Chemical Reactivity and Safener Activity of Acetal Compounds*

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Although detailed examinations have been published on structure-activity relationships of herbicide safeners, only a few data are available on chemical reactivity-safener activity relationships. Chemical reactivity of acetamide type compounds as well as their safener activity against thiocarbamate herbicides change with the number of chlorine substituents in the order: non-chlorinated < monochloro < dichloro. Several compounds of another chemical group, acetals (*e.g.* MG-191, 2-dichloromethyl-2-methyl-1,3-dioxolane), are also effective safeners for thiocarbamate herbicides. According to our growth room studies, the safener activity of acetals also increases with increasing chlorine content up to two chlorine atoms on the same carbon. A number of differently chlorinated acetals have been synthesized and their acid-catalyzed hydrolysis rate determined in order to establish a relationship between their bioactivity and chemical reactivity. The hydrolysis rate order of acetals containing no, one or two chlorine atoms: non-chlorinated > monochloro > dichloro, is just the opposite than what has been found for acetamides. Thus, safener activity of acetals increases with decreasing chemical reactivity. The opposite reactivity order of acetamides and acetals can be explained by the different mechanisms of their hydrolysis. Dichloroacetals may not be effective safeners in their original structure. In plants, however, they can be biologically activated to active safeners by a transformation other than hydrolysis.

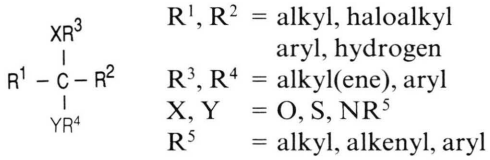
Introduction

Although detailed examinations have been published on structure – activity relationships of herbicide safeners [1–7], only limited data are available on chemical reactivity – safener activity correlations [1, 2, 8, 9].

In the majority of the known cases, a biological response is associated with some characteristic (bio)chemical transformation of the active ingredient. Consequently, if a structure – reactivity relationship, existing in a given chemical reaction, parallels the observed chemical reactivity – bioactivity correlation, this (bio)chemical transformation is apparently responsible for the biological phenomenon [9].

Research based on this concept has demonstrated that the safener activity of acetamides against thiocarbamate herbicides increases with increasing reactivity in transacylation, a process that is probably involved in the safener activity [1, 2].

A number of compounds characterized by the general formula also showed safener activity against thiocarbamate herbicides. Acetals ($R^1=CH_3$, $R^2=H$, $X=Y=O$, $R^3=R^4=$alkyl, alkylene) and ketals ($R^1=CH_3$, $R^2=$alkyl, $X=Y=O$, $R^3=R^4=$alkyl, alkylene) containing chloro atom(s) in R^1 were found to be more effective safeners than other derivatives [8].



Structurally, acetals and ketals are diethers of the hydrates (geminal diols) of aldehydes and ketones, respectively. Their most common reaction is hydrolysis. Due to their ether character, acetals and ketals are resistant to bases, but sensitive to acids; their acid-catalyzed hydrolysis goes generally on under mild conditions resulting in the corresponding aldehydes or ketones.

The effect of several C- and O-substituents (non-branching and branching alkyl, alkenyl, aralkyl and aryl groups) on the hydrolysis kinetics of acetals and ketals was determined in detailed studies [10, 11]. Nevertheless, kinetic data on

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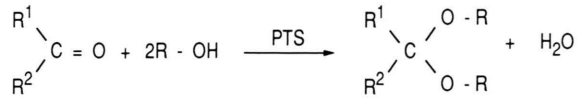
hydrolytic reactivity of acetals (ketals) carrying a chloromethyl function on their central carbon atom are rare and even not available when $R^1 = Cl_2CH$ or Cl_3C.

Searching for a relationship between chemical reactivity and safener activity, we determined and compared the hydrolysis rate constants of different acetals and ketals in kinetic studies as well as their safener effectiveness against EPTC (S-ethyl dipropylthiocarbamate) injury to maize in growth room experiments.

Materials and Methods

Acetals (Fig. 1) were synthesized [12] in a condensation reaction of acetaldehyde, chloroacetaldehyde, dichloroacetaldehyde, trichloroacetaldehyde or benzaldehyde and methanol, ethanol or ethylene glycol using a trace of *p*-toluenesulfonic acid (PTS) as catalyst:



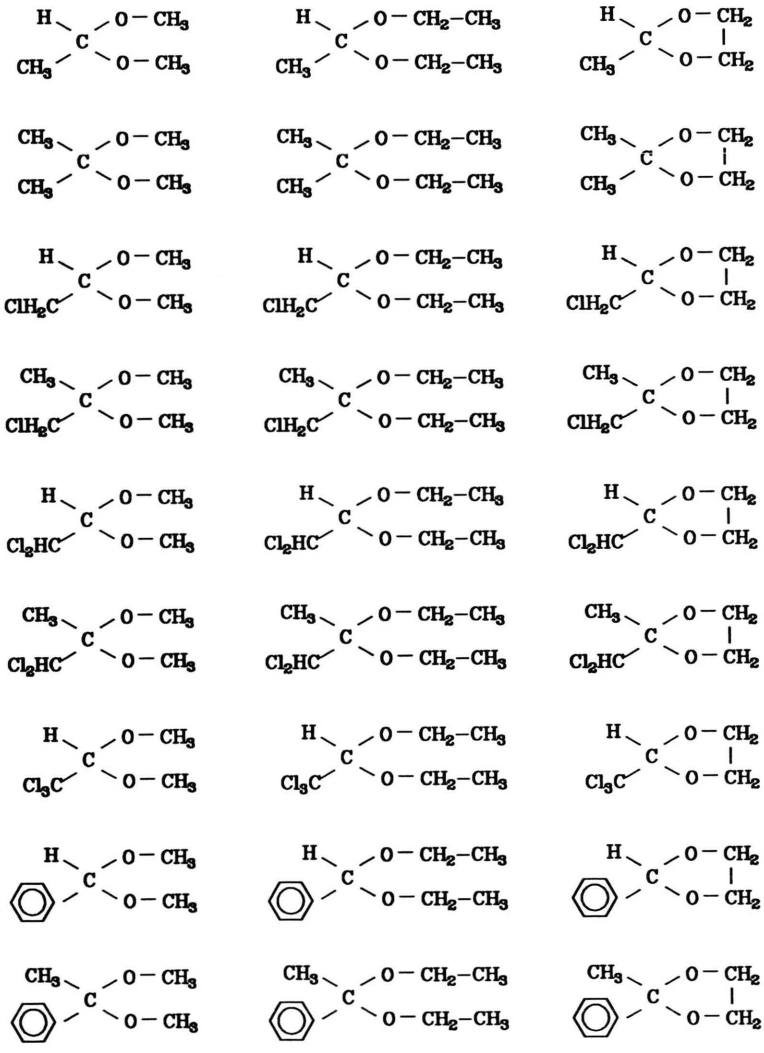


Fig. 1. Structures of the acetals and ketals studied.

Ketals (Fig. 1) were prepared from acetone, chloroacetone, dichloroacetone or acetophenone on the same manner. The equimolar quantities of the alcohol and the carbonyl compound were refluxed in benzene until the theoretical quantity of water was removed by azeotropic distillation with the solvent (2–20 h). To neutralize the reaction mixture, it was washed with 5% sodium hydrogen carbonate solution and then the benzene extract was dried over anhydrous sodium sulfate. The solvent was removed by vacuum evaporation, the residue was distilled either at atmospheric or under diminished pressure and the pure acetal or ketal was identified by elementary analysis.

Kinetic measurements

The rates of hydrolysis of acetals and ketals were measured spectrophotometrically by following the appearance of the aldehyde or ketone products (maximum absorbance of the carbonyl group was at 200–250 nm) in water at different pH values. Hydrochloric acid or formic acid were used to adjust the acid concentration where the hydrolysis rate of the studied compound was measurable. The acetal or ketal dissolved in ethanol was added to the aqueous solution in a cuvette thermostated (30 ± 0.2 °C) in the cell compartment of the spectrophotometer by a calibrated dropping pipet. The solution closed by a teflon stopper was then shaken fast and vigorously. The rates were generally followed to 75–90% completion. Pseudo-first-order rate constants (k) were obtained from the slopes of $\ln([A_o]/[A])$ *vs.* time plots (see Eqn. (1)–(3) in Results).

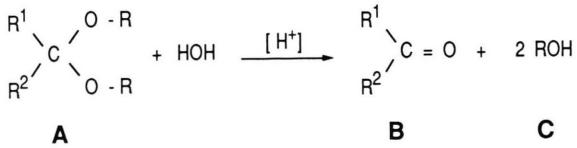
Growth room studies

Plastic boxes (12 × 12 cm, 9 cm deep) were filled up with a homogeneous mixture of a treatment solution (250 ml/box) containing 10^{-4} M EPTC ± 10^{-5} M acetal or ketal as safener and foundry sand (1500 g/box). Maize (*Zea mays* L., var. Pioneer 3737) seeds (8 g/box) were planted in the boxes 2.5 cm deep. The conditions in the growth room were: 60–70% relative humidity, 16 h light period, light intensity of 10 klux, and temperatures of 23 °C and 16 °C during the light and dark periods, respectively. The plants were watered three times per week up to the weight of the boxes at the first watering (1750 g). Every third watering was with half-strength Hoagland's nutrient solution [13]. Height and fresh weight of the shoots were obtained three weeks after planting to facilitate a comparison of safener effectiveness against EPTC injury. The experimental data were statistically analyzed by descriptive statistics followed by a Duncan's Multiply Range test (DMRT) with $P < 0.05$.

Results

Hydrolysis rate of acetal and ketal compounds

The reaction kinetic of acid-catalyzed acetal and ketal hydrolysis ([*A*], [*B*] and [*C*] are the actual



concentrations of the compounds) can be described by the equation

$$[A] = [A_o]\, e^{-kt} \quad [A] = [A_o] \text{ when } t = 0 \qquad (1)$$

where $k(\text{min}^{-1})$ is the pseudo-first-order rate constant (t = time). Writing (1) in a logarithmic form

$$\ln([A_o]/[A]) = kt \qquad (2)$$

and substituting the actual acetal or ketal concentration with the concentration of the forming carbonyl compound,

$$\ln\{[A_o]/([A_o]-[B])\} = kt \quad [A] = [A_o] - [B] \qquad (3)$$

k becomes equal to the slope of the curve given by Eqn. (3).

Most of the acetals and ketals could be hydrolyzed by measurable rates in solutions containing substantially different amounts of hydrochloric or formic acid. In order to make a comparison, a second-order rate constant

$$k_H = k/[H^+] \qquad [\text{dm}^3\ \text{mol}^{-1}\ \text{min}^{-1}] \qquad (4)$$

was calculated. These values are given in Tables I and II for acetals and ketals, respectively. The hydrolysis rate of compounds synthesized with ethanol was consequently higher compared with the corresponding compounds containing methoxy groups. This means that the longer the O-alkyl chain the faster the hydrolysis. Acetals and ketals containing five-member rings had always signifi-

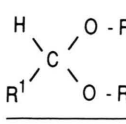


Table I. Second-order rate constants of acetal hydrolysis (k_H [$dm^3\ mol^{-1}\ min^{-1}$]).

R	R^1 CH_3	$ClCH_2$	Cl_2CH	C_6H_5
Methyl	2.54×10^1	8.47×10^{-6}	10^{-13}	4.90×10^3
Ethyl	1.64×10^2	2.19×10^{-6}	10^{-13}	1.17×10^4
Methylene	1.25×10^{-2}	2.53×10^{-5}	10^{-8}	1.90×10^2

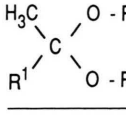


Table II. Second-order rate constants of ketal hydrolysis (k_H [$dm^3\ mol^{-1}\ min^{-1}$]).

R	R^1 CH_3	$ClCH_2$	Cl_2CH	C_6H_5
Methyl	9.91×10^4	4.50×10^{-3}	10^{-10}	1.57×10^5
Ethyl	3.10×10^5	4.68×10^{-3}	10^{-10}	3.65×10^5
Methylene	1.06×10^1	2.61×10^{-3}	10^{-7}	5.58×10^1

cantly smaller second-order rate constants than the opened molecules with the same number of carbon. The difference was usually around four orders of magnitude. Chlorine caused a dramatic reduction (10^7 times/chlorine atom) in the rate of hydrolysis. Compounds with trichloromethyl groups could not be hydrolyzed under the conditions employed (no detectable *oxo* compound in a concentrated formic acid solution over a few months). Ketals were hydrolyzed 10^3 times faster than the corresponding acetals (Tables I and II).

The few exceptions to these rules were usually compounds with C-phenyl ring instead of a C-methyl group. The reason for their exceptional behaviour is their different mechanism of hydrolysis [11, 14].

Acetals and ketals as safeners for EPTC in maize

EPTC caused more than 60% injury in maize shoot height (Fig. 2) at the rate applied (3.30 kg/ha) in sand. With the exception of the trichloromethyl and some non-chlorinated acetals and ketals all compounds produced a significant protection. However, there were considerable differences between the effectiveness of the differentially chlorinated safeners. Acetals and ketals with no chlorine reduced shoot height injury by only 5–11%. Protection by compounds containing

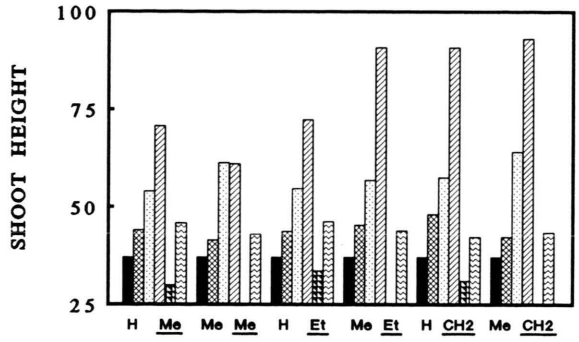


Fig. 2. Comparative effects (shoot height: % of control) of acetals (H) and ketals (Me) of methanol (Me), ethanol (Et) and ethylene glycol (CH2) as safeners for EPTC in maize. ■, EPTC (E); ▨, E + methyl; ▨, E + chloromethyl; ▨, E + dichloromethyl; ■, E + trichloromethyl; ▨, E + phenyl compounds.

chloromethyl group was greater (17–27%). Chloroacetone dimethylacetal and 2-chloromethyl-2-methyl-1,3-dioxolane were the most effective safeners from this group. Dichloromethyl acetals and ketals were usually the best safeners to EPTC. Although dichloroacetone dimethylketal and chloroacetone dimethylketal were equally effective (24% protection), dichloroacetaldehyde dimethyl- and diethylacetal also produced a similar, but better protection (33–36%) while dichloroacetone diethylacetal, 2-dichloromethyl-1,3-dioxolane and 2-dichloromethyl-2-methyl-1,3-dioxolane almost completely overcame the serious corn injury caused by EPTC. Trichloromethyl acetals were not found to be safeners but herbicide synergists.

According to our unpublished field trial results, ketals were generally better safeners than acetals. Compounds containing the dioxolane ring were always more effective compared with the open acetal and ketal molecules.

Discussion

Early studies with acetamide compounds [1–6] showed that their safener effectiveness increase in the order: non-chlorinated < monochloro < dichloro. Their ability to be hydrolyzed also increases with the number of chlorine atoms. Although a similar relationship

CH_3-	<	$ClCH_2-$	<	Cl_2CH-	≫	Cl_3C-
NO		FAIR SAFENER		GOOD		HERBICIDE SYNERGIST

was found between the chlorine content and safener effectiveness of acetals and ketals, their rate of hydrolysis decreases with increasing number of chlorine substituents.

A clear explanation for the same safener effectiveness and the opposite chemical reactivity order of differentially chlorinated acetamides and acetals needs further investigation. From the data obtained so far, hydrolysis is likely not involved in safener mode of action. From the stabilizing effect of chlorine atom(s) two conclusions can be reached:

1. Acetals and ketals may be active as safeners in their original form or

2. they can be biologically activated to actual safeners by transformation other than hydrolysis.

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