Metabolism of Trichloroethylene & Covalent Binding of Reaction Products

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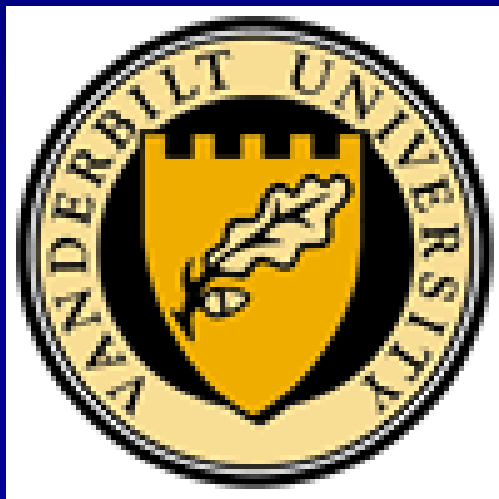

Trichloroethylene in Dickson (TN), 2003

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

Brockovich to investigate Dickson landfill

Cochran's law firm shows interest in Dickson landfill

Legal eagles may fall flat

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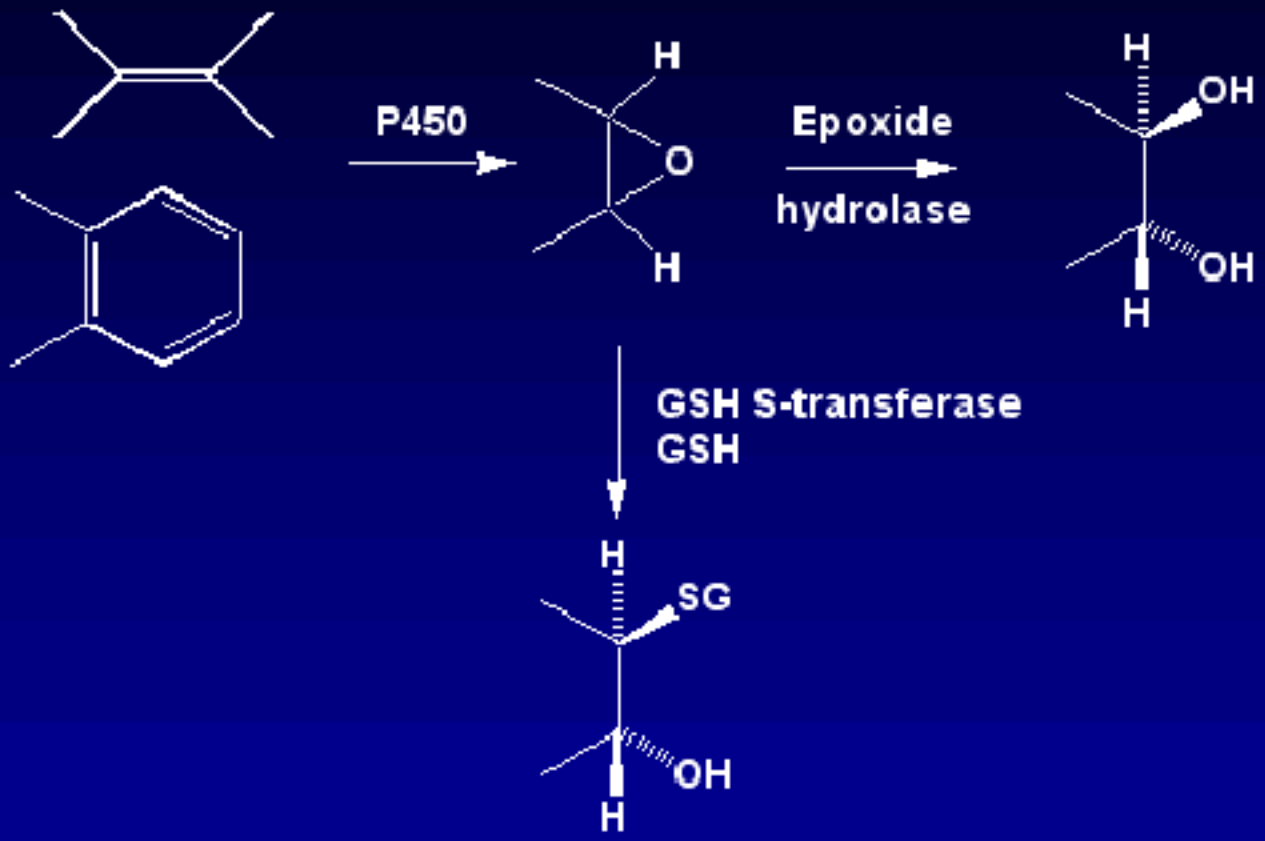
Enzymatic formation & reactions of epoxides

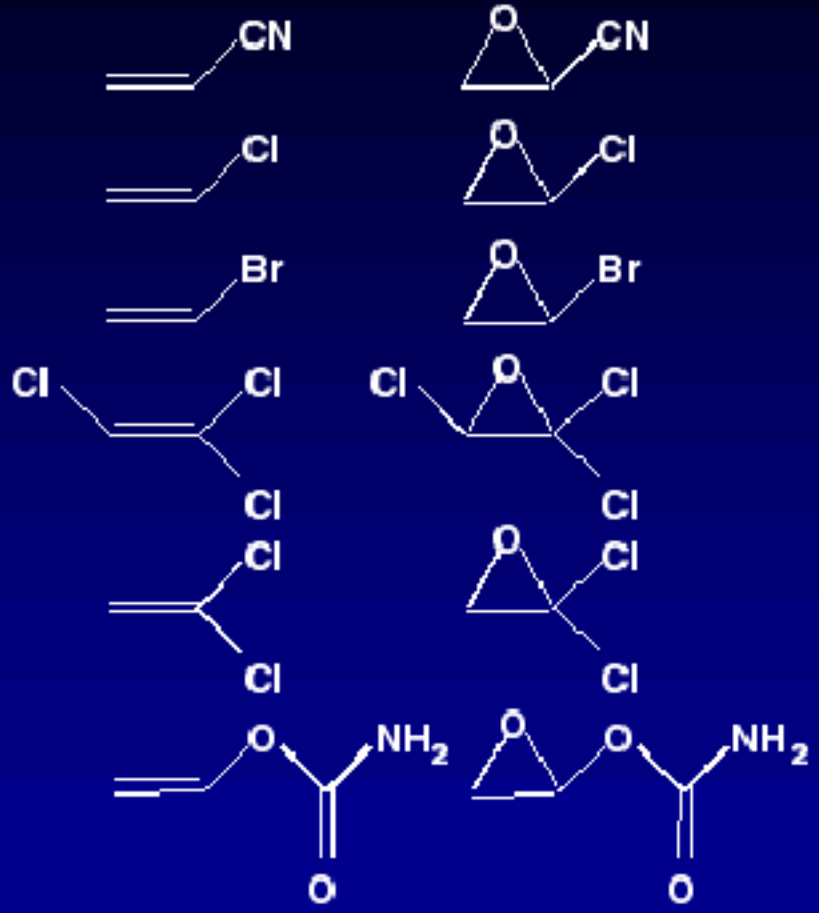


Epoxide stability: relation to biological activity

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

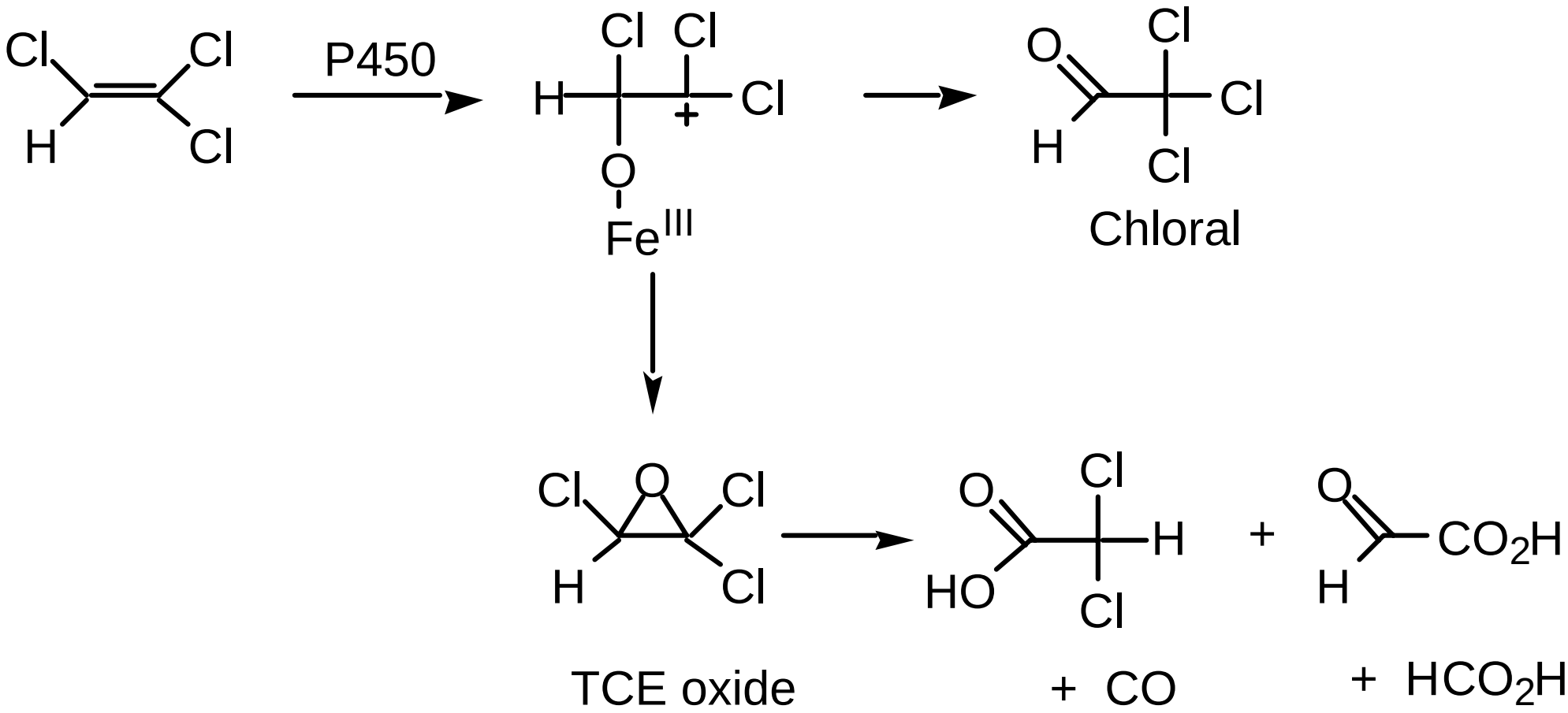
	$t_{1/2}$, min	Conc. needed to unwind superhelical DNA, mM	*S. typh.* TA98 revertants/ nmol
Benzo[*a*]pyrene diol epoxide	38	0.023	460
1-Phenyloxirane	46	0.027	540
9-Methyl-10-anthryloxirane	21	0.10	110
6-Chrysenyloxirane	141	0.22	70
9-Anthryloxirane	172	0.24	53
9-Phenanthryloxirane	140	0.9	25
2-Benzanthryloxirane	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



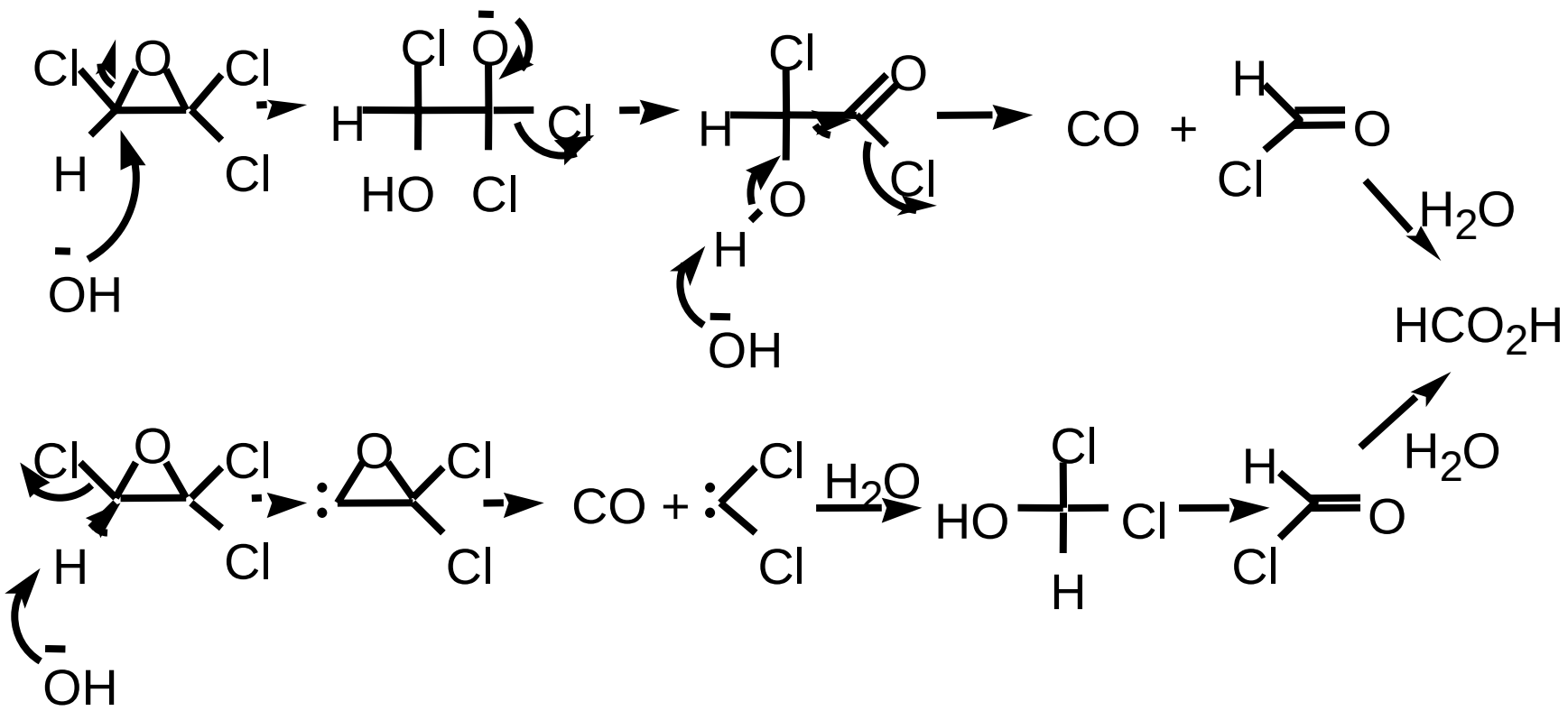
	$t_{1/2}$, s (23° C)
	7200
	90
	40
	12
	~2
	60
	1

Oxidation of trichloroethylene (TCE) by P450



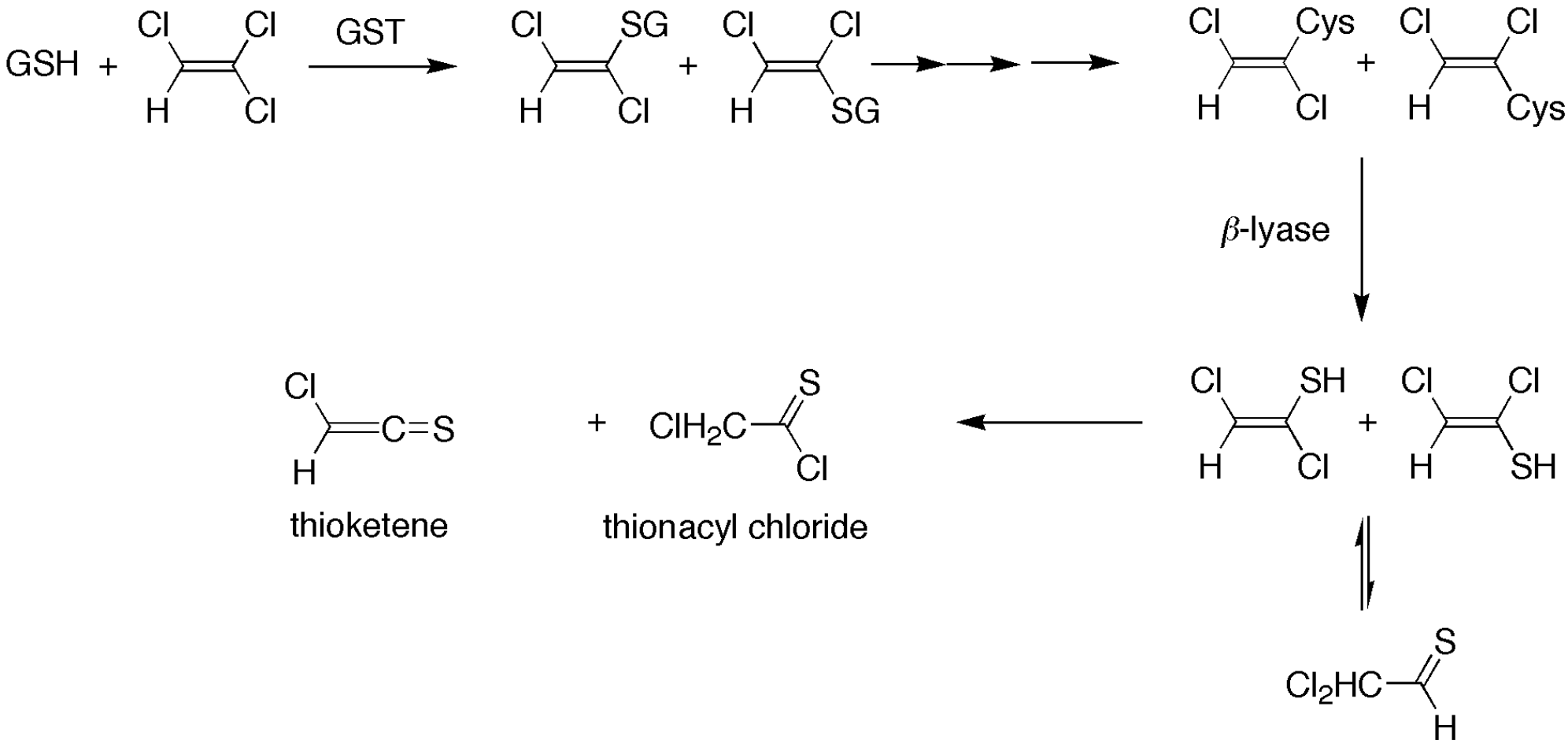
Miller & Guengerich (1982) *Biochemistry* **21**, 1090-1097

Some possible mechanisms for scission of TCE oxide



Miller & Guengerich (1982) *Biochemistry* **21**, 1090-1097

Activation of TCE by GSH conjugation



For review see Goeptar et al. (1995) *Chem. Res. Toxciol.* **8**, 3-21

Carcinogenic Substrates for Human P–450 Enzymes

P–450 1A1	P–450 1A2	P–450 2E1	P–450 3A4
B(a)P	2–NH_2 anthracene	Me_2N–N=O	Aflatoxin B_1
	2–AAF	Et_2N–N=O	Aflatoxin G_1
	2–NH_2 fluorene	Me, propyl N–N=O	Sterigmatocystin
	4–NH_2 biphenyl	Me, benzyl N–N=O	B(a)P–7,8–diol
	2–Naphthylamine	Vinyl Cl	BA–3,4–diol
	Glu P–1	Vinyl Br	DMBA–3,4–diol
	Glu P–2	Acrylonitrile	BFA–9,10–diol
	IQ	Vinyl carbamate	*tris*(2,3–Br_2 propyl)PO_4
	MeIQ	Urethan	6–NH_2 chrysene
	MeIQx	Styrene	MOCA
	PhIP	Benzene	Senecionine
	Trp P–2	CCl_4	
	NNK	$CHCl_3$	
		Trichloroethylene	

Re TCE, see Guengerich et al. (1991) *Chem. Res. Toxciol.* **4**, 168-179

Variability in human enzymes (expression level/activity)

- P450 2E1 & GST T1-1 (CH_2Cl_2 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

		Uncertainty factor
P450 2D6: non-phenotyped aducts, EMs		2.7-4.1
	PMs	15-18
	Children	22-45

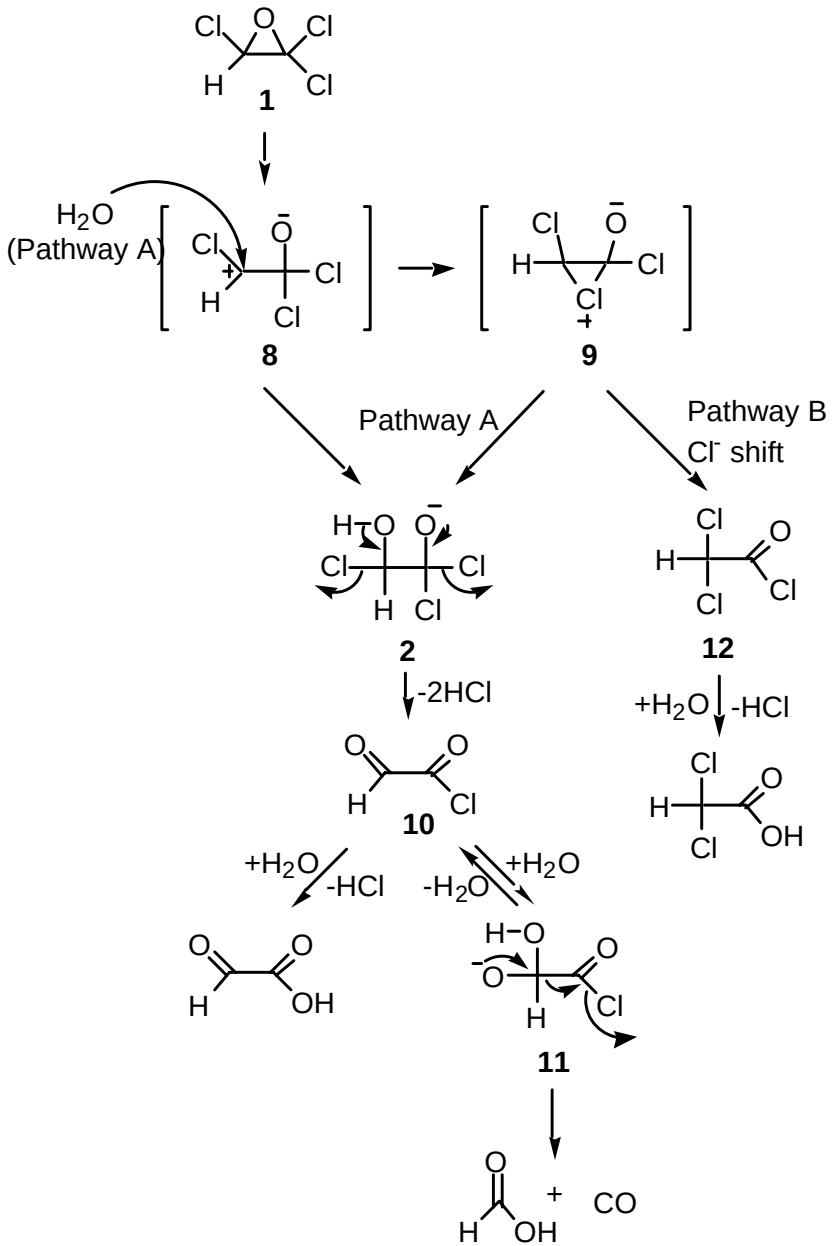
Doren et al. (2003) *Food Chem. Toxicol.* **41**, 201-224

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

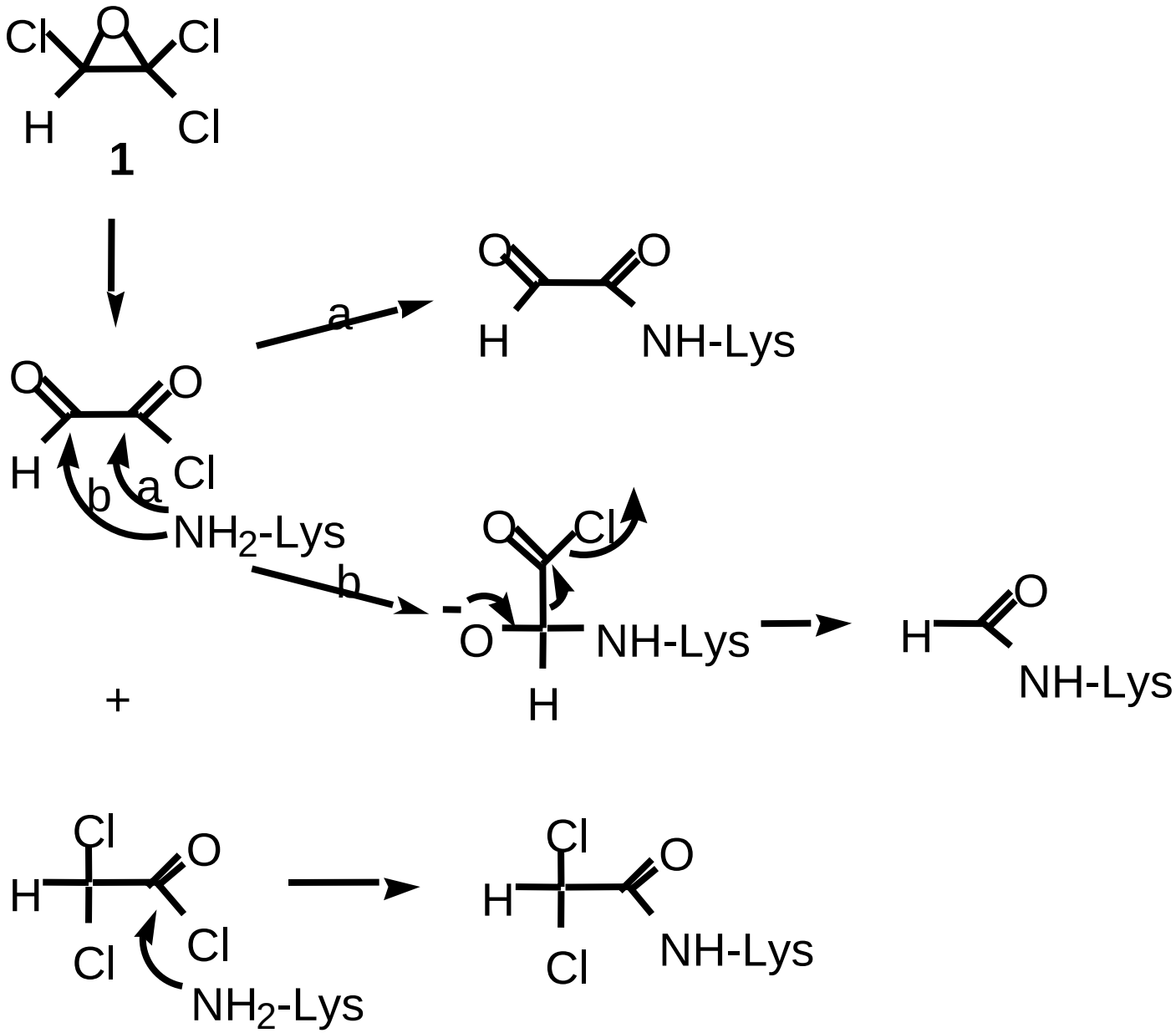
(determined by ^{18}O & ^{2}H labeling & mass spectrometry)



Cai & Guengerich (1999) *J. Am. Chem. Soc.* **121**, 11656-11663

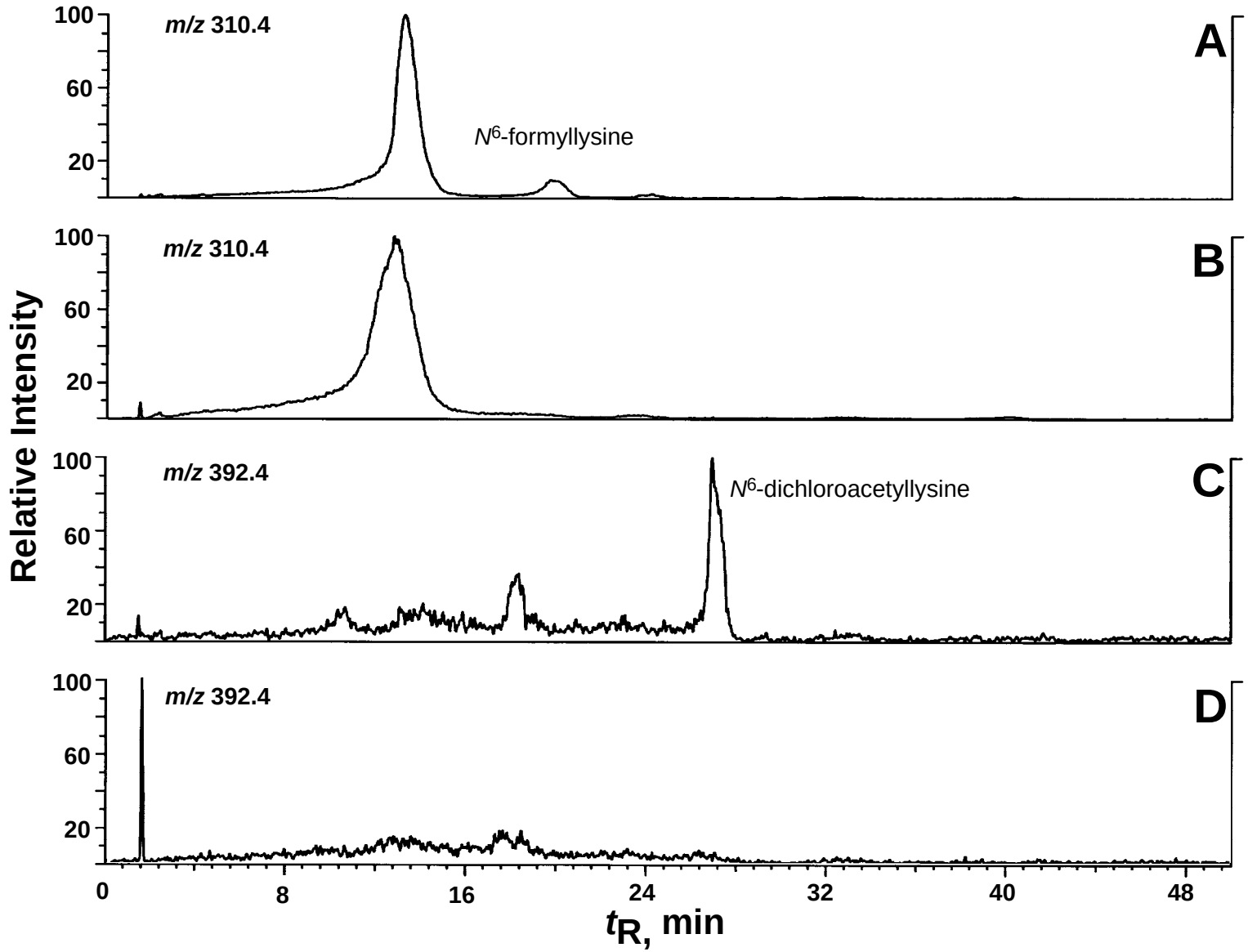
Mechanisms of reaction of TCE oxide with lysine

(determined by ^{18}O & ^{2}H labeling & mass spectrometry)



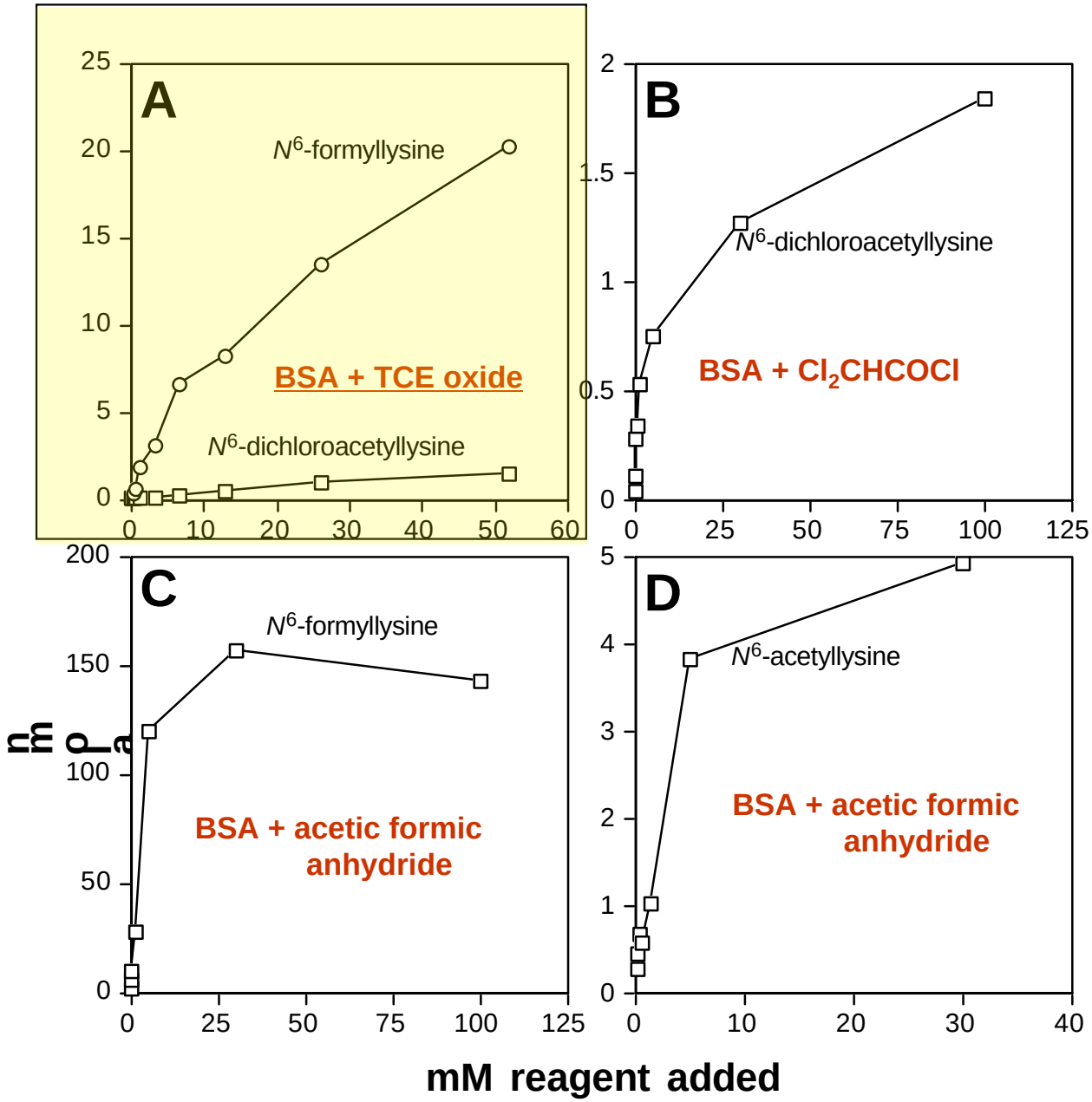
Cai & Guengerich (1999) *J. Am. Chem. Soc.* **121**, 11656-11663

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



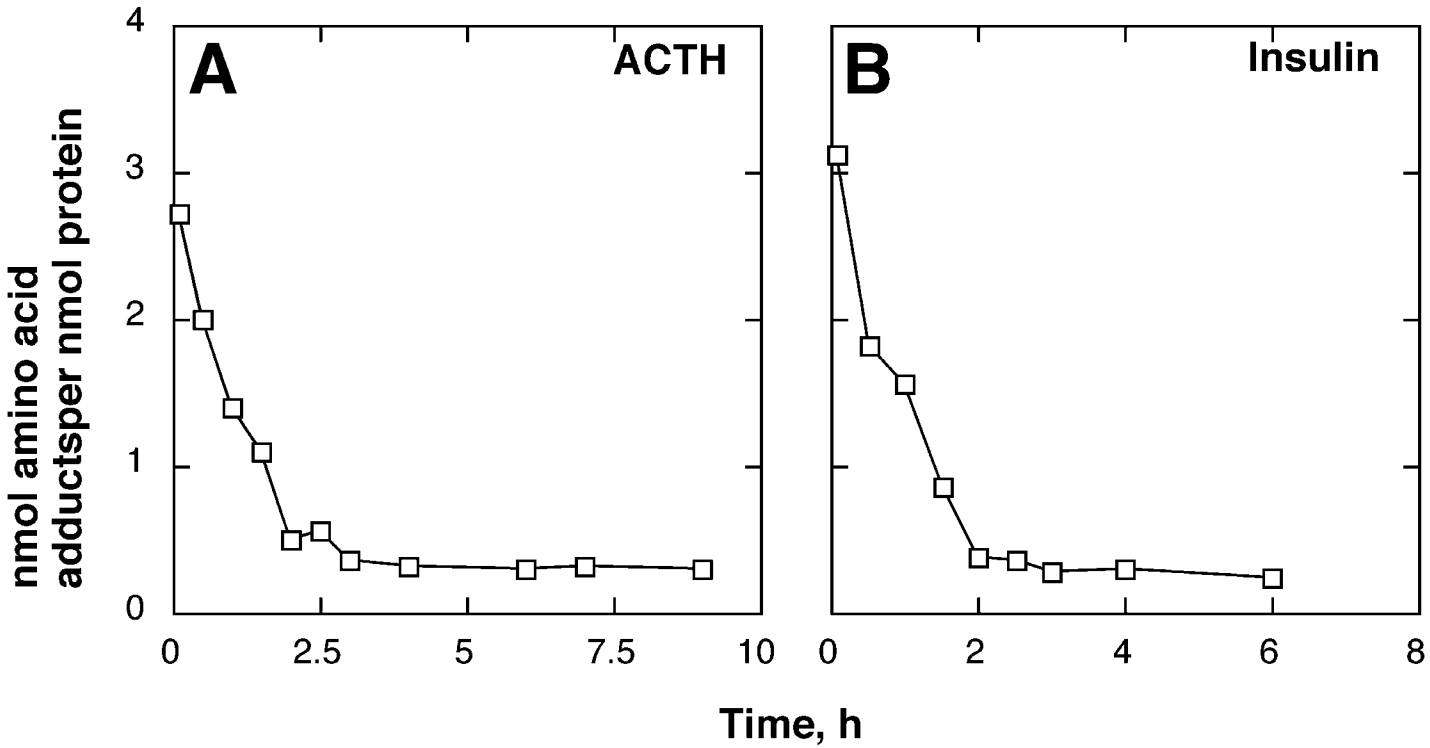
Cai & Guengerich (1999) *J. Am. Chem. Soc.* **121**, 11656-11663

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



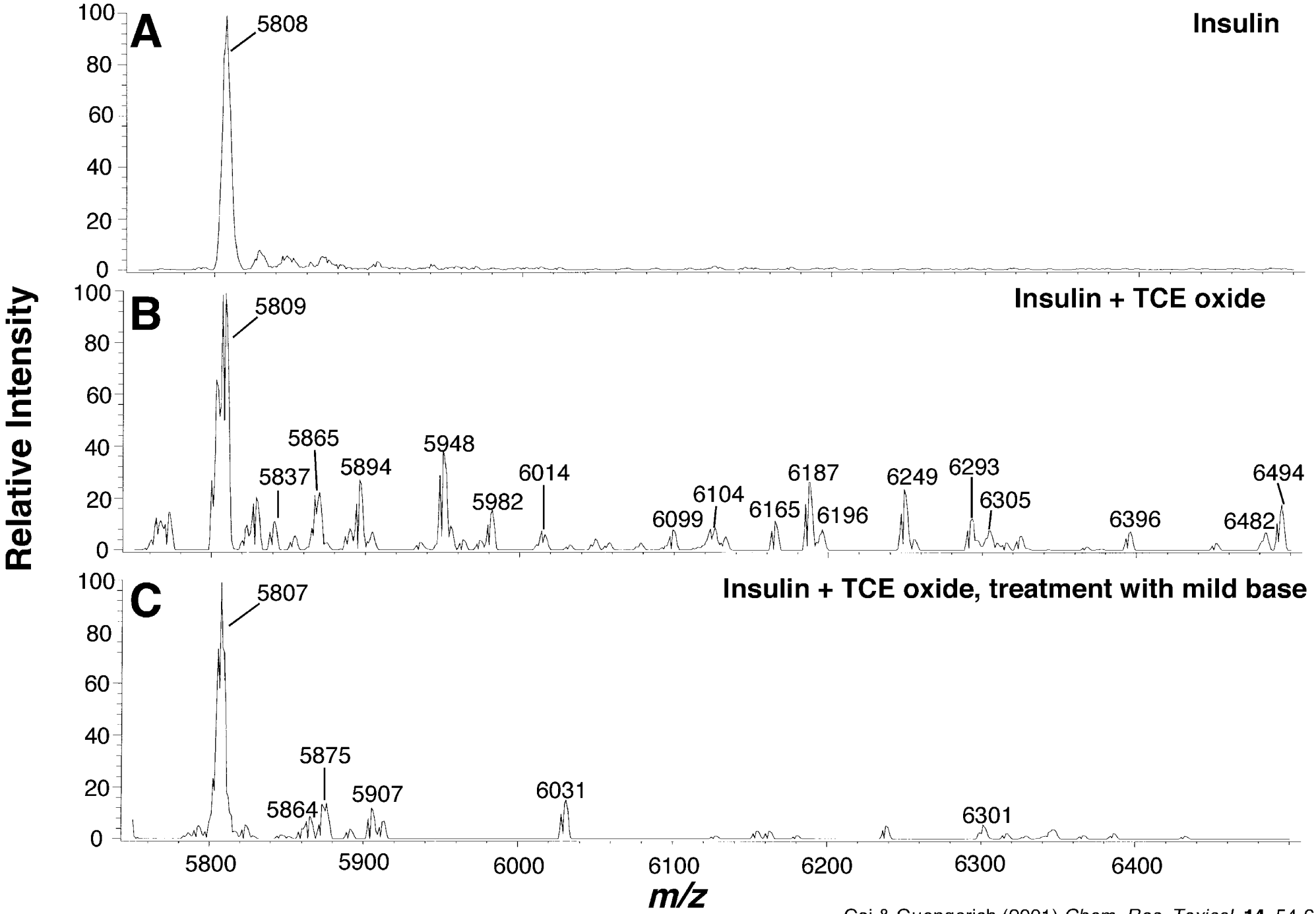
Cai & Guengerich (2000) *Chem. Res. Toxicol.* 13, 327-335

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



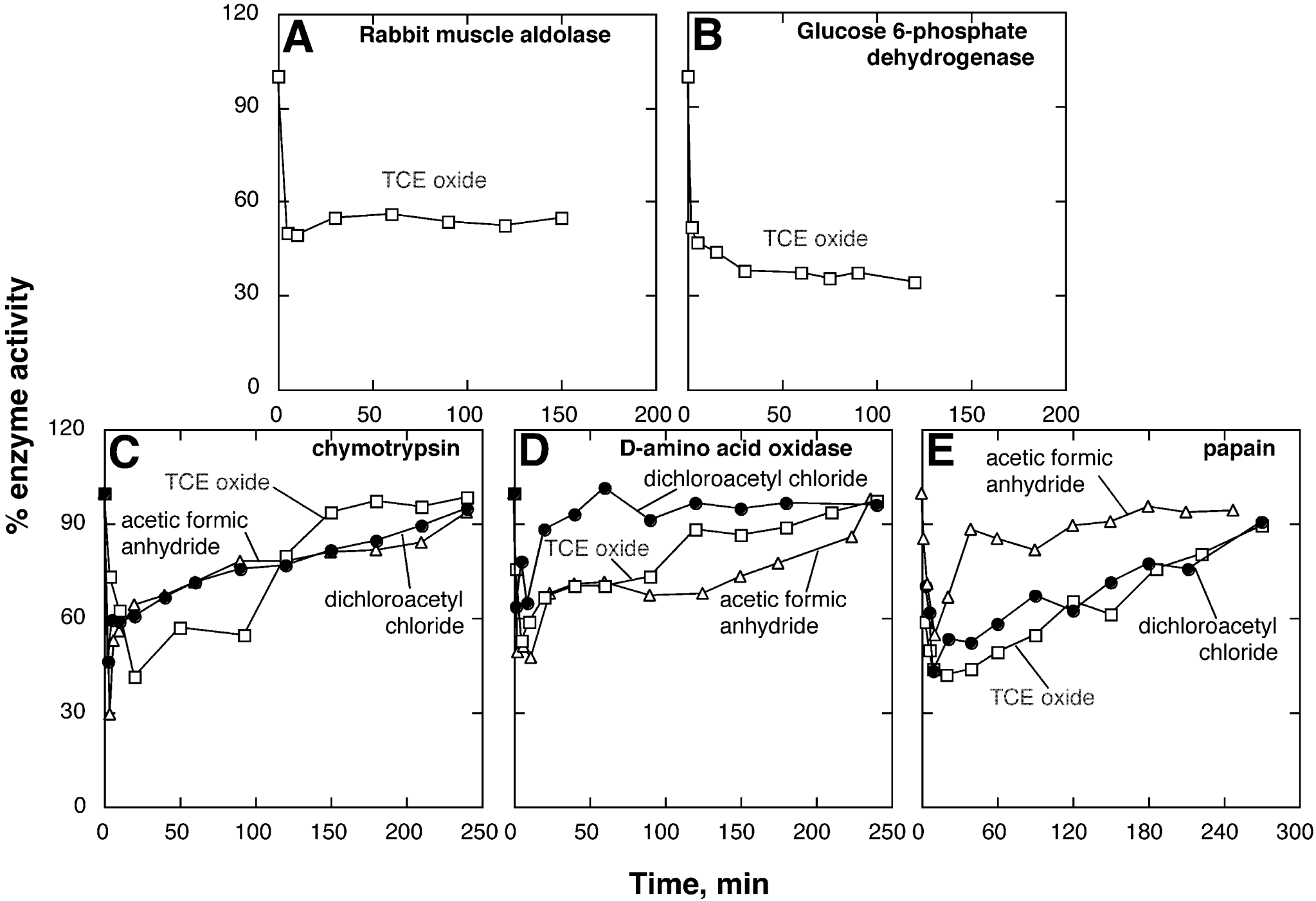
Cai & Guengerich (2001) *Chem. Res. Toxicol.* **14**, 54-61

Reaction of TCE oxide with small proteins: insulin



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

Time Course of Enzyme Activity of Adducted Proteins



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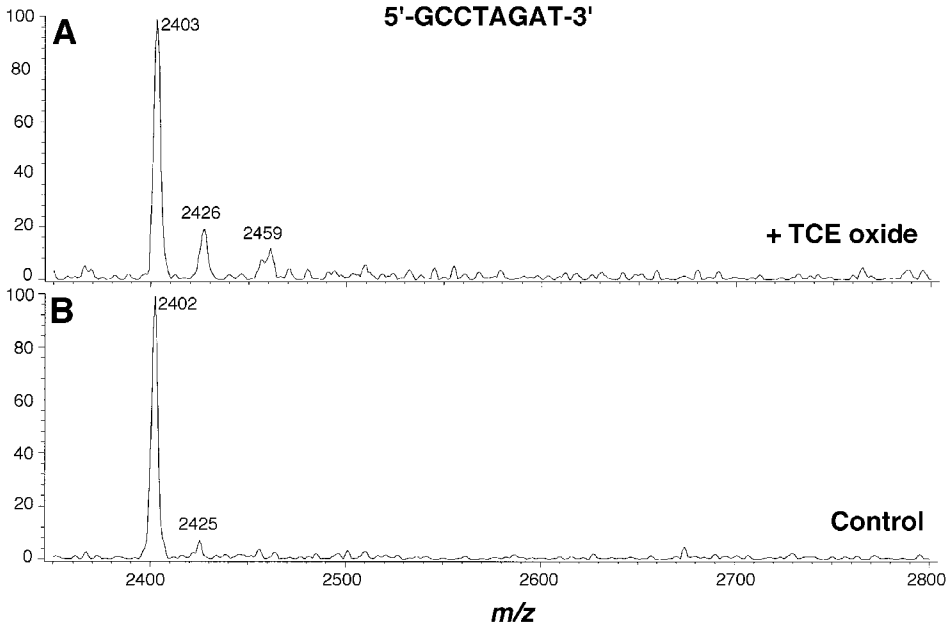
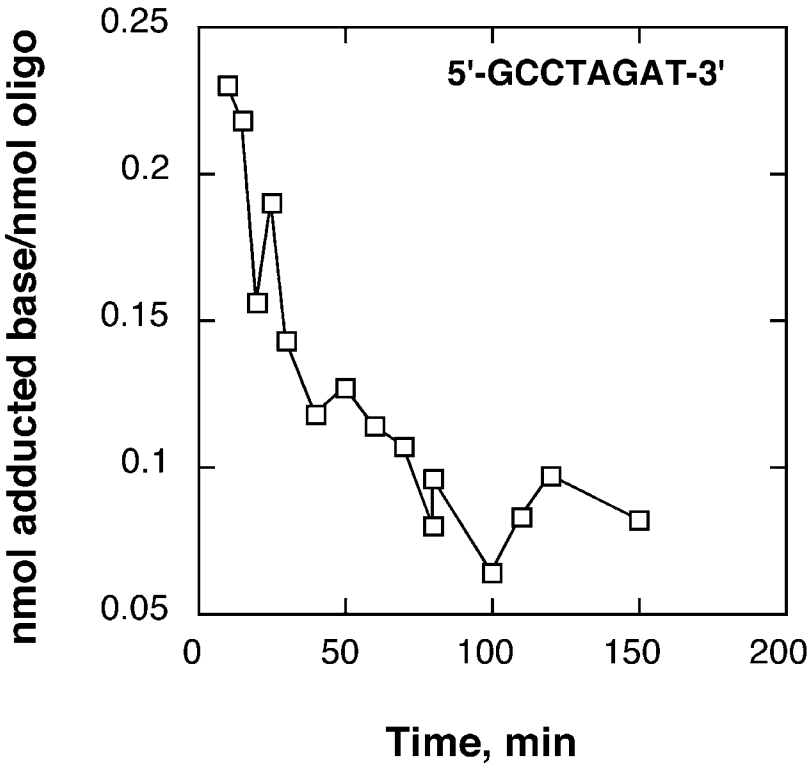
TCE Oxide-Derived 8-mer Oligonucleotide Adducts

Reaction



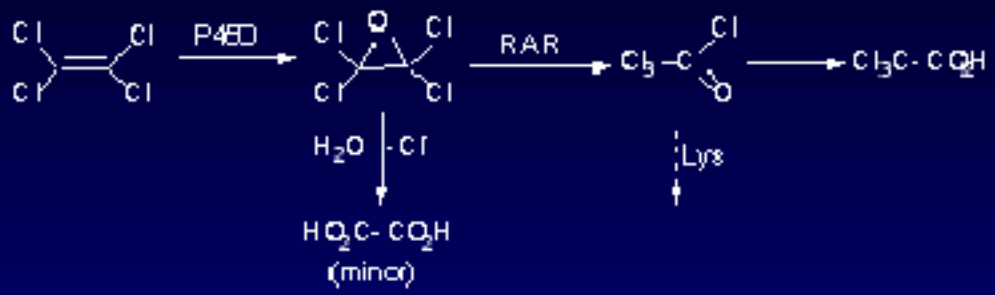
Stability



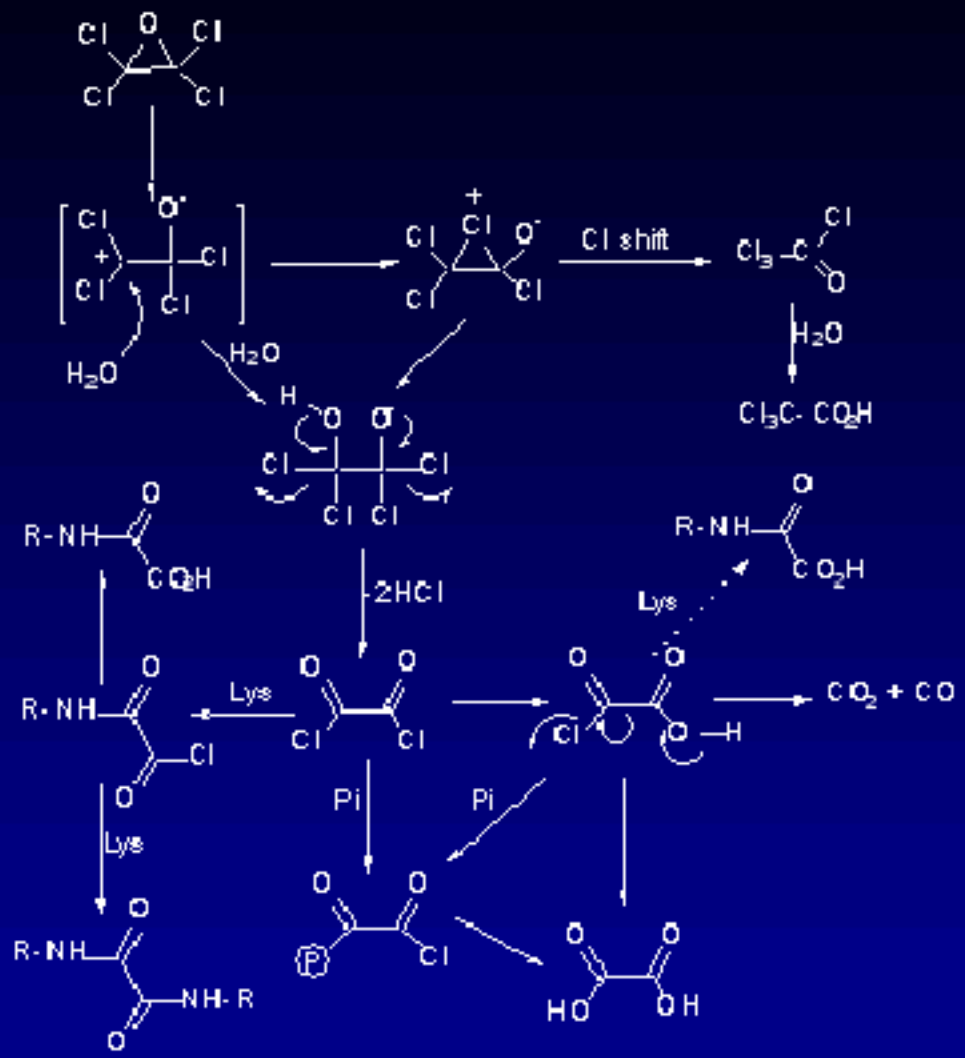
Cai & Guengerich (2001) *Chem. Res. Toxicol.* **14**, 54-61

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

e.g., Reichert (1983) *Xenobiotica* Res.123, 411-429)

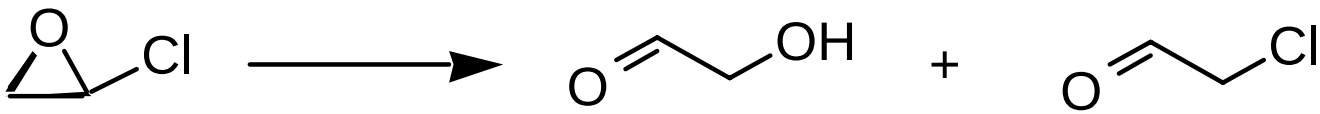


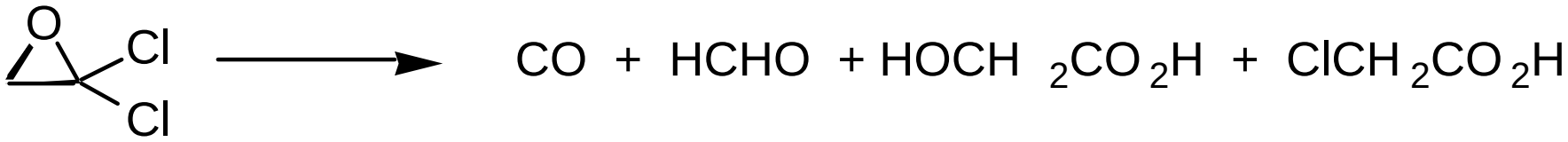
Revised scheme for reactions of perchloroethylene oxide

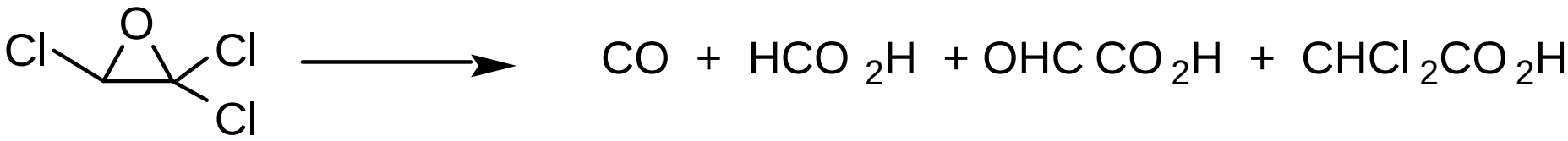


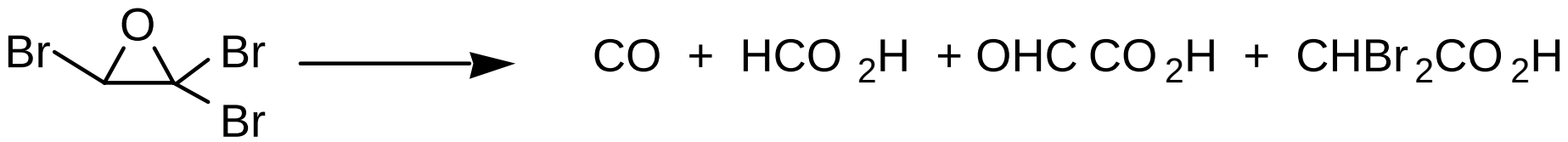
Yoshioka & Guengerich (2002) *Chem. Res. Toxicol.* **15**, 1096-1105

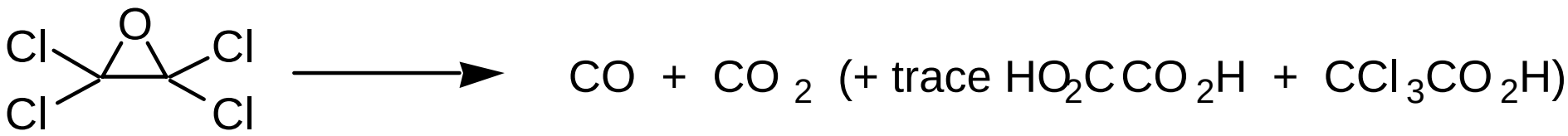
Generality of Halooxirane Hydrolysis











Yoshioka et al. (2002) *Chem. Res. Toxicol.* **15**, 1414-1420

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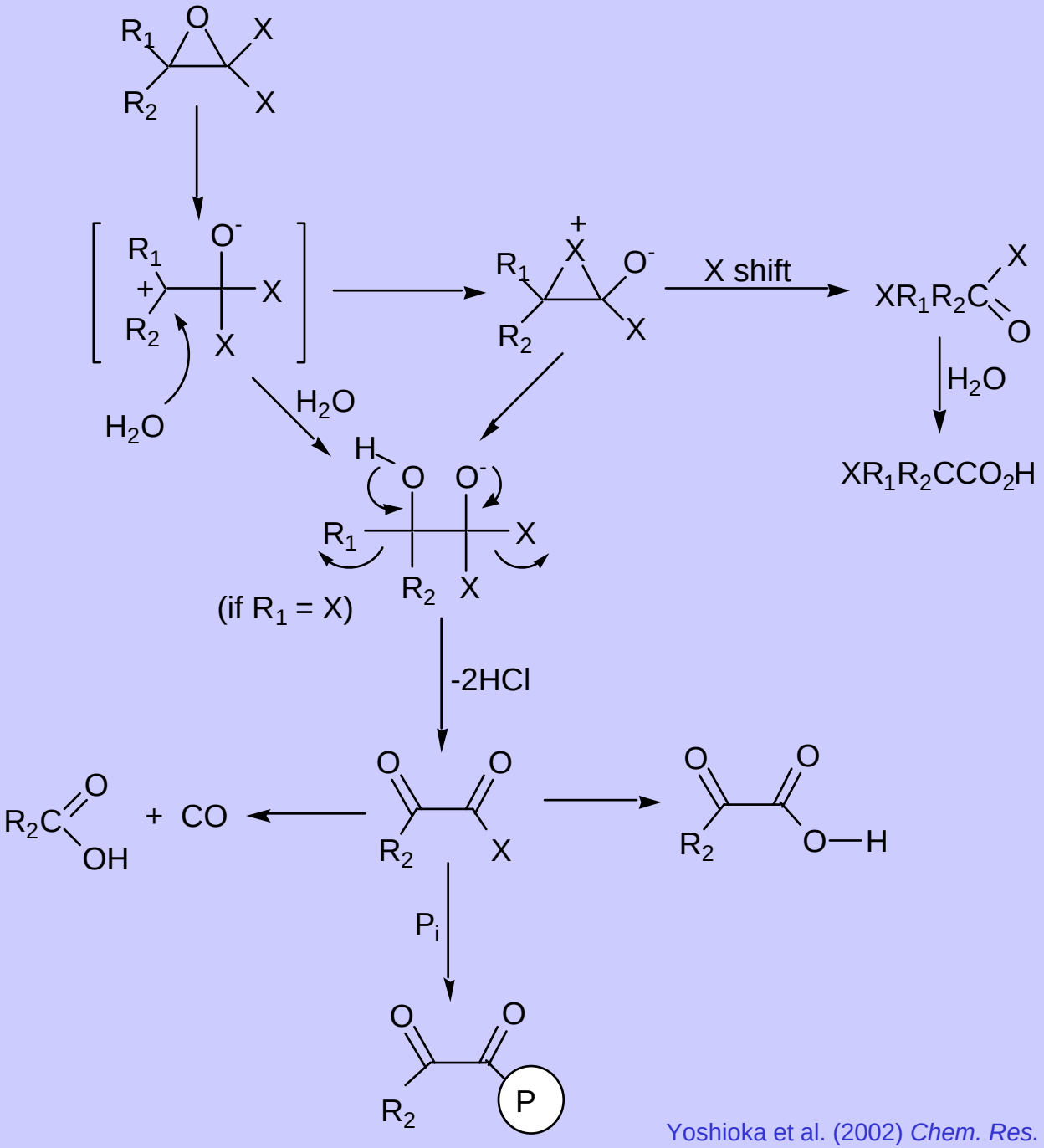
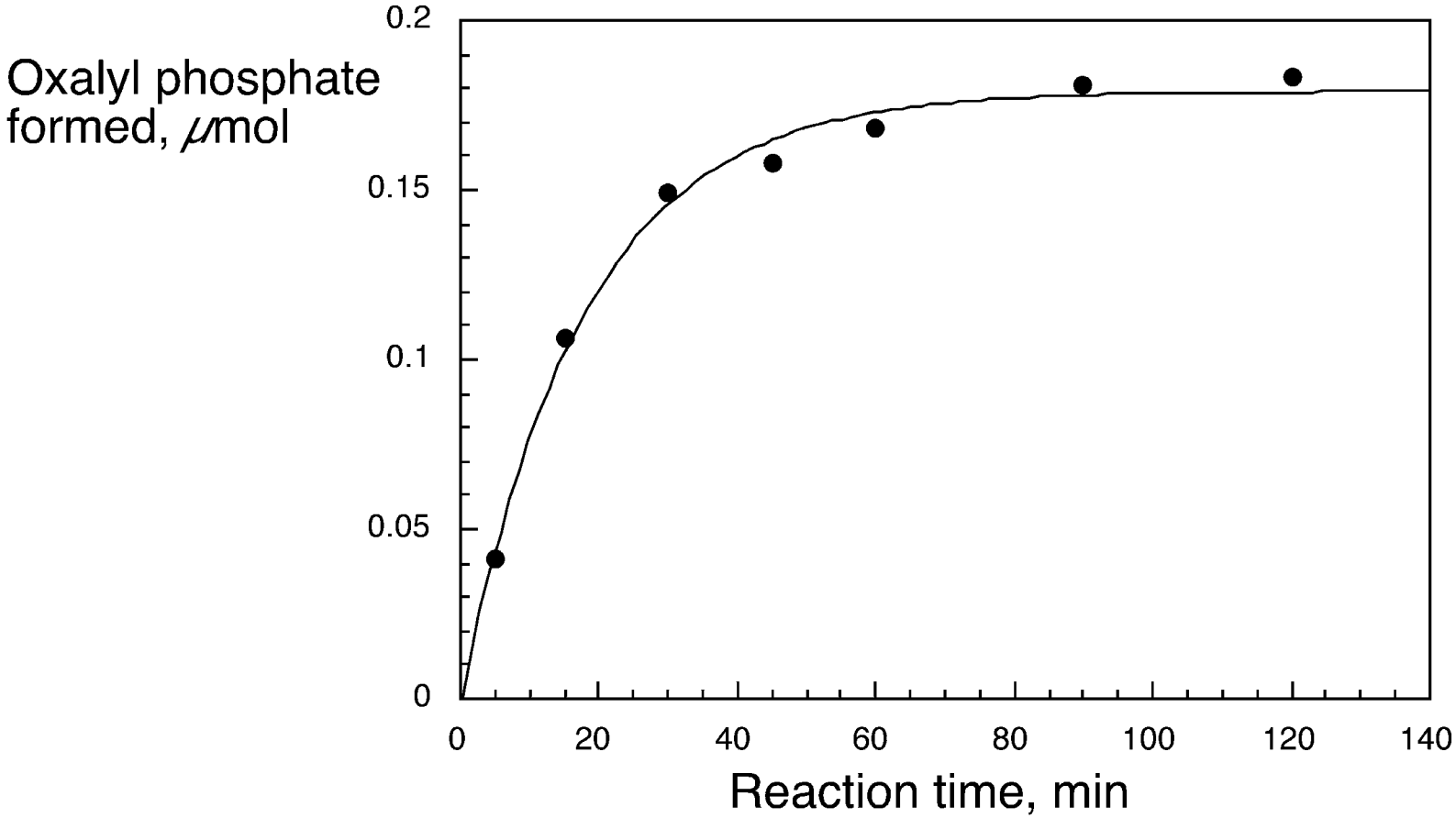


Yoshioka et al. (2002) *Chem. Res. Toxicol.* **15**, 1414-1420

Reaction of Perchloroethylene Oxide with Phosphate Buffer to Form Oxalyl Phosphate



Yoshioka & Guengerich (2002) *Chem. Res. Toxicol.* **15**, 1096-1105

Summary points

- P450 (2E1) + TCE ⟶ mainly chloral, some epoxide
- TCE epoxide ⟶ acyl halide ⟶ 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 ⟶ chloral
  - Consider human variation in activation process

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)