THE THERMAL REVERSIBILITY OF THE MICHAEL REACTION

V. THE EFFECT OF THE STRUCTURE OF CERTAIN THIOL ADDUCTS ON CLEAVAGE

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ABSTRACT

A large number of Michael adducts have been prepared from β-morpholinoethanethiol and α,β-unsaturated compounds bearing a variety of functional groups. The extent of cleavage of 23 of these under reversal conditions has been determined quantitatively. The relation between structure and amount of cleavage has been discussed. A few heterocyclic thiols were also employed, to extend the generality of the reactions. With the latter, the thiol-cleaved product was separated and identified, to show that the cleavage was normal.

It has been noted earlier that an arrangement of functional groups in the order of their activation of the Michael reaction would be useful (1). In our previous paper (2), morpholinoethanethiol adducts of α,β-unsaturated ketones (chalcones) having substituents in the ortho, meta, and para positions of both aromatic rings were described. Furthermore, the extent of their cleavage (reversibility of the Michael reaction) in hot water was determined. Adducts Nos. 1–4 (Table I) (2) illustrate similar reactivity in the present work. It was noted that related Michael adducts lacking an aryl group in the beta position were cleaved slightly or not at all under the same conditions, but were converted, in varying degrees, into their components in aqueous alkaline solution. To compare adducts with and without beta substituents, a study was made of a considerable number of such adducts lacking β-aryl groups. The addend, β-morpholinoethanethiol, was always the same so that the reversal would depend upon only the structure of the acceptor molecule (2); thus the functional groups in the latter were varied. The α,β-unsaturated compounds included those bearing open-chain (COAr, $COCH_3$) and cyclic ketonic, acidic ($CONH_2$, COOH), and neutral (CN, NO_2, $COOC_2H_5$) groups as well as two sulfones and three vinylpyridines. The degrees of cleavage of the substances investigated are shown in Table I. The adducts of heterocyclic mercaptans (Table II) underwent a similar reversal. In some of these instances, the reaction was not observed analytically, but instead, the resulting mercaptan was isolated and identified.

DISCUSSION OF RESULTS

Study suggests that the reversal reactions reached equilibrium rapidly at reflux, thus minimizing the dependency of the comparisons on rates. The data determined after 1 h of reflux (Table I) appear to represent equilibrium. The comparison of substituent effects was made under these conditions.[1] Previously, few quantitative data have been available on the position of the equilibrium (3).

[1]*A referee has suggested that: "It would be risky to equate relative yields after a fixed reaction period with relative reactivities. Discussion of substituent effects must relate to potential-energy variations, but it is entirely possible that two reactions could have the same energy of activation, thus leading to rate differences which have nothing to do with electronic effects of substituents. In the absence of a demonstration that all the reported reversals have similar entropies of activation, a correlation of relative yields with substituent effects may or may not be valid; some reservations should be expressed concerning the correlation."*

TABLE I

Determination of the extent of reversal of the conjugate addition of mercaptans (or thiols); % cleavage
(adduct = $R'CR''HCH_2R$, where R' = —$SCH_2CH_2NC_4H_8O \cdot HCl$)

No.	β-Substituent	R	Boiling H_2O for 2 min	20 ml of 0.1 *N* NaOH for 1 h		40 ml each of 1 *N* NaOH and C_2H_5OH		
						At 25 °C		
				At 25 °C	At reflux	For 0.5 h	For 1 h	At reflux for 1 h
		Ketones						
1	C_6H_5	COC_6H_5[d]	18, 18.5					
2	C_6H_5	COC_6H_5	58.2, 59.8					
3	C_6H_5	$COC_6H_4CH_3$-4	36.2					
4	C_6H_5	COC_6H_4OH-4	38.9					
5	C_6H_5	$COCH_3$				95.6[a]		95.8
6	None	$COCH_3$		48.5		65.9	65.7	78.2
7	None	COC_6H_5				65.3	65.3	88.5
8	None	$COC_6H_4OCH_3$-4				60.6	60.0	80.6
		Esters						
9	None	$(COOC_2H_5)_2$[c]				66.2[a]	65.3	65.0
10	C_6H_5	$(COOC_2H_5)_2$[c]				94.0[a]	95.0	94.5
11	4-$CH_3OC_6H_4$	$(COOCH_3)_2$[c]				93.5[a]	94.5	97.5
12	None	$COOCH_3$		2.3	16.0		0.7	7.0
		Nitrile						
13	None	CN		6.6	42.2		23.4	69.8
		Amide						
14	None	$CONH_2$		4.1	28.4		10.9	55.8
		Acids						
15	None	COOH		0	16.0		0	3.0
16	None	α-$C_6H_4NO_2$-4[b]COOH					49.8	70.6
		Nitro compound						
17	C_6H_5	NO_2				14.9[a]	23.9	60.2
		Sulfones						
18	None	$SO_2C_2H_5$					17.8	73.7
19	None	$SO_2C_6H_5$					20.5	78.0
		Heterocyclic rings						
20	None	Maleimide					5.0	66.3
21	None	2-Vinylpyridine·2HCl		0	20.5		0	4.5
22	None	4-Vinylpyridine·2HCl		0	89.0		0	48.4
23	None	4-Vinylpyridine·$2CH_3I$		79.5			19.9	

[a]For 10 min.
[b]α-Substituent.
[c]Malonate adducts; have the chain $R'CR''HCHR_2$.
[d]Free base.

TABLE II

R = —SCH$_2$CH$_2$N⟨O⟩	Yield (%)	Melting point (°C)	Empirical formula	Analyses (%) Calculated C	Calculated H	Calculated N	Found C	Found H	Found N
A. Adducts of 2-morpholinoethanethiol									
RCH$_2$CH$_2$COCH$_3$	53								
RCH$_2$CH$_2$COCH$_3$·HCl	82	118–119[a]	$C_{10}H_{20}ClNO_2S$	47.3	7.9	5.5[p]	47.6	8.0	5.6
RCH(C$_6$H$_5$)CH$_2$COCH$_3$·HCl	59	124–125[a]	$C_{16}H_{24}ClNO_2S$	58.3	7.3	4.2	57.9	8.1	4.4
RCH$_2$CH$_2$COC$_6$H$_5$·HCl	83	186[b]	$C_{15}H_{22}ClNO_2S$	57.0	7.0	4.4	57.1	7.1	4.5
RCH$_2$CH$_2$COC$_6$H$_4$OCH$_3$-4·HCl	81	147[b]	$C_{16}H_{24}ClNO_3S$	55.6	7.0	4.1	55.5	7.3	3.8
RCH$_2$CH$_2$CN	86	123 at 0.05[a]	$C_9H_{15}N_2OS$	54.0	8.0	14.0[q]	54.4	8.3	14.1
RCH$_2$CH$_2$CN·HCl	78	134–135[a]	$C_9H_{17}ClNO_2S$	45.7	7.2	11.8	45.7	6.8	11.6
RCH$_2$CH$_2$CN·HClO$_4$	33	82–84[c]	$C_9H_{17}ClNO_2S$			9.3			9.1
RCH$_2$CH$_2$CONH$_2$	96	89–90[d]	$C_9H_{17}N_2O_2S$	49.5	8.3	12.8	49.0	8.5	12.7
RCH$_2$CH$_2$CONH$_2$·HCl	91	130[a]	$C_9H_{18}ClN_2O_2S$	42.4	7.5	13.9	42.5	7.6	13.9
RCH$_2$CH$_2$CONH$_2$·HClO$_4$	100	97–99[c]	$C_9H_{18}ClN_2O_6S$			8.8			9.1
RCH$_2$CH$_2$CO$_2$CH$_3$	76	114 at 0.05[o]	$C_{10}H_{19}NO_3S$	51.5	8.3	6.0[r]	51.8	8.4	5.6
RCH$_2$CH$_2$CO$_2$CH$_3$·HCl	61	144–145[b]	$C_{10}H_{20}ClNO_7S$		13.1	5.2		13.2	5.6
RCH$_2$CH$_2$CO$_2$CH$_3$·HClO$_4$	88	85–87[c]	$C_{10}H_{20}ClNO_7S$			4.2			3.8
RCH$_2$CH$_2$COOH	82	75[b]	$C_9H_{17}NO_3S$	49.3	7.8	6.4	49.0	7.8	6.7
RCH$_2$CH$_2$COOH·HCl	97	122–123[b]	$C_9H_{18}ClNO_3S$	42.3	7.1	5.5	42.3	7.0	5.4
RCH$_2$CH$_2$COOH·HClO$_4$	68	83–88[a]	$C_9H_{18}ClNO_7S$		10.8	4.2		11.2	3.8
RCH$_2$CH(C$_6$H$_4$NO$_2$-4)COOH·HCl	91	162[f]	$C_{15}H_{21}ClN_2O_5S$	47.8	5.6	7.4	48.1	5.9	7.6
RCH$_2$CH(COOC$_2$H$_5$)$_2$·HCl	61	122–123[a]	$C_{14}H_{26}ClNO_5S$	47.2	7.4	3.9	46.8	7.0	3.4
RCH(C$_6$H$_5$)CH(COOCH$_3$)$_2$·HCl	94	167	$C_{18}H_{26}ClNO_5S$	53.5	6.5	3.5	53.8	6.6	3.5
RCH(C$_6$H$_5$)CH(COOC$_2$H$_5$)$_2$·HCl	93	130[g]	$C_{20}H_{30}ClNO_5S$	55.7	6.8	3.2	55.9	7.1	3.1
RCH(C$_6$H$_4$OCH$_3$-4)CH(COOCH$_3$)$_2$·HCl	89	165[a]	$C_{19}H_{28}ClNO_6S$	52.6	6.5	3.1	52.5	6.4	3.2
RCH$_2$CH$_2$SO$_2$C$_2$H$_5$·HCl	85	134[b]	$C_{10}H_{22}ClNO_3S_2$	39.5	7.3	4.6	39.9	7.4	4.6
RCH$_2$CH$_2$SO$_2$C$_6$H$_5$·HCl	50	122[b]	$C_{14}H_{22}ClNO_3S_2$	47.8	6.3	4.0	48.0	6.4	3.8
RCH(C$_6$H$_5$)CH$_2$NO$_2$·HCl	86	182–183[b]	$C_{14}H_{21}ClN_2O_3S$	50.5	6.4	8.4	50.5	6.4	8.7
RCH$_2$CH$_2$⟨N⟩·2HCl	68	217[h]	$C_{13}H_{22}Cl_2N_2OS$	48.0	6.8	8.6	47.8	7.1	8.5
RCH$_2$CH$_2$⟨N⟩·2HCl	56	229[h]	$C_{13}H_{22}Cl_2N_2OS$	48.0	6.8	8.6	47.9	6.9	8.9
RCH$_2$CH$_2$⟨N⟩·2CH$_3$I	49	191[h]	$C_{15}H_{26}I_2N_2OS$	33.6	4.8	5.2	33.8	5.2	4.9
R⟨NH⟩	30	89–90[b]	$C_{10}H_{16}N_2O_3S$	49.2	6.6		49.0	6.5	
R⟨NH·HCl⟩	30	190–191	$C_{10}H_{17}ClN_2O_3S$	42.8	6.1		43.1	6.4	

TABLE II (*Continued*)

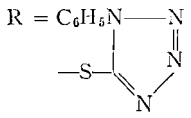
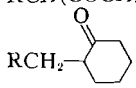
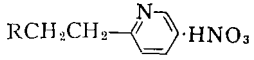
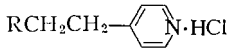
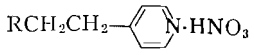
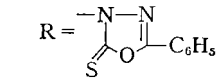
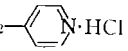
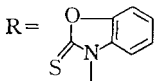
	Yield (%)	Melting point (°C)	Empirical formula	Analyses (%) Calculated C	H	N	Found C	H	N
B. Adducts of heterocyclic thiols									
									
$RCH_2CH_2COCH_3$	86	72[i]	$C_{11}H_{12}N_4OS$	53.2	4.9	22.6	53.1	5.3	22.5
$RCH_2CH_2COC_6H_5$	65	95[i]	$C_{16}H_{14}N_4OS$	61.9	4.5	18.0	61.8	4.9	18.3
$RCH_2CH_2COC_6H_4OCH_3$-4	62	114[b]	$C_{17}H_{16}N_4O_2S$	60.0	4.7	16.5	60.0	4.8	16.8
$RCH(COCH_3)CH_2COCH_3$	51	93[j]	$C_{16}H_{14}N_4OS$	53.8	4.9	19.3	53.6	5.1	19.6
	42	77[k]	$C_{14}H_6N_4OS$	58.3	5.6	19.4	58.5	5.6	19.8
	40	129[b]	$C_{13}H_{14}N_4OS$	56.9	5.1	20.4	57.2	5.3	21.0
	43	128[b]	$C_{14}H_{16}N_4OS$	48.5	4.1	24.3	48.9	4.3	24.5
	90	200[l]	$C_{14}H_{14}ClN_4S$	52.6	4.4	21.9	52.6	4.5	22.0
	56	122[b]	$C_{14}H_{16}N_4OS$	48.5	4.1	24.3	48.5	4.2	24.3

TABLE II (*Concluded*)

	Yield (%)	Melting point (°C)	Empirical formula	Analyses (%) Calculated C	H	N	Found C	H	N
R = 									
$RCH_2CH_2COCH_3$	52	55[l]	$C_{11}H_{12}N_2O_2S$	58.0	4.9	11.2	58.0	4.8	11.3
$RCH_2CH(COOCH_3)_2$	45	99[h]	$C_{14}H_{14}N_2O_5S$	52.2	4.4		52.5	4.7	
$RCH_2CH(COOC_2H_5)_2$	67	80[h]	$C_{16}H_{18}N_2O_5S$	54.8	5.2		55.2	5.1	
RCH_2CH_2-  ·HCl	45	200[b]	$C_{15}H_{24}ClN_2OS$	56.3	4.4	13.1	56.5	4.5	13.3
R = 									
$RCH_2CH(COOC_2H_5)_2$	17	67–68[h]	$C_{15}H_{17}NO_5S$	55.7	5.3		55.6	5.6	
$RCH_2CH_2SO_2CH_2CH_2R$	38	168[m]	$C_{18}H_{16}N_2O_4S_3$	51.4	3.8	6.7	51.6	3.8	7.0

[a]Recrystallized from methanol – ethyl acetate.
[b]Recrystallized from ethanol.
[c]Recrystallized from water.
[d]Recrystallized from benzene.
[e]Recrystallized from ethanol–benzene–ether.
[f]Recrystallized from ether–ethanol.
[g]Recrystallized from ethyl acetate.
[h]Recrystallized from methanol–ethanol.
[i]Recrystallized from ether.
[j]Recrystallized from ether–ligroin (b.p. 35–60°).
[k]Recrystallized from methanol.
[l]Recrystallized from ligroin (b.p. 35–60°).
[m]Recrystallized from xylene.
[n]n_D^{25} 1.5118.
[o]n_D^{25} 1.4968.
[p]Anal. Calcd.: S, 12.6. Found: S, 12.7.
[q]Anal. Calcd.: S, 16.0. Found: S, 16.4.
[r]Anal. Calcd.: S, 13.7. Found: S, 14.0.

In general, activation of the α-hydrogen atom appears to activate the adduct towards reversal, as expected by electronic theory. Thus, the cleavage may largely be predicted. The order of cleavage indicated is ketone > nitrile > amide > acid. Esters are not included within this order because of their probable hydrolysis to carboxylic acids (cf. Nos. 12 and 15). However, the adduct of methyl vinyl ketone was observed to reverse upon attempted distillation, whereas the adducts of acrylonitrile and methyl acrylate were unchanged upon distillation. These orders support that of Connor's generalization: ketones > esters > nitriles (1). The activating influence of a β-phenyl group is evident from a comparison of the ketones (Nos. 5 and 6). The adduct of a phenyl ketone (No. 7) appears to be more reactive than that of a methyl ketone (No. 6). An electron-repelling group in the para position (No. 8) measurably decreases the activity. On this basis, the relative reactivities of ketones is expected to be $-COC_6H_4NO_2$-4 > $-COC_6H_5$ > $-COCH_3$ = $-COC_6H_4OCH_3$-4. The adduct of acrylic acid (No. 15) is practically stable, whereas the derivative bearing a strong electron-attracting alpha substituent (No. 16) shows activation towards cleavage. Cleavage is particularly large because of activation by two carbonyl groups, as in the adducts of methylenemalonic esters (Nos. 9–11). A β-phenyl effect is also evident (No. 10). The cleavage reactivity of adducts of conjugated sulfones (Nos. 18 and 19) suggests significant α-hydrogen activity. The adducts of the heterocyclic unsaturated compounds (Nos. 21–23) indicate that the adduct from 4-vinylpyridine is more reactive than that from 2-vinylpyridine. The forming of a quaternary ammonium salt is expected to increase the reactivity.

EXPERIMENTAL

Adduct Formation

Mercaptans have been used to a limited extent in Michael additions (4–6); they add to α,β-unsaturated ketones without a catalyst more readily than to esters (7). In this work the procedure was varied depending upon the components. β-Morpholinoethanethiol was added to the second component, even to acrylic acid, simply by refluxing in alcohol; the amine moiety probably functioned as a catalyst (method A). Similarly, heterocyclic mercaptans were added to 2- and 4-vinylpyridine. The addition failed, however, with methyl cinnamate, methyl crotonate, and cinnamonitrile. A similar failure has been noted when nitromethane and an amine catalyst were used (8). 5-Mercapto-1-phenyltetrazole and 2-mercapto-5-phenyl-1,3,4-oxadiazole were added to conjugated ketones effectively in acetic acid (method B). In a few instances, when sodium acetate and refluxing in acetic acid were used (method C), appropriate Mannich bases served as the source of vinyl ketones. The addition of 2-mercaptobenzoxazole was catalyzed by sodium methoxide (method D).

Dimethyl malonate (9), dimethyl benzalmalonate (10), diethyl methylenemalonate (11), β-dimethylaminopropiophenone hydrochloride (12), maleimide (13), ethyl vinyl sulfone (14), and phenyl vinyl sulfone (15) were prepared as described in the literature. Diethyl benzalmalonate and dimethyl p-methoxybenzalmalonate were preferably prepared by the use of a continuous reactor (16). The latter ester solidified after distillation, b.p. 130–135° at 0.03 mm, m.p. 59–60° after crystallization from ethanol (66% yield).

Anal. Calcd. for $C_{13}H_{14}O_5$: C, 62.4; H, 5.6. Found: C, 62.4; H, 5.7.

Method A

Equimolar amounts of the acceptor component and β-morpholinoethanethiol in absolute ethyl alcohol were refluxed for 1 h and the solvent was removed under reduced pressure. Volatile products were fractionated through a 10 cm column filled with glass helices. Nonvolatile products, whether oils or solids, were dissolved in ether, and converted into salts with hydrogen chloride. Perchlorates were prepared by treating the hydrochlorides in methanol with sodium perchlorate.

Method B

Equimolar amounts of the acceptor molecule and β-morpholinoethanethiol in acetic acid were refluxed for 1 h, unless the acceptor had a low boiling point (methyl vinyl ketone, methyl acrylate); in these instances the reaction mixture was maintained at 70–80° for 30 min and then boiled for 10 min. Most of the solvent was removed under reduced pressure. When the residue was allowed to stand overnight, the crude product crystallized.

Method C

(*i*) A suspension of 0.2 mole of either component (42.6 g of β-dimethylaminopropiophenone hydrochloride or 54.8 g of the corresponding p-methoxypropiophenone hydrochloride), 29.5 g of β-morpholinoethanethiol, and 19.5 g of dry potassium acetate in 500 ml of xylene was refluxed for 1 h, during which time the solids

became a fine powder. The reflux condenser was removed and the mixture was boiled to remove the dimethylamine. After filtration of the precipitated potassium chloride, the solvent was removed under reduced pressure, leaving a brown oil. Addition of hydrogen chloride to a solution of this oil in ether gave the hydrochloride, which crystallized after being allowed to stand for 1 h. β-Dimethylamino-*p*-methoxypropiophenone hydrochloride was made by the usual procedure and used without purification.

(*ii*) A mixture of 0.04 mole of β-dimethylamino-α-(*p*-nitrophenyl)propionic acid (17), 6.9 g of β-morpholinoethanethiol, 4.1 g of potassium acetate, and 100 ml of acetic acid was maintained at 80° for 15 min, and then boiled for 10 min. Hydrogen chloride was passed through the cooled mixture, and sufficient ether was then added to precipitate the hydrochloride as an oil. After the oil had been decanted, addition of a small amount of ether–alcohol caused crystallization. The product was collected and recrystallized, after filtration of any salt present.

(*iii*) 5-Mercapto-1-phenyltetrazole formed adducts (Table IIB) on treatment of the hydrochlorides of β-dimethylaminopropiophenone, β-dimethylamino-*p*-methoxypropiophenone, and β-dimethylaminomethylcyclohexanone (18) in the following manner. Equimolar amounts of the Mannich base and potassium acetate in acetic acid were boiled for 15 min and then poured into 15 volumes of ice water. The product crystallized when allowed to stand overnight.

Method D

Sufficient sodium methoxide was added to a solution of 11.8 g (0.1 mole) of divinyl sulfone and 30.2 g (0.2 mole) of 2-mercaptobenzoxazole in 300 ml of hot ethanol to make the solution basic. The adduct began to separate as the mixture was refluxed for 1 h. The reaction mixture was then concentrated and the product was collected.

Cleavage of Adducts

Iodometric Estimation of Thiols

About 1 meq of adduct was placed in the alkaline solution, at the temperature and for the time indicated (Table I). An equivalent of hydrochloric acid was added, to render the solution approximately neutral, followed by 60 ml of acetic acid. Five milliliters of 0.25% starch indicator was then added, and the mixture was titrated with 0.1 *N* iodine solution to a blue end point. The results are shown in Table I.

Identification of Thiols

One gram (0.004 mole) of β-(1-phenyltetrazolyl-5-thio)propiophenone was dissolved in 10 ml of methanol, and a solution of 0.5 g of potassium hydroxide in 5 ml of water was added. The mixture was diluted with 15 ml of water and stirred for 10 min at room temperature. After removal of the methanol under reduced pressure, the mixture was acidified with hydrochloric acid. The precipitated 5-mercapto-1-phenyltetrazole (0.62 g, 87%) was collected; the melting point was 155°, and the mixture melting point was not depressed. Satisfactory elemental and infrared analyses of the compound, after it had been recrystallized from xylene, were obtained. Related adducts obtained from 3-hexene-2,5-dione, β-dimethylaminomethylcyclohexanone, and 2-cyclohexanone (Table IIB) gave a similar result. An analogous treatment of 1 g (0.0029 mole) of 2-(5-phenyl-1,3,4-oxadiazolyl-2-thio)-1,1-dicarbethoxyethane in 200 ml of methanol, with 1 g of potassium carbonate in 200 ml of water, yielded 0.4 g (79%) of 2-mercapto-5-phenyl-1,3,4-oxadiazole, m.p. 215–217°; the mixture melting point was not depressed.

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