpin™ Aldol Condensation continued

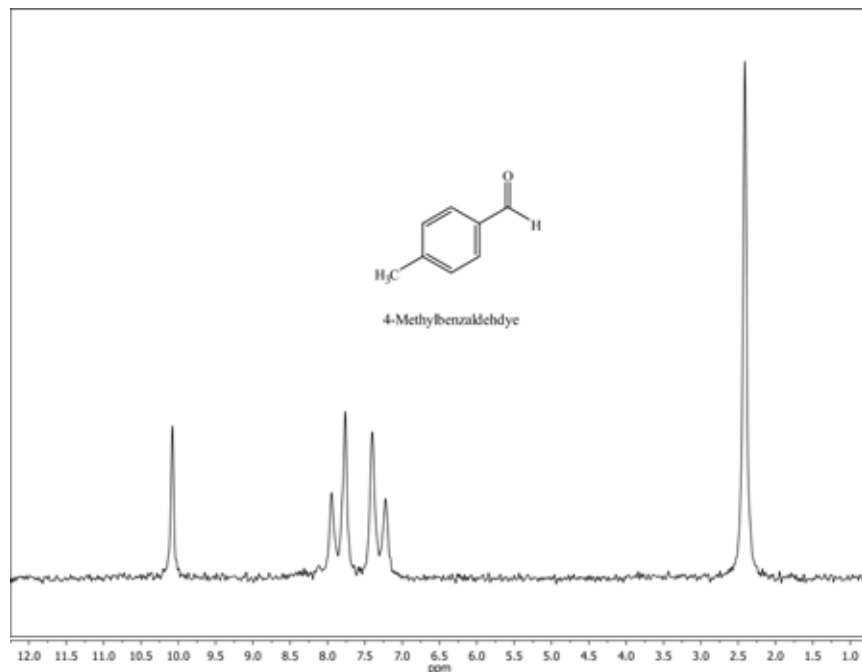


Figure 8. picoSpin-45 NMR Spectrum of 4-Methylbenzaldehyde (neat, 16 scans).

two different chemical environments, generating a characteristic doublet of doublets splitting pattern. Protons ortho (position 2 and 6) to the aldehyde are in the deshielding zone of the carbonyl bond, whereas protons in the meta position (3 and 5) move up field due to resonance shielding by the adjacent methyl ester.

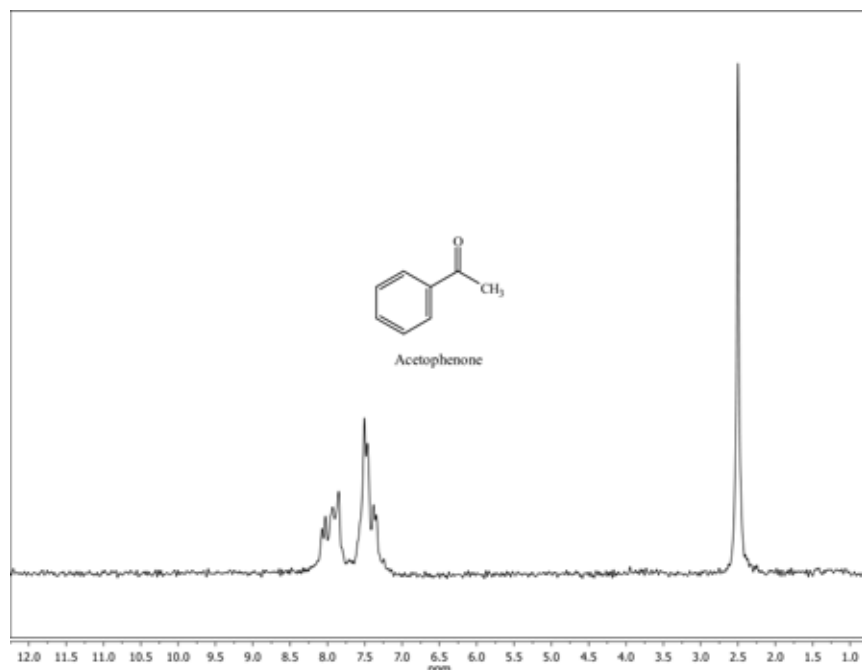


Figure 9. picoSpin-45 NMR Spectrum of Acetophenone (neat, 16 scans).

Applications for picoSpin™ **Aldol Condensation** *continued*

Ring currents in the aromatic group produce similar anisotropy, deshielding the in-plane protons of the benzene ring. Lower symmetry, arising from asymmetric para disubstitution of the benzene ring, affects the chemical environment for protons in the ortho (2 and 6) and meta (3 and 5) positions, giving rise to a doublet of doublets signal. The ortho protons, further deshielded by the adjacent aldehyde group, appear down field ($\delta 7.81$), while the meta protons appear up field ($\delta 6.95$) with respect to a center frequency of $\delta 7.38$ – each proton being split by one nearest neighbor proton, giving rise to a doublet of doublets signal.

Integration of peak areas reveals an expected 1:4:3 proton ratio for both 4-methoxybenzaldehyde and 4-methylbenzaldehyde.

Like the substituted benzaldehydes in **Figures 7 and 8**, the proton NMR spectrum of acetophenone (**Figure 9**) exhibits multiple peaks in the 7.3-8.2 ppm region, but the splitting pattern is complicated by overlap of signals from five benzylic protons in three different chemical environments. At first glance, the signal pattern in the aromatic region appears as a doublet of triplets signal, but closer scrutiny of the splitting pattern and asymmetric

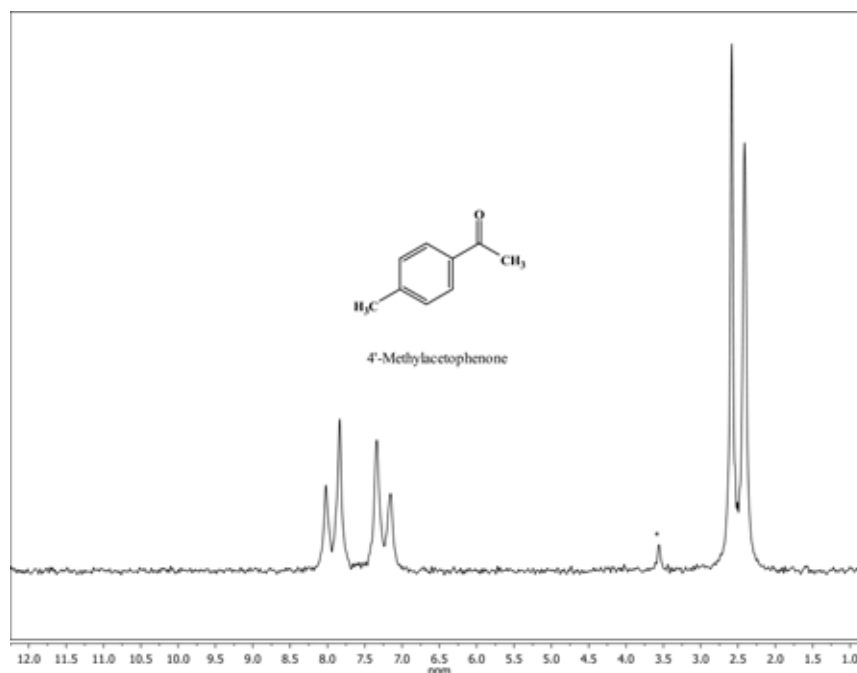


Figure 10. picoSpin-45 NMR Spectrum of 4'-Methylacetophenone (neat, 16 scans).

signal intensity reveals overlapping multiplicities. Protons in positions 2 and 6 are each split by neighboring protons in positions 3 and 5, producing doublet signals. The proton in the para position is split by two adjacent and identical protons into a triplet signal and overlaps strongly with the doublet signal from the meta protons. Ortho protons shift farther down field due to deshielding by the aldehyde group, and their signal is resolved more easily.

The three methyl protons on the ketone experience less shielding and shift to ~ 2.6 ppm, producing only a single peak. Peak area integration shows a 3:5 ratio. By comparison, the reactant acetone would produce a similar signal and chemical shift ($\delta 2.5$) but with an integral area equivalent to the six homotopic protons for the absorption peak.

Applications for picoSpin™ **Aldol Condensation** *continued*

Substitution by a methyl group in the para position in 4'-methylacetophenone (**Figure 10**) clears up issues with overlapping signals in the aromatic region, showing only ortho and meta protons being split by each other.

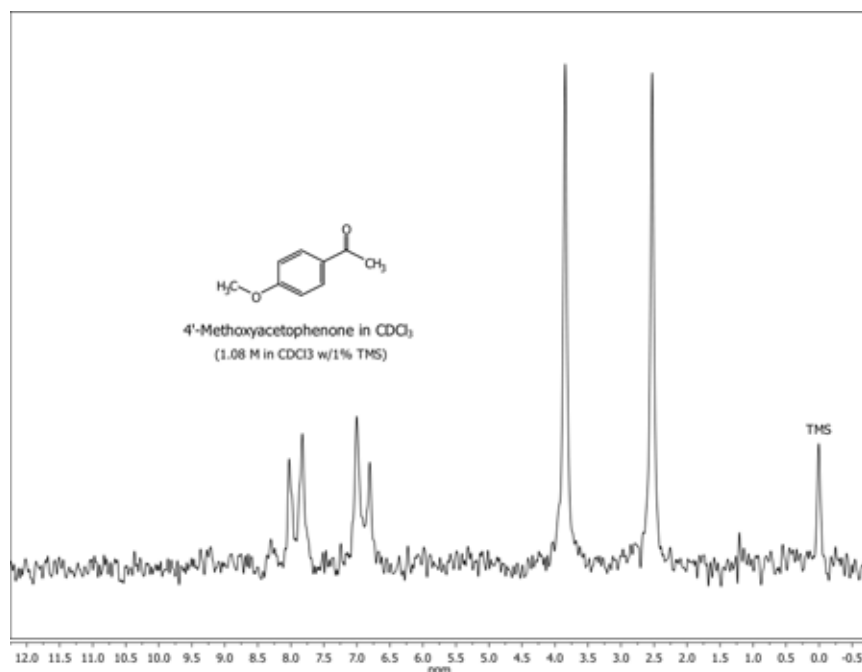


Figure 11. picoSpin-45 NMR Spectrum of a 4'-Methoxyacetophenone in CDCl₃ (1.08 M, 36 scans)

Adding a methyl group on the benzene ring introduces an additional alkyl signal (δ 2.34) near the keto-methyl signal (δ 2.50), but this is clearly resolved in the spectrum.

Replacing the methyl substituent in the para position of 4'-methylacetophenone with a methoxy group in 4'-methoxyacetophenone (**Figure 11**) separates the two methyl groups by shifting the methoxy methyl downfield 3.79 ppm. The solid sample 4'-methoxyacetophenone was dissolved in CDCl₃ at a concentration of 1.08 M and its spectrum, measured at 40 °C. Considering the concentration of the 4'-methoxyacetophenone solution and sample volume within the spectrometer's RF coil, we are measuring signal arising from approximately 38 nano-moles of material.

This simple analysis is an excellent opportunity for students to learn about substituent effects, splitting patterns, sample preparation and dilution.

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