

Metabolism of Trichloroethylene & Covalent Binding of Reaction Products

F. P. Guengerich

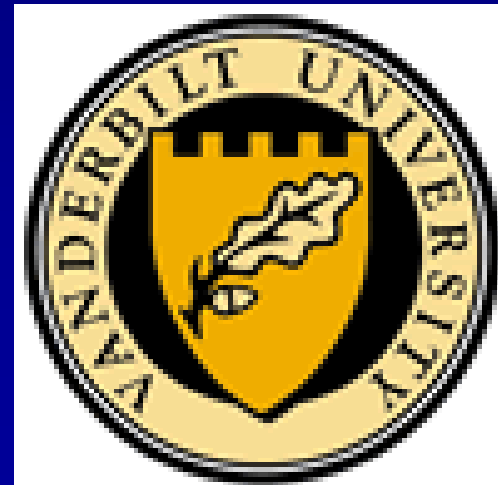
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<http://isihighlycited.com/author.cgi?&link1=Browse&link2=Results&id>

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Trichloroethylene in Dickson (TN), 2003

<http://www.toxicology.mc.vanderbilt.edu/TCE>

Recent Articles on TCE in Dickson

[Chemicals, illnesses hard to link, federal agency says](#)

[Family blames health woes on Dickson's landfill](#)

[Water assurances were lies, commissioners told](#)

[Dickson landfill area will be warned](#)

[Water contamination must be state priority](#)

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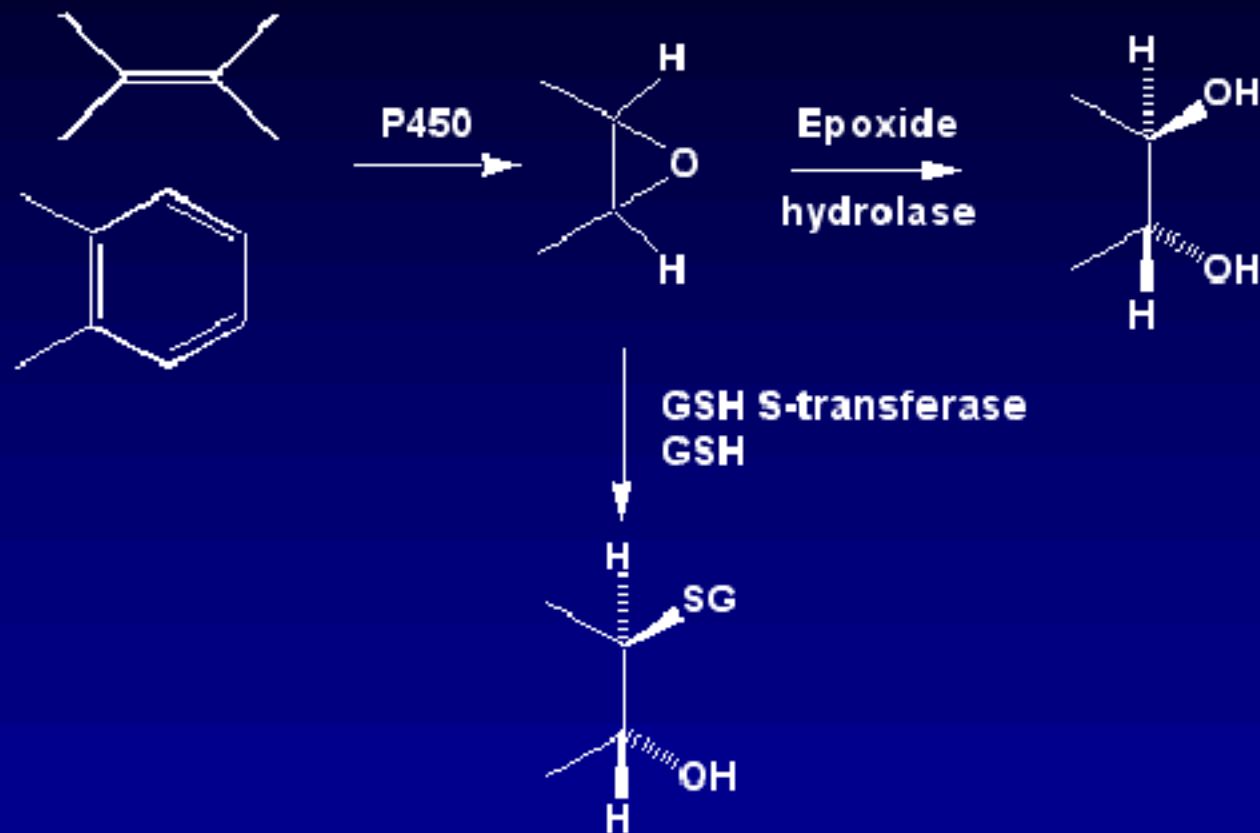
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Enzymatic formation & reactions of epoxides









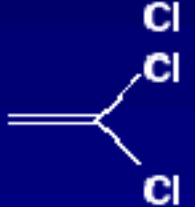

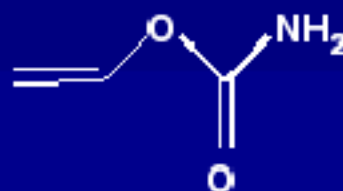
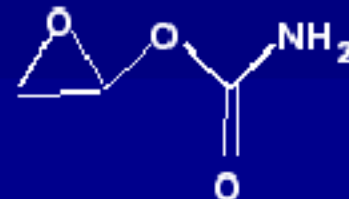


Epoxide stability: relation to biological activity

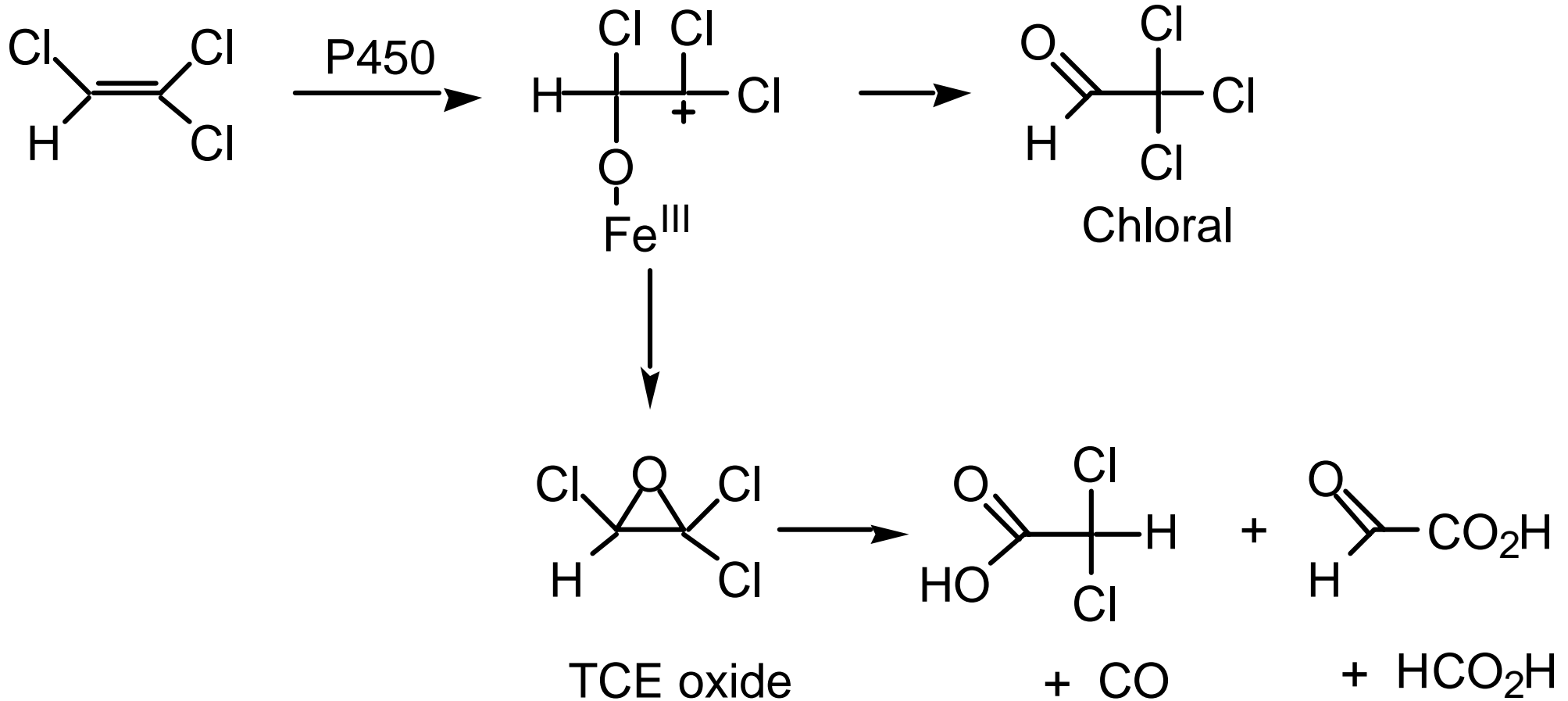
Drinkwater *et al.* (1978) *Cancer Res.* 38, 3247-3255

	$t_{1/2}$, min	Conc. needed to unwind superhelical DNA, mM	<i>S. typh.</i> TA98 revertants/ nmol
Benzo[a]pyrene diol epoxide	38	0.023	460
1-Phenyloxirane	46	0.027	540
9-Methyl-10-anthryloxirane	21	0.10	110
6-Chrysenyloxirane	141	0.22	70
9-Anthryloxirane	172	0.24	53
9-Phenanthryloxirane	140	0.9	25
2-Benzanthryloxirane	115	1.1	20
2-Naphthyloxirane	103	>2	3.0
Styrene oxide	340	>3	0.001

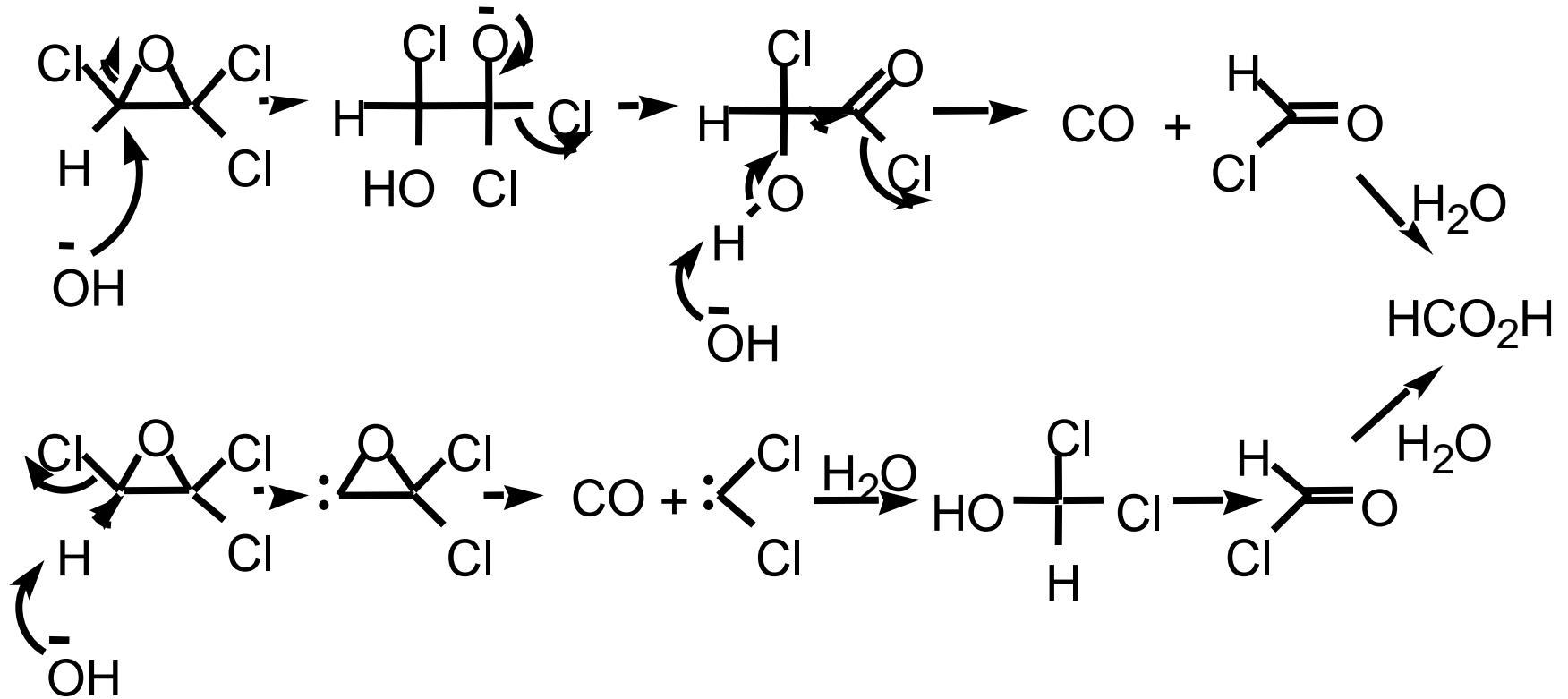
Stabilities of some epoxides of relevance in toxicology & cancer

		<u>$t_{1/2}$, s (23° C)</u>
		7200
		90
		40
		12
		~2
		60
Aflatoxin B ₁	Aflatoxin B ₁ 8,9oxide (<i>exo</i>)	1

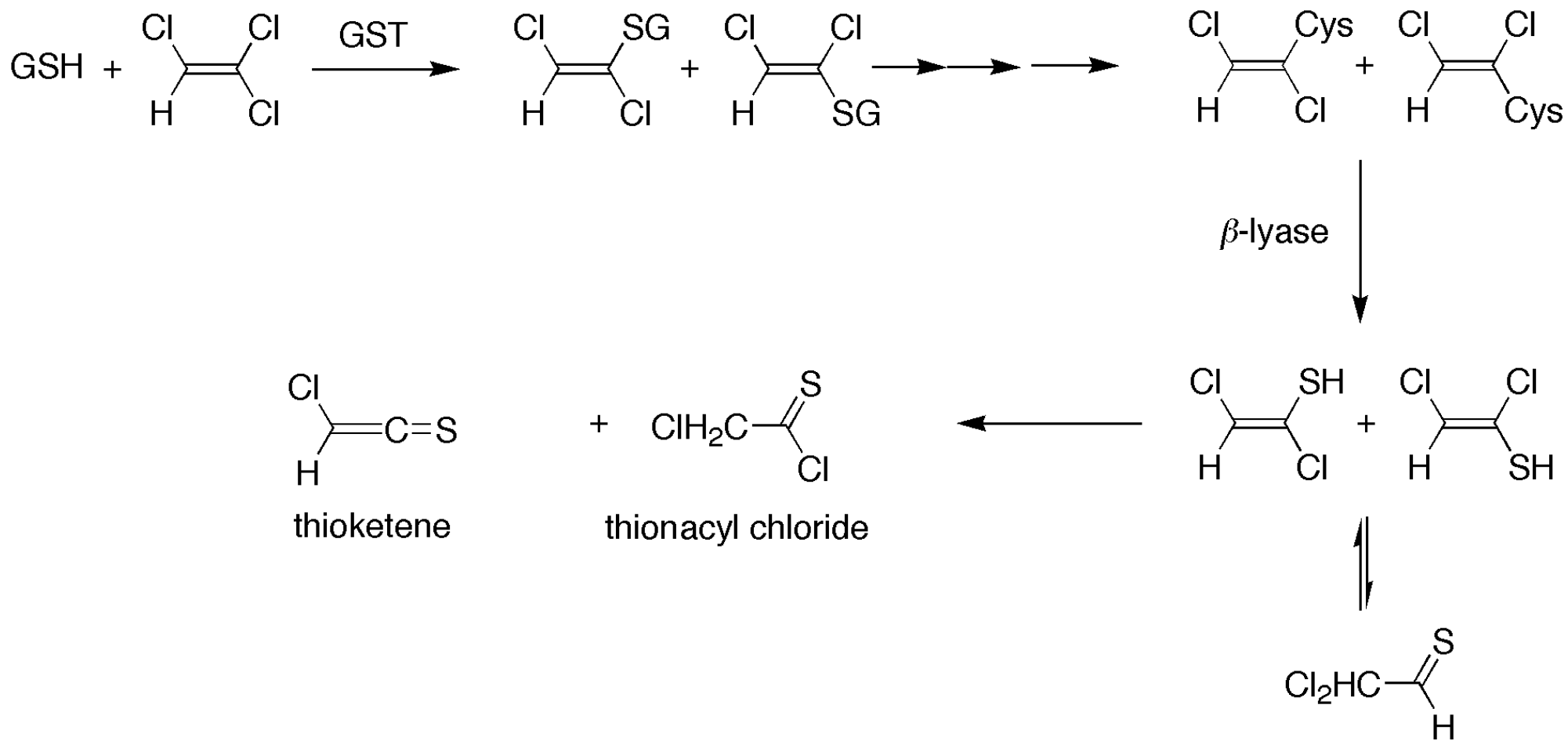
Oxidation of trichloroethylene (TCE) by P450



Some possible mechanisms for scission of TCE oxide



Activation of TCE by GSH conjugation



Carcinogenic Substrates for Human P-450 Enzymes

P-450 1A1

B(a)P

P-450 1A2

2-NH₂ anthracene
2-AAF
2-NH₂ fluorene
4-NH₂ biphenyl
2-Naphthylamine
Glu P-1
Glu P-2
IQ
MeIQ
MeIQx
PhIP
Trp P-2
NNK

P-450 2E1

Me₂N-N=O
Et₂N-N=O
Me, propyl N-N=O
Me, benzyl N-N=O
Vinyl Cl
Vinyl Br
Acrylonitrile
Vinyl carbamate
Urethan
Styrene
Benzene
CCl₄
CHCl₃
Trichloroethylene

P-450 3A4

Aflatoxin B₁
Aflatoxin G₁
Sterigmatocystin
B(a)P-7,8-diol
BA-3,4-diol
DMBA-3,4-diol
BFA-9,10-diol
tris(2,3-Br₂ propyl)PO₄
6-NH₂ chrysene
MOCA
Senecionine

Variability in human enzymes (expression level/activity)

- P450 2E1 & GST T1-1 (CH₂Cl₂ liver & lung cancers)
 - Kirman et al. (1999) *Toxicologist* **48**, 83 & Rish et al. (1999) *Toxicologist* **48**, 143
 - Issues: Which in vitro parameters to use (V_{max} , K_m , V_{max}/K_m)?
 - Lack on information regarding extent of variation in extrahepatic human tissues (e.g. lung, brain)

More recent drug studies (using *in vivo* clearance)

Doren et al. (2002) *Food Chem. Toxicol.* **40**, 1633-1656

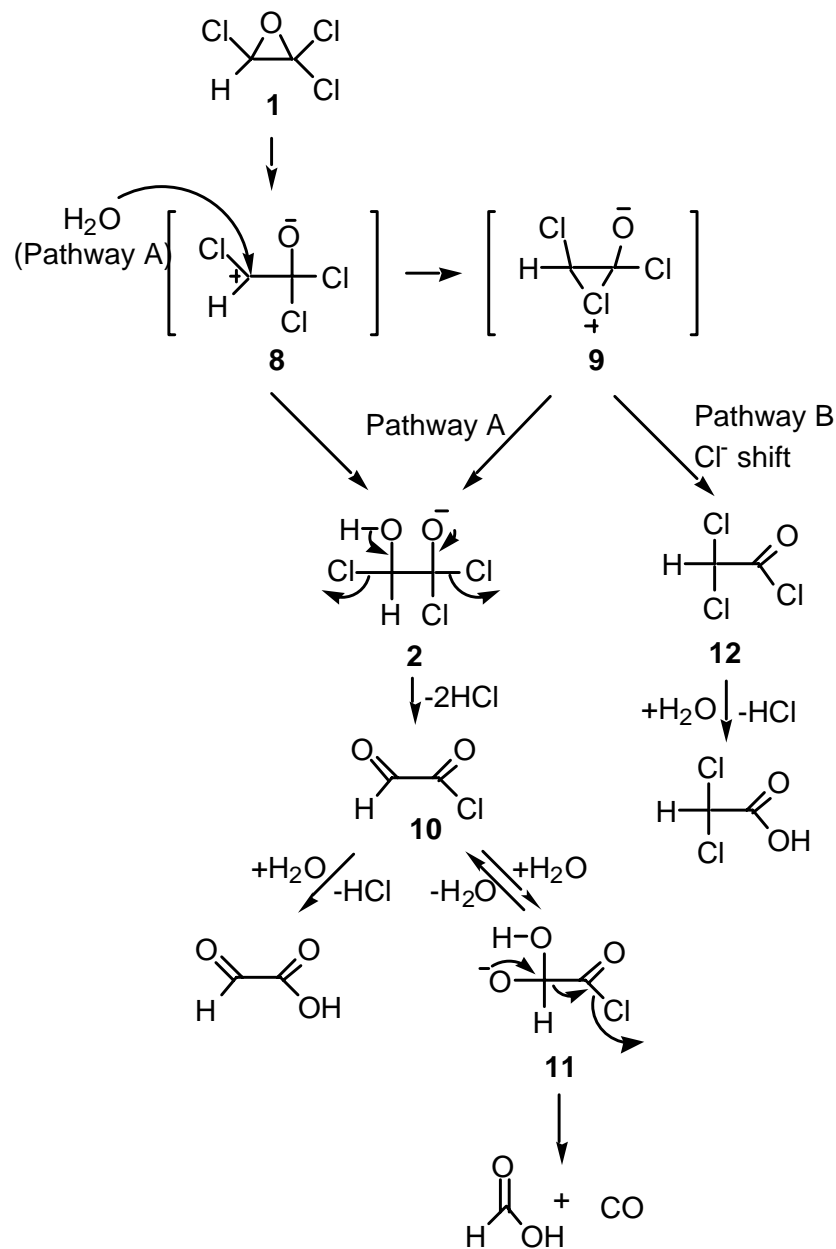
	<u>Uncertainty factor</u>
P450 2D6: non-phenotyped adults, EMs	2.7-4.1
PMs	15-18
Children	22-45

Doren et al. (2003) *Food Chem. Toxicol.* **41**, 201-224

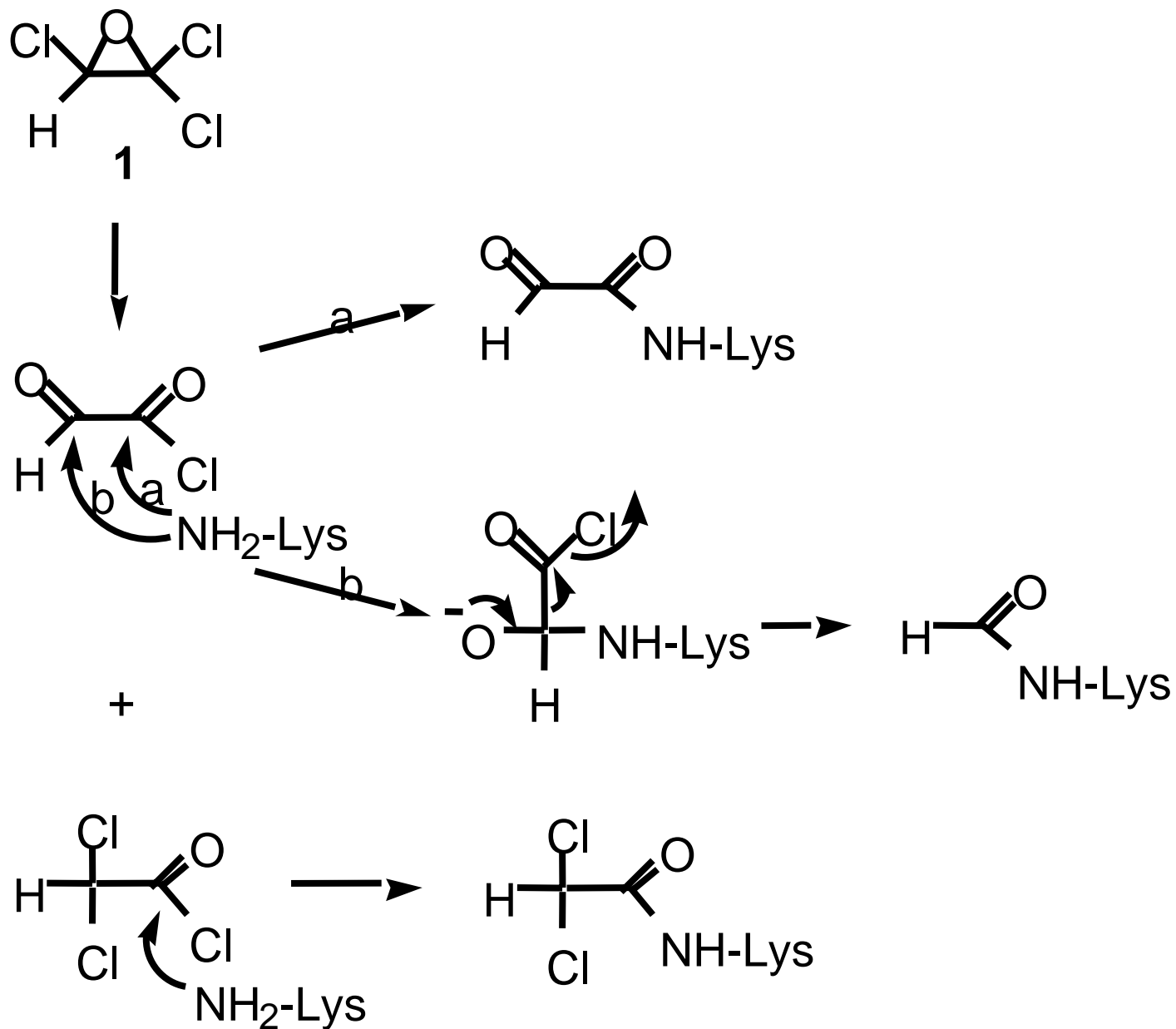
P450 3A4:	Adults	3.2
	Children	12

Factors increase with increase in fraction of metabolism due to a single enzyme (exponential relationship, $r^2 = 0.8$)

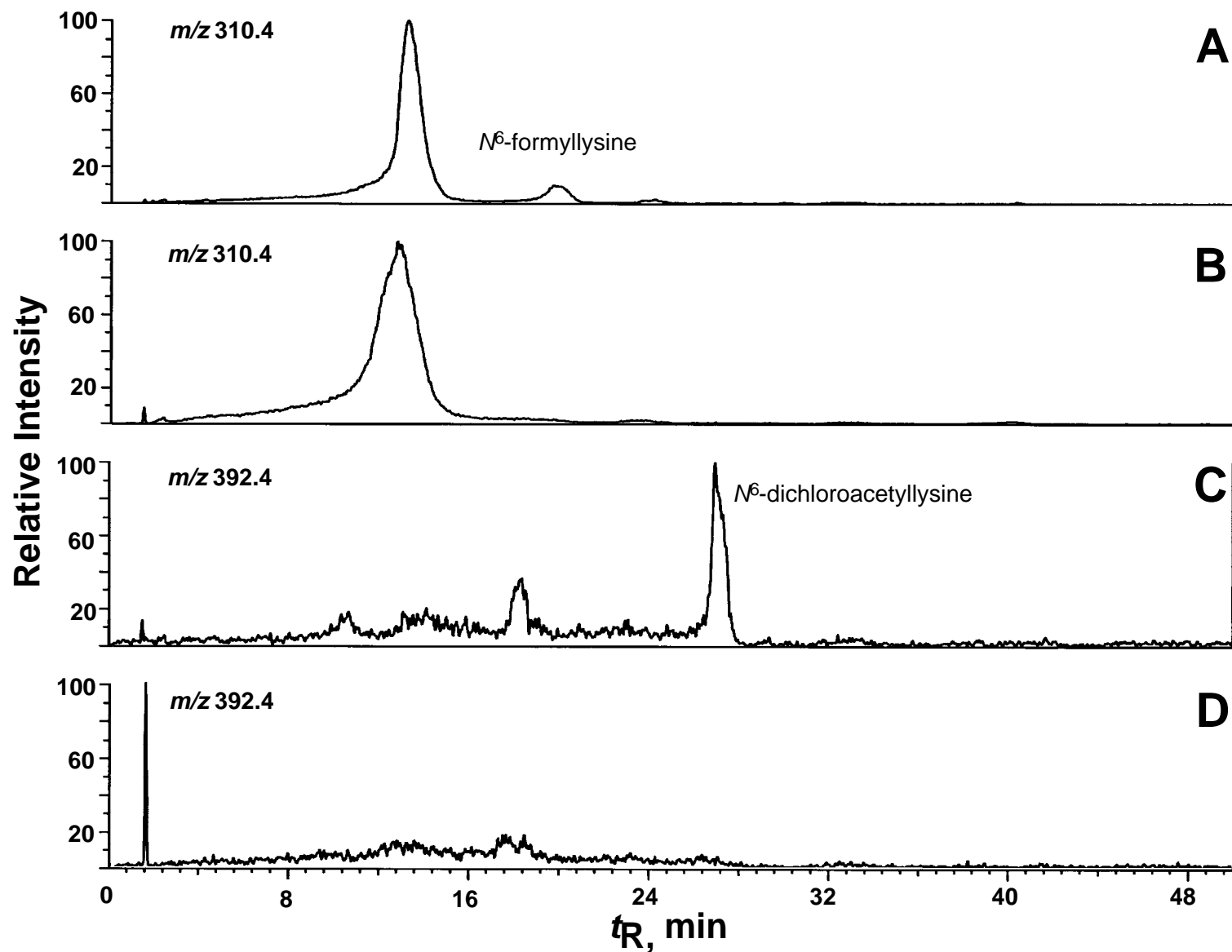
Mechanisms of hydrolytic decomposition of TCE oxide (determined by ^{18}O & ^2H labeling & mass spectrometry)



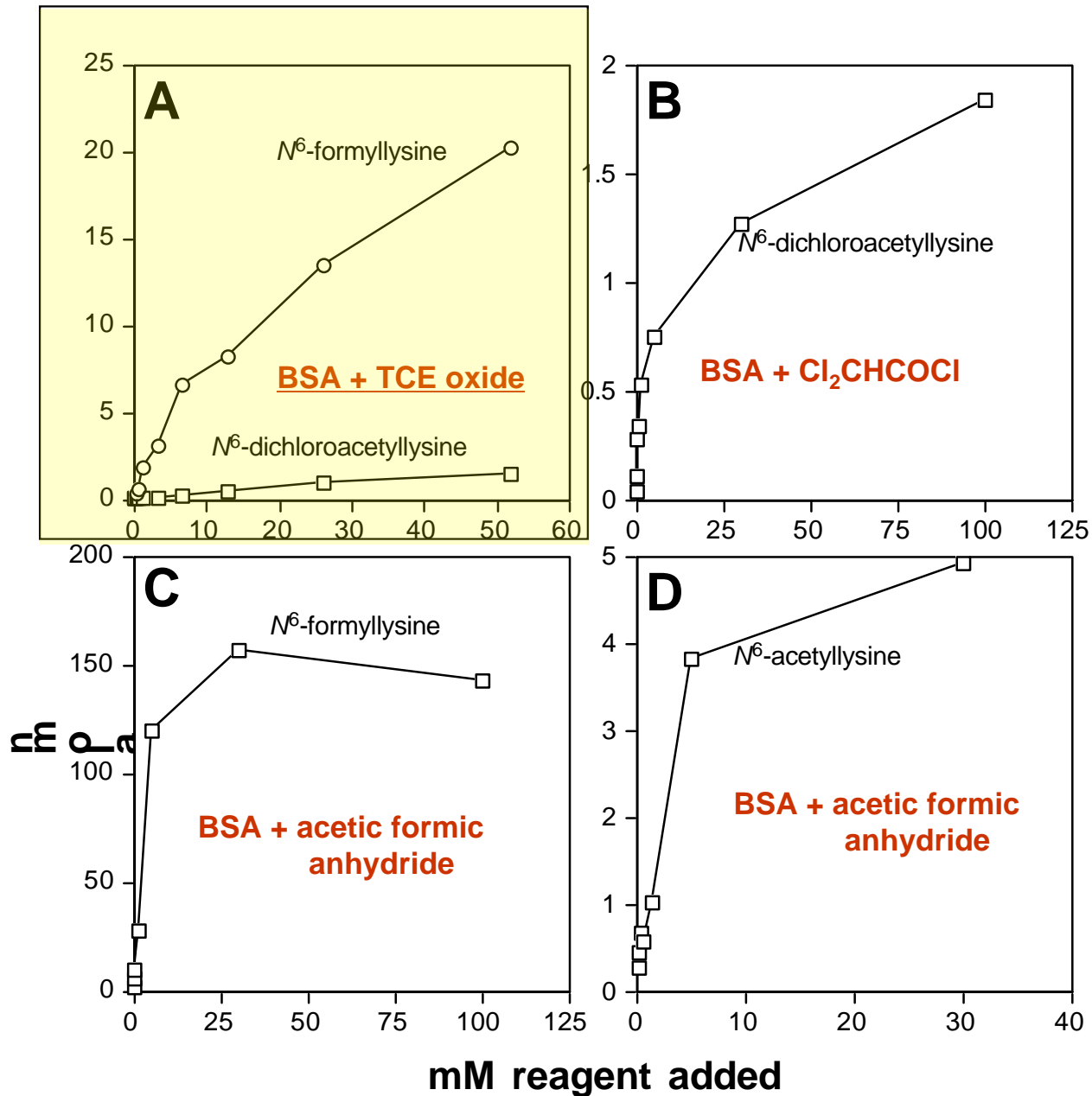
Mechanisms of reaction of TCE oxide with lysine (determined by ^{18}O & ^2H labeling & mass spectrometry)



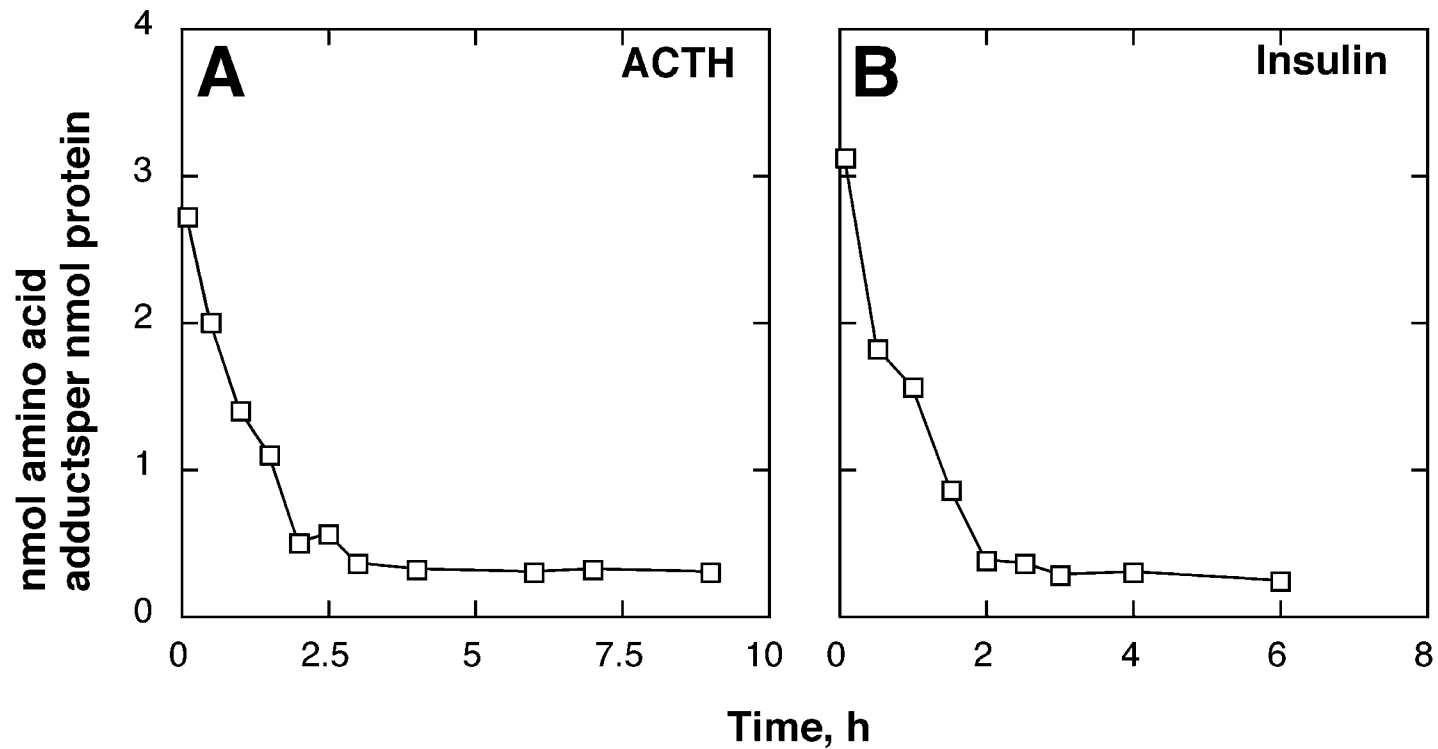
The products of reaction of TCE oxide with lysine are predominantly formyl adducts



The products of reaction of TCE oxide with lysine in bovine serum albumin (BSA) are predominantly formyl adducts (part A)

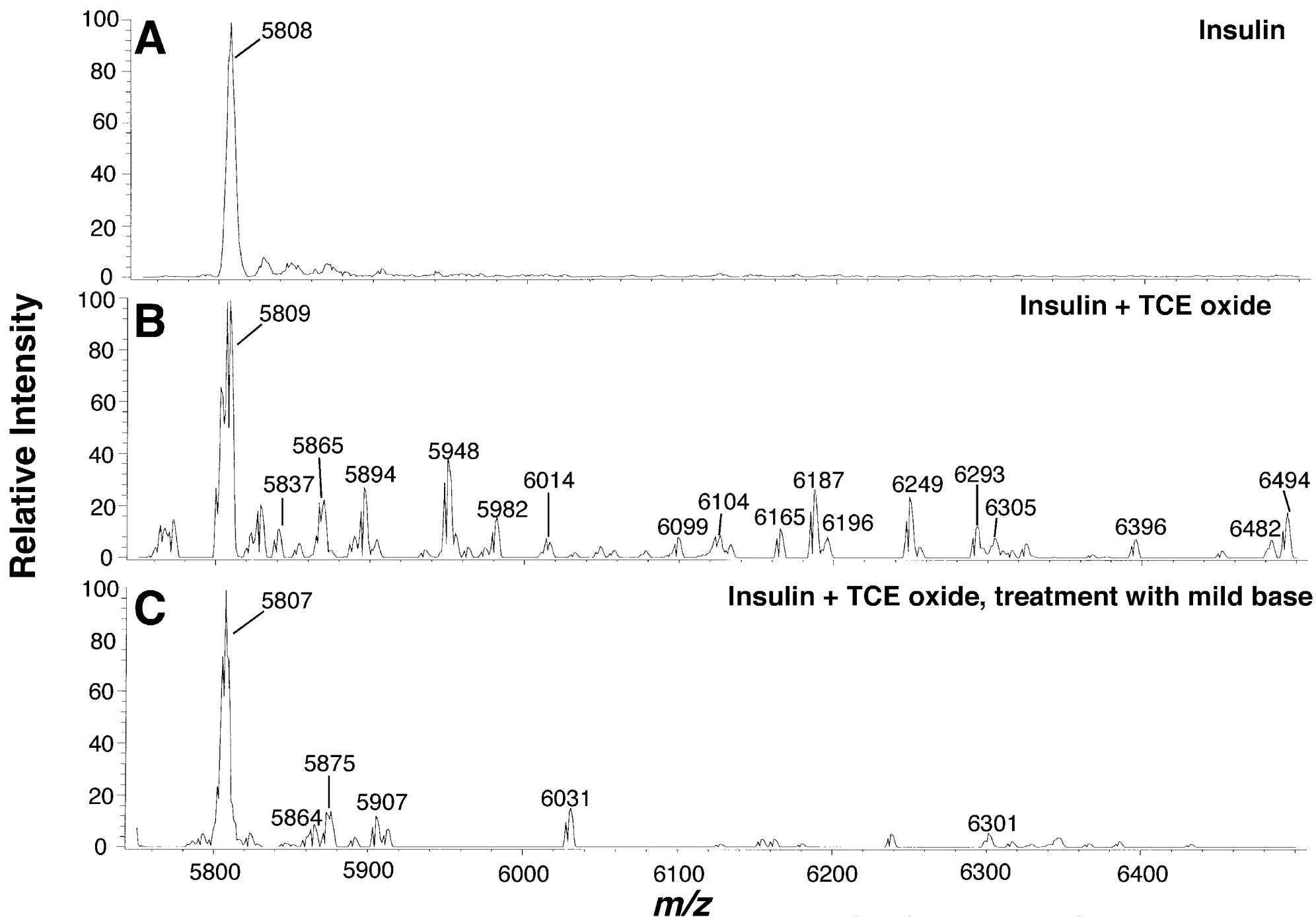


Loss of Protein Adducts Formed from Reactions of Insulin or ACTH (1-24) with TCE Oxide at pH 7

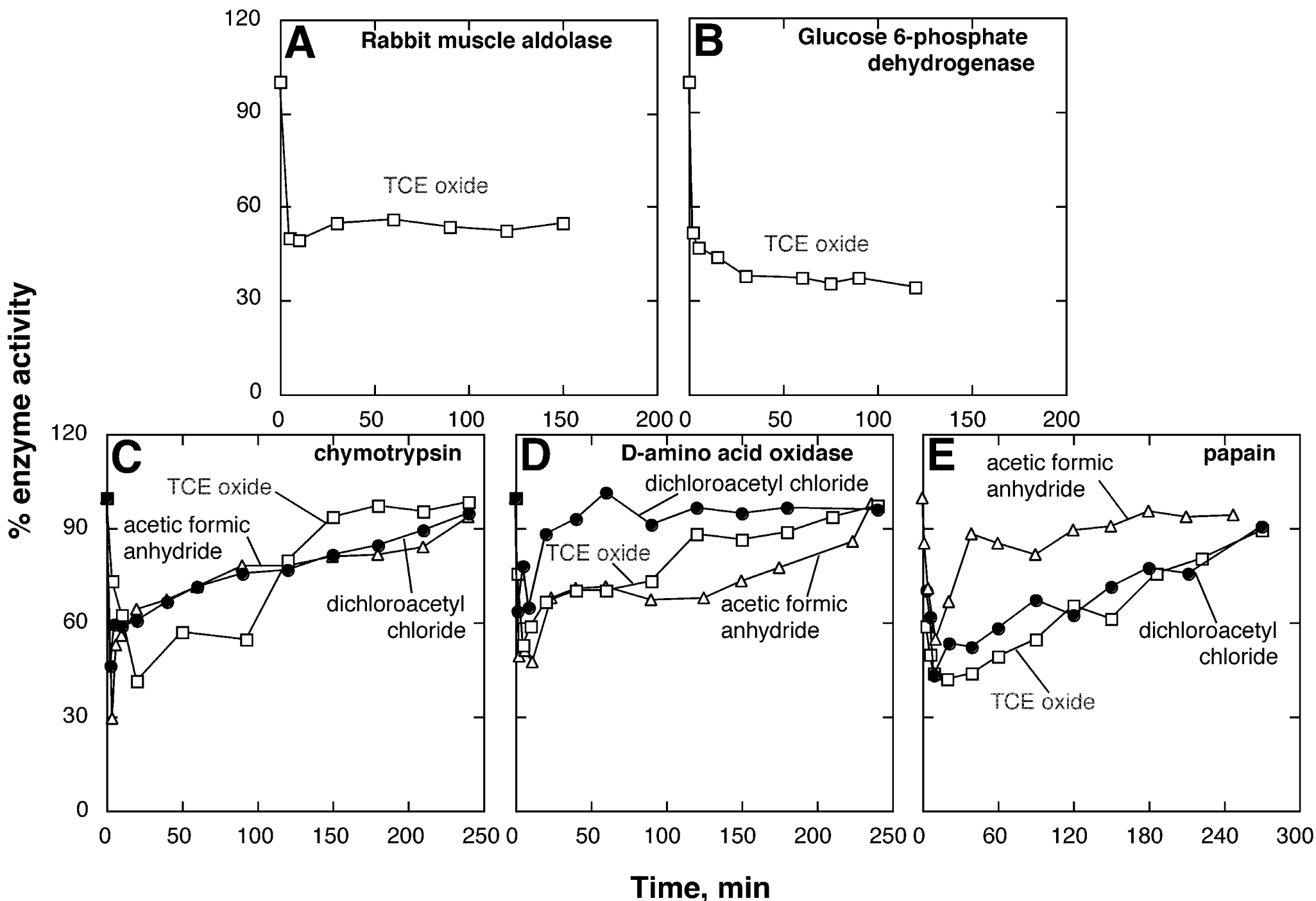


Cai & Guengerich (2001) *Chem. Res. Toxicol.* **14**, 54-61

Reaction of TCE oxide with small proteins: insulin

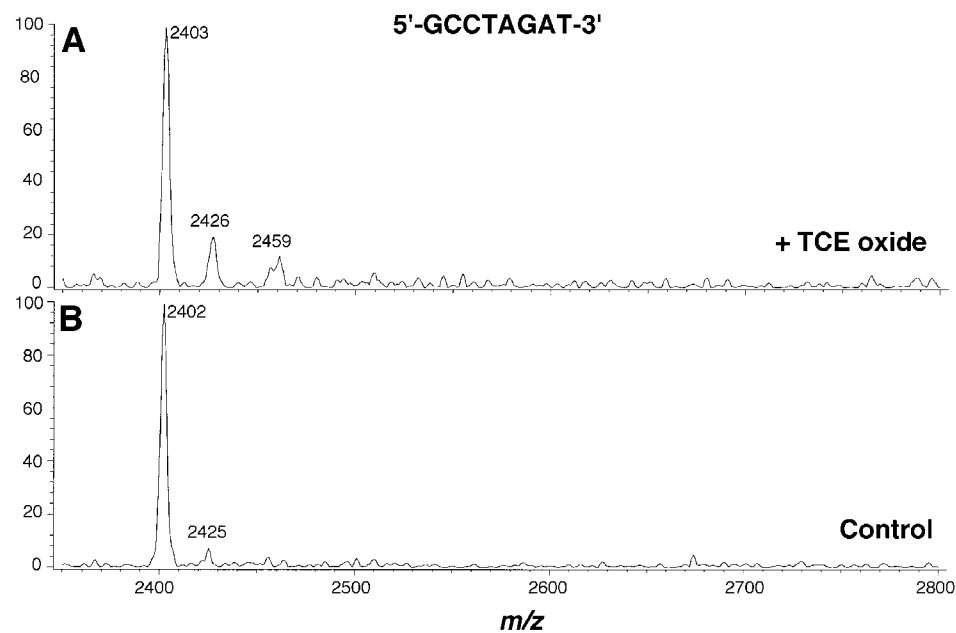


Time Course of Enzyme Activity of Adducted Proteins

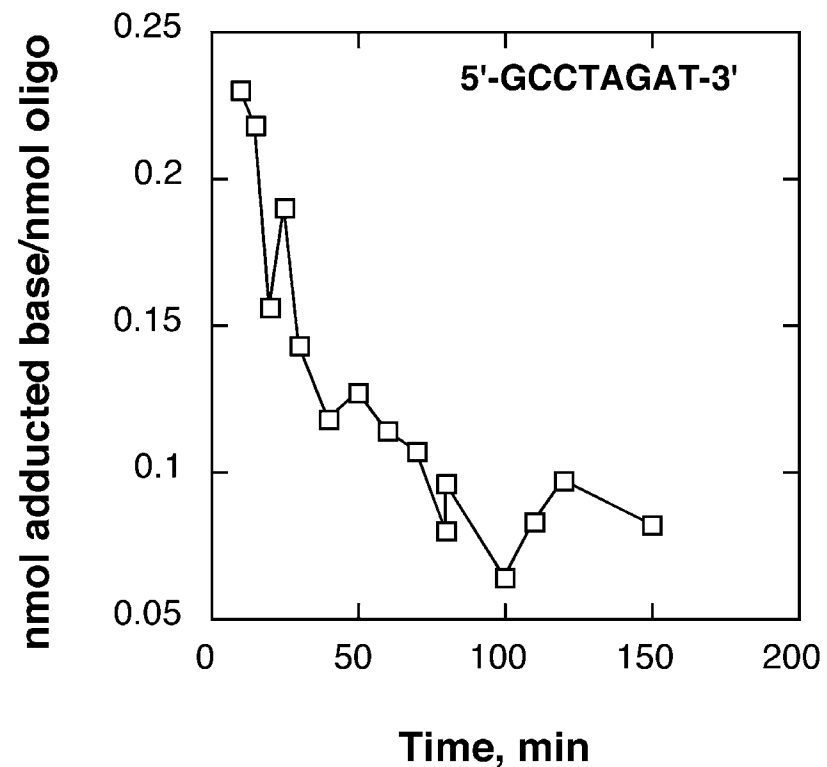


TCE Oxide-Derived 8-mer Oligonucleotide Adducts

Reaction



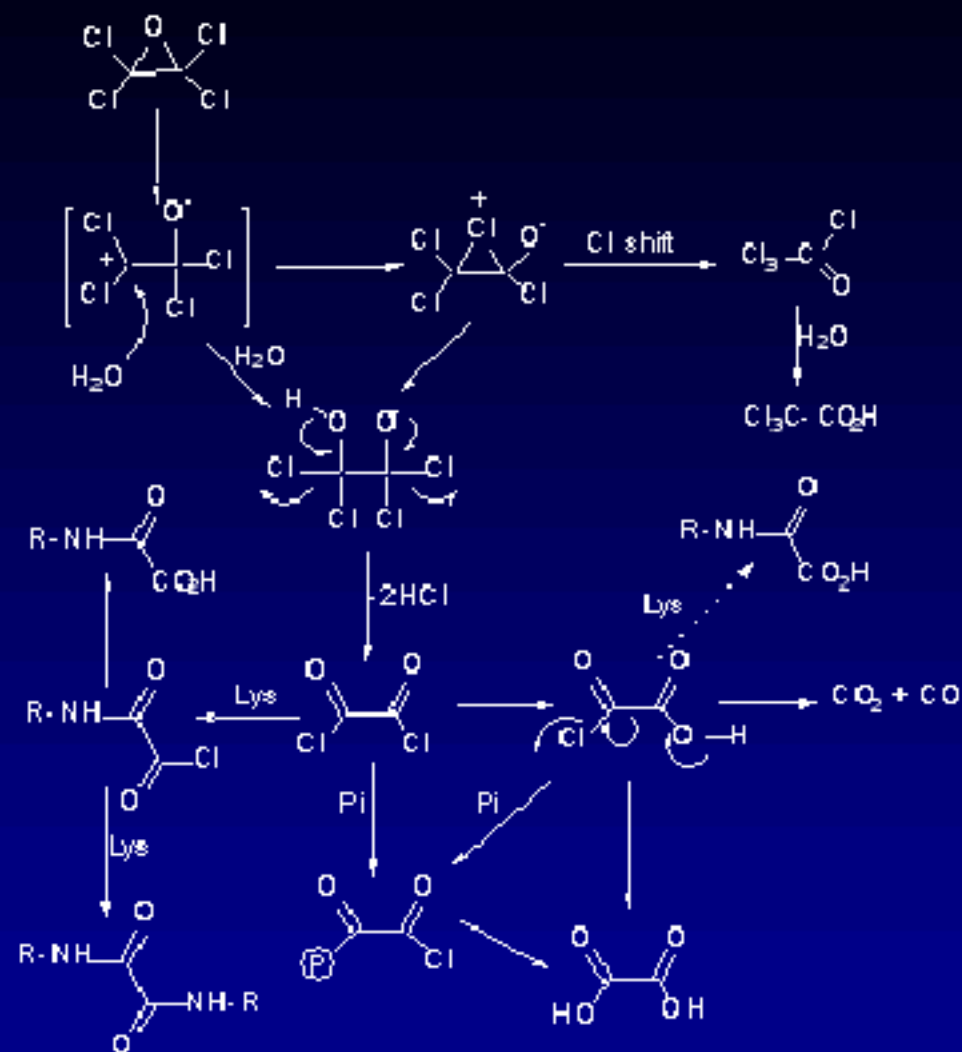
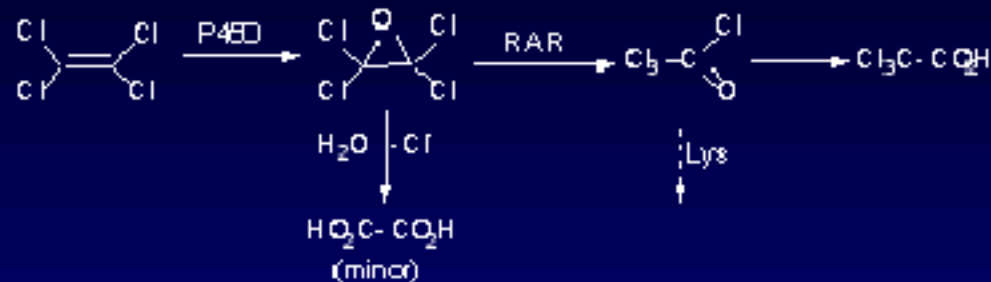
Stability



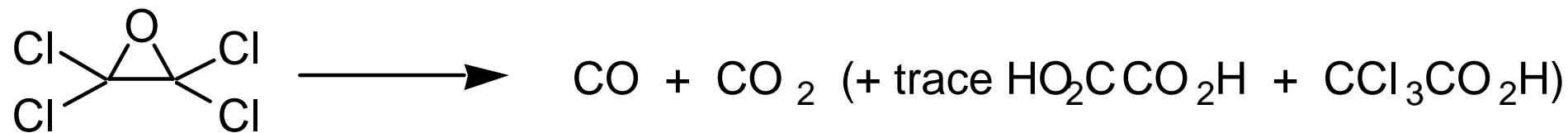
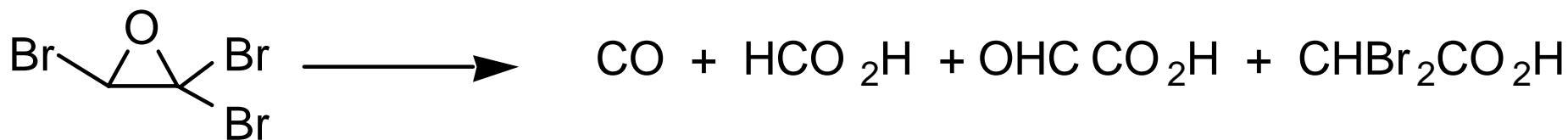
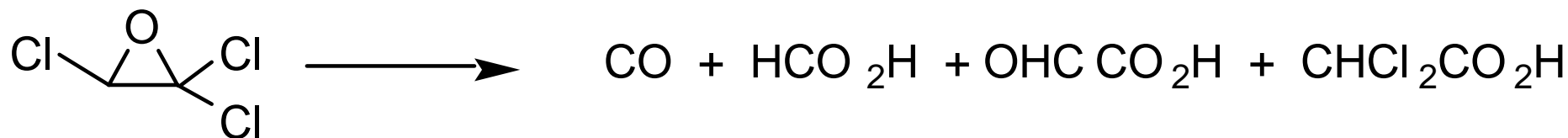
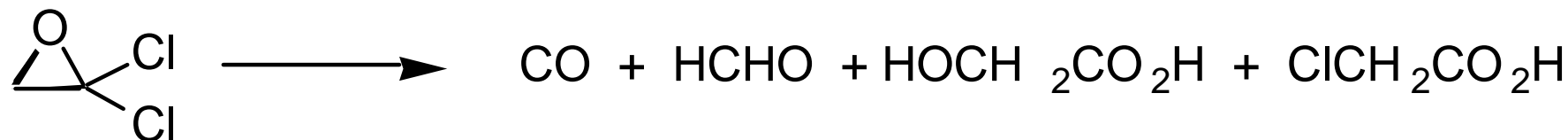
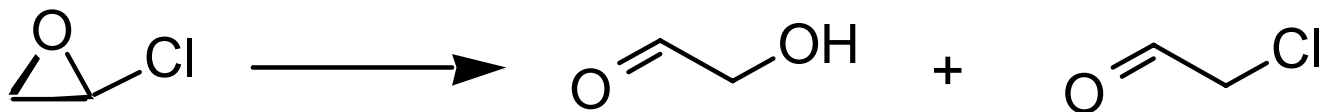
Revised scheme for reactions of perchloroethylene oxide

Literature scheme for formation & reactions of tetrachloroethylene (perchloroethylene)oxide

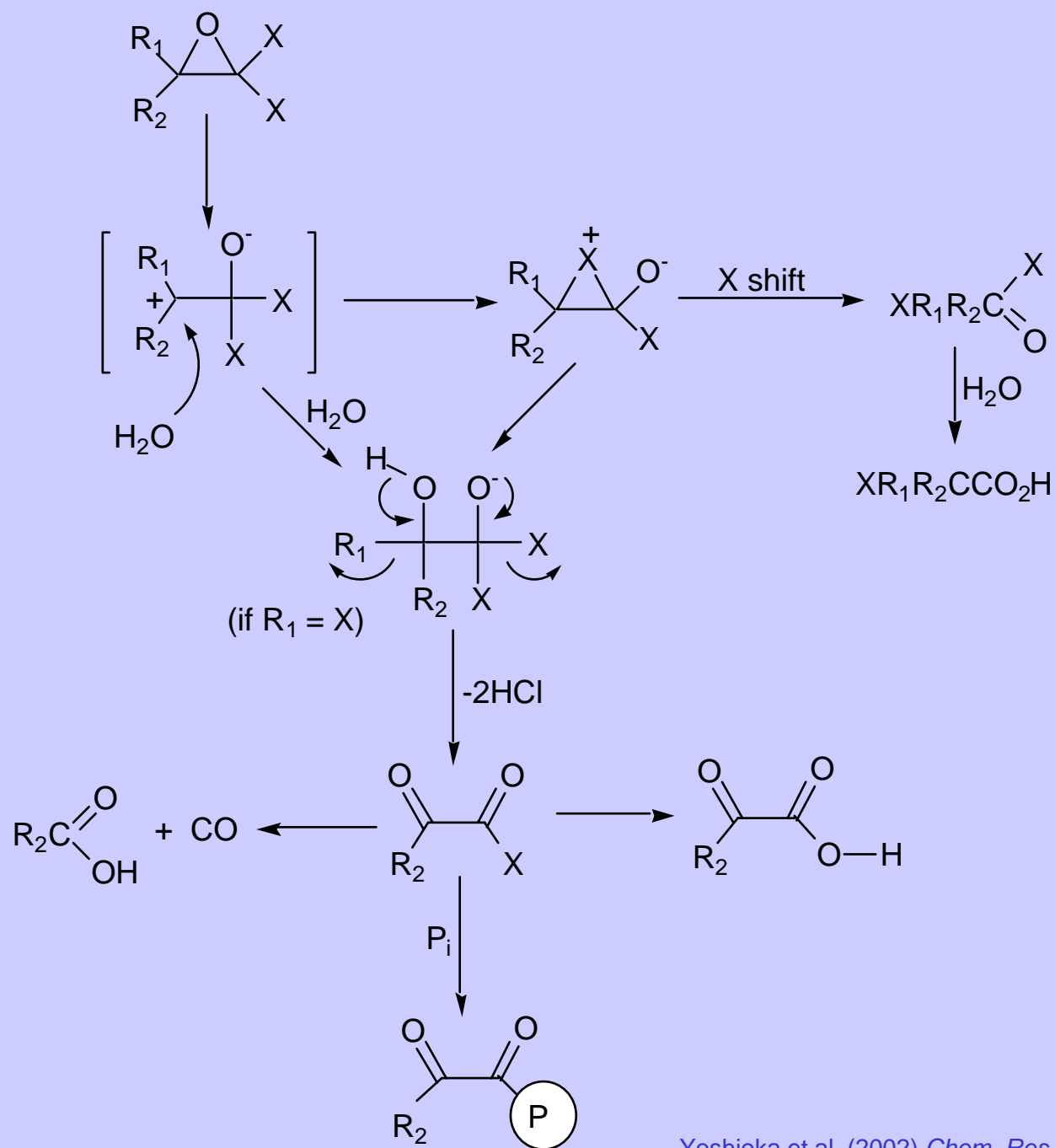
e.g., Rebertus (1963) *Mutation Res.* 123, 411-429



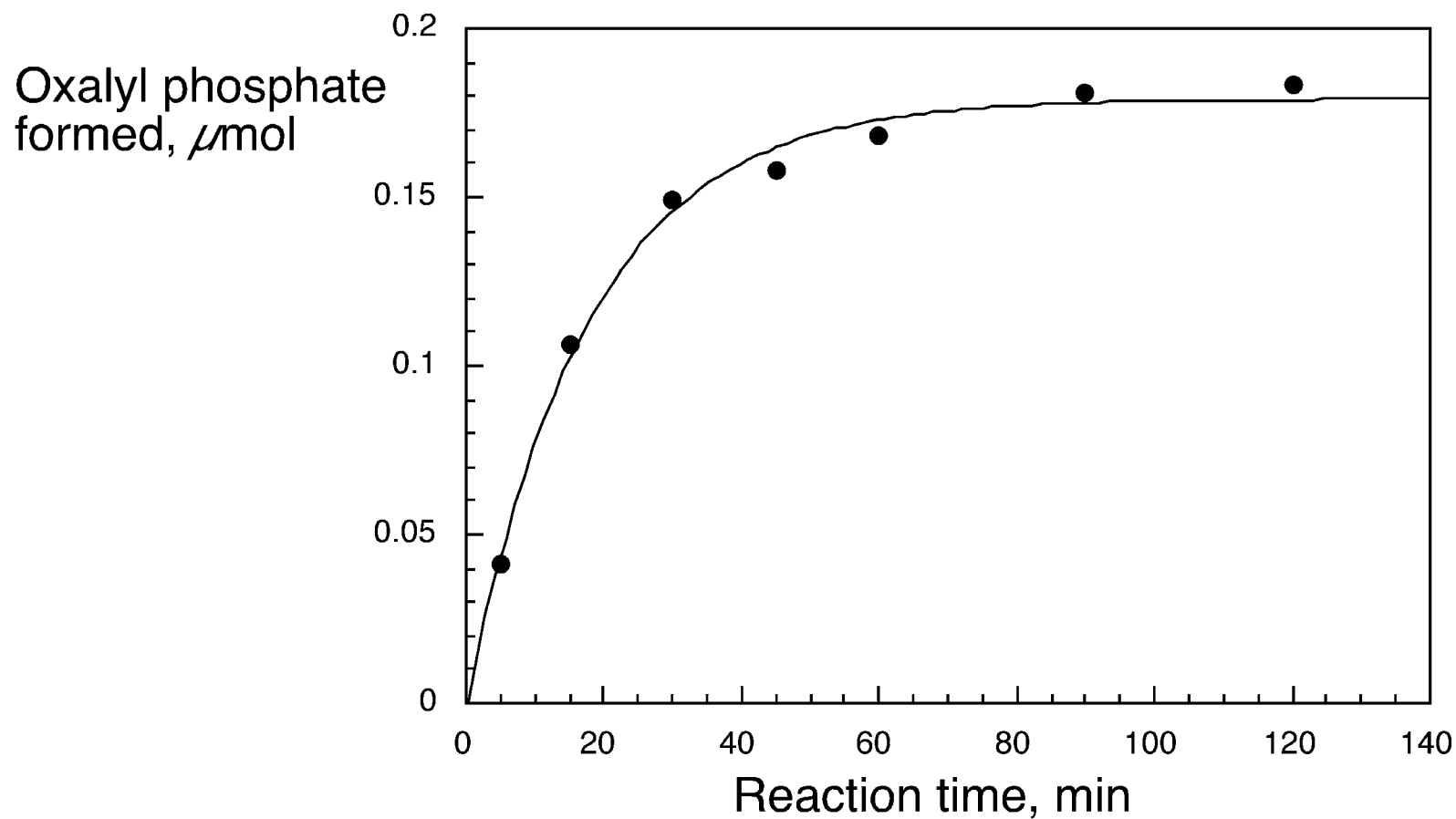
Generality of Halooxirane Hydrolysis



Generality of Halooxirane Hydrolysis



Reaction of Perchloroethylene Oxide with Phosphate Buffer to Form Oxalyl Phosphate



Summary points

- P450 (2E1) + TCE \longrightarrow mainly chloral, some epoxide
- TCE epoxide \longrightarrow acyl halide \longrightarrow reaction with nucleophiles
- Protein reactions: Lys, -OH (Ser, Thr, Tyr) (& phosphate buffer)
- Issue of semi-stable protein adducts
 - Can affect biological activity transiently
 - Does their existence raise or lower risk?
- PBPK models
 - Should not be based on epoxide \longrightarrow chloral
 - Consider human variation in activation process

Hongliang Cai



You didn't just join a lab—it's a fraternity!

Also thanks to T. Yoshioka for PCE & TBE work
& to NIH (R35 CA44353, P30 ES00267, R01 ES10546)

