

## CORRESPONDENCE

### Comment on Influence of the Chemical Environment on Metolachlor Conformations

*Sir:* Recently, Jayasundera et al. (1999) drew conclusions from NMR spectra on different distinct conformers of the chiral herbicide metolachlor which, according to these authors, have potential implications on the environmental fate of the compound. We noticed several factual errors and questionable conclusions in the paper, and we were unable to reproduce some of their data. Therefore, we would like to state our own view on this matter.

Due to the axial- and C-chirality of the compound, metolachlor consists of four stereoisomers stable at ambient temperature with *aSS*, *aRS*, *aSR*, and *aRR* configurations (*aSS*, the isomer with *aS*,1'*S* configuration, etc.) (Moser et al., 1982). The hindered rotation [ $k < 10^{-12} \text{ s}^{-1}$  at 298 K, calculated from Moser et al. (1982)] of the aromatic ring around the phenyl–N bond has not been questioned so far: (i) *Racemic (rac)*-metolachlor, either as the liquid or when dissolved in solvents, does not change diastereomer composition over several years (Buser and Müller, 1995). (ii) Different batches of metolachlor show a varied ( $\approx 1:1$  to  $2:1$ ) diastereomer composition, likely as a result of different conditions during synthesis (Buser and Müller, 1995; Aga et al., 1999); these compositions changed to  $1:1$  when heated to high temperatures ( $200 \text{ }^\circ\text{C}$ ) and then remained at this ratio when kept at room temperature (Buser and Müller, 1995). (iii) The four stereoisomers were synthesized by Moser et al. (1982) and no *aS/aR* isomerization was reported at room temperature. (iv) Under environmental conditions (surface water) there is little if any isomerization of metolachlor because residues in several lakes indicate a very similar diastereomer composition as the herbicide used in the catchment areas of the lakes (Müller and Buser, 1995; Buser et al., 2000). All of these data suggest that the atropisomers are conformationally stable at ambient temperature.

Jayasundera et al. (1999) now claim that “within very specific chemical environments, metolachlor atropisomers *aSS(aRR)* and *aRS(aSR)* freely interchange, and consequently, the multiple conformations also interchange”. The authors report NMR data measured in pure solvents (DMSO- $d_6$ ,  $\text{CDCl}_3$ , Bz- $d_6$ ) and in solvent mixtures ( $\text{CDCl}_3/\text{Bz-}d_6$ ; DMSO- $d_6/\text{Bz-}d_6$ ) at 298 K. With the help of molecular mechanics calculations (gas phase), the assignments of the *aSS/aRR* and *aSR/aRS* diastereomers based on data from Moser et al. (1982) and nuclear Overhauser experiments (NOE), various conformers of metolachlor in solution are discussed in detail. Against all expectations, the authors observed broad  $^1\text{H}$  NMR lines in binary DMSO- $d_6/\text{Bz-}d_6$  solvent mixtures. This was explained by an unhindered (“free”)

rotation of the aromatic ring leading to coalescence of NMR resonances and isomerization of metolachlor atropisomers. From these spectra the authors derived a rate constant of isomerization of metolachlor atropisomers of  $k = 61.8 \text{ s}^{-1}$  at 298 K. This rate is  $\approx 10^{14}$  times faster than that extrapolated from our data (see below) and that of Moser et al. (1982). The rotation was quenched by adding a small amount of water ( $\text{D}_2\text{O}$ ) to the DMSO- $d_6/\text{Bz-}d_6$  solvent mixture, and the  $\approx 2:1$  ratio between NMR signal intensities was reestablished.

The claimed “free rotation” of metolachlor atropisomers would have considerable consequences for former and future work. We therefore repeated the NMR experiments described by Jayasundera et al. (1999). The solvents DMSO- $d_6$  (99.9 atom % D, code 12682) and Bz- $d_6$  (99.95 atom % D, code 57920) were from Glaser, Basel, Switzerland. To examine and control the effect of water on the NMR spectra, DMSO- $d_6$  and Bz- $d_6$  were further dried with a 4-Å molecular sieve and over metallic sodium, respectively, and the water contents were determined by coulometric Karl Fischer titration (48.5 ppm, DMSO- $d_6$ ; 91.5 ppm, Bz- $d_6$ ). A 60:40 DMSO- $d_6/\text{Bz-}d_6$  mixture with 42 mg of *rac*-metolachlor/mL was prepared in a dried NMR tube under argon. In contrast to Jayasundera et al. (1999), our NMR spectra at 400 MHz of this solution at 298 K showed no broad NMR resonances, and there was no indication for isomerization. Variation of the metolachlor concentration (from 5 to 20 mg) or use of nondried Bz- $d_6$  did not change the spectrum. All NMR resonances are explained by the  $\approx 2:1$  diastereomer composition of the sample (Aga et al., 1999), and in fact the same ratio is indicated by the data reported by Jayasundera et al. (1999).

The postulated free rotation of the aromatic ring was also investigated with enantioselective (“chiral”) high-resolution gas chromatography. For this purpose, *rac*-metolachlor and two single isomers, *aSS*- and *aRR*-metolachlor (purity > 98%), were dissolved separately in nondeuterated DMSO/Bz (60:40). The solvents were used as received and contained, according to the labels, <0.03% (benzene) and <0.2% (DMSO) of water. After 9 days at room temperature, the samples were reanalyzed. *rac*-Metolachlor showed no change of its diastereomer composition, and the two single isomers did not isomerize to the corresponding atropisomers. However, at higher temperatures ( $200 \text{ }^\circ\text{C}$ ) the isomers rapidly interconvert ( $k = 0.04 \text{ min}^{-1}$ ) and the ratios converged to  $1:1$ .

In summary, we were unable to reproduce the experimental results of Jayasundera et al. (1999). There is no indication for a free rotation of the aromatic ring in metolachlor from our NMR spectra, not in the special solvent mixture(s) as used by Jayasundera et al. (1999) and not in solvents with a very low water content. The authors were not critical of the result that the trace amount of water in DMSO- $d_6$  did not influence the

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postulated exchange of metolachlor atropisomers, whereas water in nondry Bz- $d_6$  stopped isomerization. In any case, the much smaller residual water signal (intensity ratio water/DMSO- $d_5$  = 1:2.1) at 3.6 ppm in our NMR spectra as compared to those in Figures 2a and 5 of Jayasundera et al. (1999) invalidates this observation. If the broad resonance lines presented in Figure 4 of Jayasundera et al. (1999) are from a coalescence phenomenon, one would still expect a sharp quintet signal from DMSO- $d_5$  at 2.5 ppm—this is not the case. Unfortunately, the clarifying NMR experiment at higher temperature to observe line-narrowing due to faster ring rotation was not performed. The poorly resolved NMR spectra of Figure 4 may be the result of incomplete solvent mixing. We could produce similar spectra when DMSO- $d_6$  and Bz- $d_6$  were not vigorously shaken prior to the NMR measurements. This effect would explain the line-narrowing observed in Figure 5b of Jayasundera et al. (1999) when two drops of water were added to a DMSO- $d_6$ /Bz- $d_6$  mixture (most likely followed by shaking the NMR tube!). In our opinion, the detailed discussion about metolachlor conformers in pure solvents and solvent mixtures cannot be followed without question. For example, the “four frequencies of unequal intensities” of the (*diastereotopic*) protons CH<sub>2</sub>-Cl in DMSO- $d_6$  and Bz- $d_6$ , discussed in terms of anisotropic solvent-molecule interactions and four possible (gas phase) conformers, simply represent the inner lines of two methylene proton AB patterns. Also, the assignment of relative positions between the chiral alkyl moiety and the unsymmetrically substituted aromatic ring concluded from NOE data remains unclear because the *aS/aR* designations are incorrectly given by Jayasundera et al. (1999). Therefore, the claim that “these results enable a structural interpretation of conformational changes that can influence the environmental fate of metolachlor” is not supported on the basis of their and our data.

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Received for review April 27, 2000. Accepted July 7, 2000.

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JF0005420