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Enantioselective Oxidation of Sulfides Catalyzed by Iron Complexes of Chiral "Twin Coronet" Porphyrins

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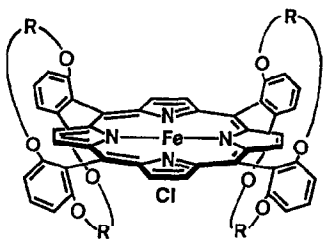
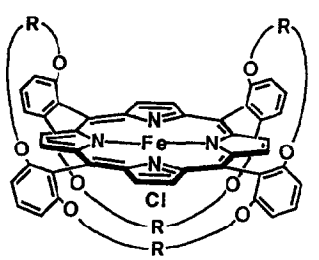
Abstract: Ferric porphyrins bearing chiral binaphthalene moieties on their both faces catalyze asymmetric oxidation of sulfides with iodosobenzene as an oxidant in moderate to good optical and chemical yields. Enantiomeric excesses (e.e.) were markedly improved in 2-3 times by the addition of 1-methylimidazole. The mechanism of oxidation and chiral induction are discussed.

Chiral sulfoxides have been proven to be useful chiral synthons upon C-C bond formation on account of their high diastereoselectivity.[1] General method for the synthesis of chiral sulfoxides with high enantiomeric purities is currently desired. Direct oxidation, especially catalytic reactions, of prochiral sulfides to chiral sulfoxides in high efficiency is considered to be the most attractive route. However, only a stoichiometric reaction using a Sharpless-type reagent has attained successful results so far.[2] Moreover, reconstituted cytochrome P-450 enzymes showed low enantioselectivity in the oxygenation of sulfides,[3] in contrast to flavin dependent oxygenases.[4]

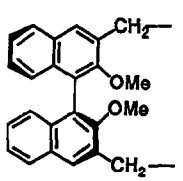


(*S*)-1:*'eclipsed'*



(*S*)-2:*'staggered'*

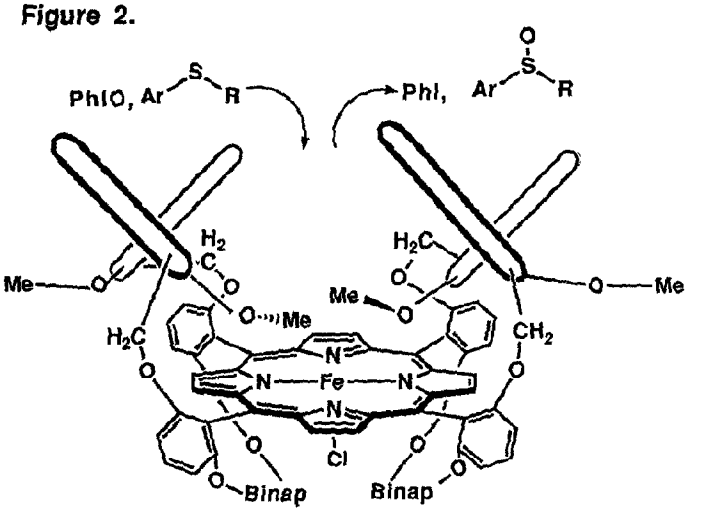
R=



(*S*)

Figure 1.

Figure 2.



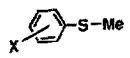
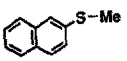
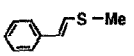
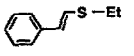
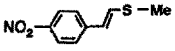
(*S*)-1

Some kinds of synthetic chiral porphyrins as cytochrome *P-450 models*[5] have been reported to catalyze enantioselective oxidation.[6] We also synthesized C_2 symmetric "twin coronet" porphyrins, which have chiral binaphthalene auxiliaries linked by ethereal bonds on both faces (Figure 1). The two binaphthalene moieties facing each other over the macrocycles can form chiral rigid cavities on the both sides and block the formation of the corresponding unreactive μ-oxo dimer and the oxidative decomposition of porphyrin rings, allowing the approach of substrates and oxidant to the active metal center (Figure 2). It was previously shown that the iron complexes (**1** and **2**) were effective catalysts for asymmetric epoxidation of styrene derivatives[7,8] and selective oxidation of aryl alkyl sulfides to the corresponding sulfoxides.[9] We disclose herein a full detail of the enantioselective oxidation of various sulfides catalyzed by the iron porphyrins (**1** and **2**) and discuss the mechanism of oxygen transfer and chiral induction. It is proposed that oxidation proceeds via initial electron transfer from substrate to oxenoid species and that the steric hindrance around the sulfur atoms dominates prochiral face recognition.

Results and Discussion

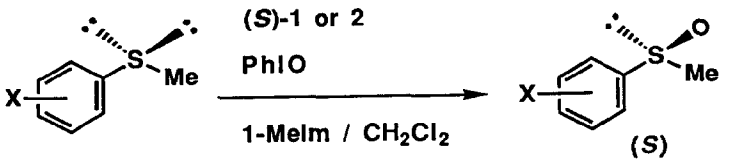
Catalytic and asymmetric oxidation by the catalyst (**1** or **2**) and iodosobenzene was performed as follows: the chiral catalyst (1 μmol), a sulfide (500 μmol) and a GLC internal standard with or without 1-methylimidazole (1-MeIm, 100 μmol) were dissolved in deaerated dry CH_2Cl_2 (1 ml). Reaction was initiated by the addition of PhIO (200 μmol) and vigorous stirring at a constant rate, under an Ar atmosphere, in the dark and a thermostated reaction vessel. With appropriate intervals, aliquots taken from the reaction mixture were quenched by a CH_2Cl_2 solution of a slight excess of PPh_3 and then analyzed by GLC. After the reaction ceased, sulfoxides produced were isolated by silica-gel flash column chromatography. The total turnover numbers were determined based on the isolated yields of the sulfoxides. Results are summarized in Table 1.

Table 1. Asymmetric Oxidation of Sulfides Catalyzed by **1** or **2**.

Sulfide		Catalyst	1-MeIm/μmol	T/°C	Time/h	T.N.[a]	e.e.(%)	Config.[b]
								
X = H	(3)	(*S*)-**1**	0	0	4	180	17	*S*
		(*S*)-**1**	100	-15	7.5	139	46	*S*
		(*S*)-**2**	100	-15	22	85	19	*S*
2-NO_2	(4)	(*S*)-**1**	100	-5	12.5	88	24	(*S*)
3-NO_2	(5)	(*S*)-**1**	100	-15	8	128	45	(*S*)
4-NO_2	(6)	(*S*)-**1**	0	0	3	173	27	(*S*)
		(*S*)-**1**	100	0	8	120	53	(*S*)
F_5	(7)	(*S*)-**1**	0	0	3	82	31	(*S*)
		(*S*)-**1**	100	-15	9	55	73	(*S*)
4-Cl	(8)	(*R*)-**1**	100	-15	19	139	35	(*R*)
4-Me	(9)	(*S*)-**1**	100	-15	18	144	54	(*S*)
4-OMe	(10)	(*R*)-**1**	100	-15	16.5	152	42	(*R*)
	(11)	(*R*)-**1**	100	-15	22	168	34	(*R*)
	(12)	(*R*)-**1**	100	-15	26	146	23	-
	(13)	(*R*)-**1**	100	-15	22.5	94	30	-
	(14)	(*R*)-**1**	100	-15	41	165	40	-

a) Total turnover numbers; [sulfoxide]/[catalyst].
b) The configurations in parentheses were estimated from analogy with the spectroscopic behavior of (*S*)-methyl phenyl sulfoxide.

Scheme 1



Total turnover numbers of sulfoxide formation were in the range of 55 to 180 (28~90% yield on the amount of PhIO used) dependent on the substrates applied. When thioanisole was oxidized by the catalyst **1** and an excess amount (500 equiv. to the amount of **1**) of iodosobenzene, the total turnover number reached 290. On the other hand, without any catalyst (**1** or **2**), the sulfide substrates were hardly oxygenated by iodosobenzene alone under the identical reaction conditions. The formation of the corresponding sulfones was negligible (< 3%) in all cases. The observed selectivity is high enough in comparison with reported ones, e.g. sulfoxide = 10~14%.[6c]

The enantiomeric excesses (e.e.) for resulting sulfoxides were determined by ^{1}H NMR measured in the presence of optically active 2,2'-dihydroxy-1,1'-binaphthyl as a chiral shift agent. The signals of α-protons to sulfur atoms were well separated. The higher magnetic-field methyl signals of aryl methyl sulfoxides can be assigned to those of (*R*)-isomers in the presence of (*R*)-reagent.[10] When (*S*)-**1** was used as a catalyst, (*S*)-sulfoxides were preferably produced in the oxidation of substituted aryl methyl sulfides. The employment of the antipode (*R*)-**1** surely led to the formation of (*R*)-sulfoxides as the preferred enantiomer. Hence, it was ascertained that both oxygen transfer and chiral induction were accomplished inside the cavities of the chiral iron porphyrin complexes. The other catalyst **2** was less effective both optically and chemically, presumably because both its overcrowding around the central metal and lack of flexibility of its tetrapyrrole ligand.

The addition of 1-methylimidazole as an axial ligand remarkably enhanced the optical yields, for instance from 31% to 73% (the highest e.e. value) for methyl pentafluorophenyl sulfide. In other instances, addition of 1-MeIm improved e.e. values comparably. This is the first example indicating such a great effect of an added nitrogen base on enantioselectivity in metalloporphyrin catalyzed oxidations.

$$\mathbf{1} \xrightarrow[1\text{-MeIm}]{K_1} \mathbf{1}\bullet 1\text{-MeIm} \xrightarrow[1\text{-MeIm}]{K_2} \mathbf{1}\bullet(1\text{-MeIm})_2$$

Next, we determined the extent of 1-MeIm coordination to the catalyst **1** by means of photometric titration (Figure 3, 4).[11] The formation constants of the imidazole complex with the iron porphyrin **1** were determined to be K_1=82 M^{-1} and K_2=2000 M^{-2} at -15 °C in CH_2Cl_2. Intrinsically, iron (III) porphyrins favor the formation of their bis-imidazole complexes. The observed ratio of the formation constants (K_2/K_1=24), however, is much smaller than that of the related iron porphyrins; e.g. Fe (III) TPPCl, with 1-MeIm, K_2/K_1=167.[11] Thus, the binaphthalene auxiliaries effectively hinder the formation of the corresponding six-coordinated unreactive complex. The ratio of the three species was estimated to be **1** : **1**•1-MeIm : **1**•(1-MeIm)$_2$ = 3 : 28 : 69 at the concentration of both **1** and 1-MeIm applied for the catalytic oxidation. Since the six-coordinated complex **1**•(1-MeIm)$_2$ would be inactive for the oxidation, the active catalyst would be the five-coordinated one, **1**•1-MeIm. Rather higher concentration of this species in the reaction mixture resulted in maintenance of the reasonable

oxidation rate compared with that in the absence of the axial ligand even at the lower temperature.[12] Hence, the remarkable increase of the optical yields is ascribed to mainly (i) distortion of the iron porphyrin conformation by the coordination of 1-MeIm,[13] and (ii) protection from the oxidative decomposition of the catalyst. Point (i) is especially important for substrate recognition, because the porphyrin distortion will strongly affect both the conformation of the binaphthalene auxiliaries and concomitantly the shape and size of the cavity.

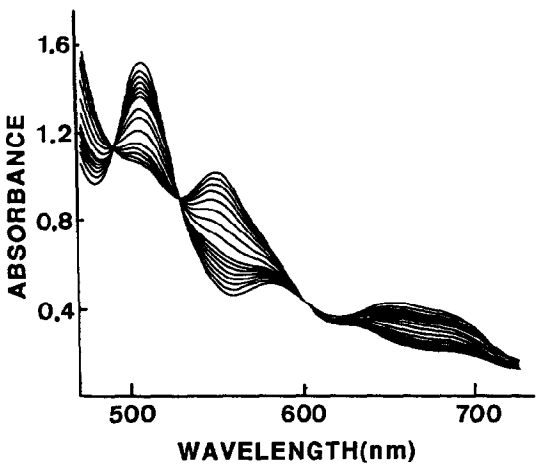


Figure 3. Visible spectral changes observed upon addition of 1-methylimidazole to an 5×10^{-5} M solution of **1** in CH_2Cl_2 at -15°C.

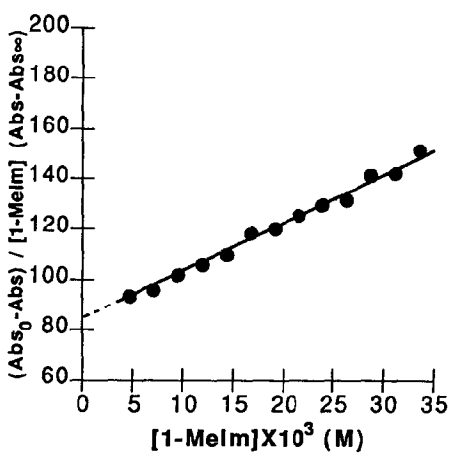
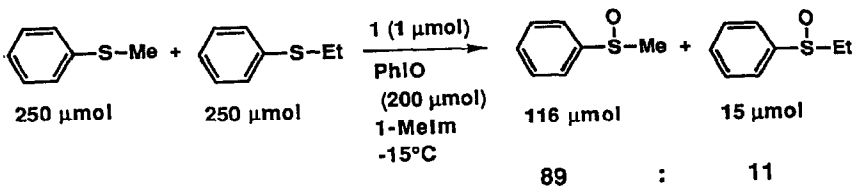


Figure 4. Method of analysis of absorbance data for the coordination of 1-MeIm to **1** in CH_2Cl_2.

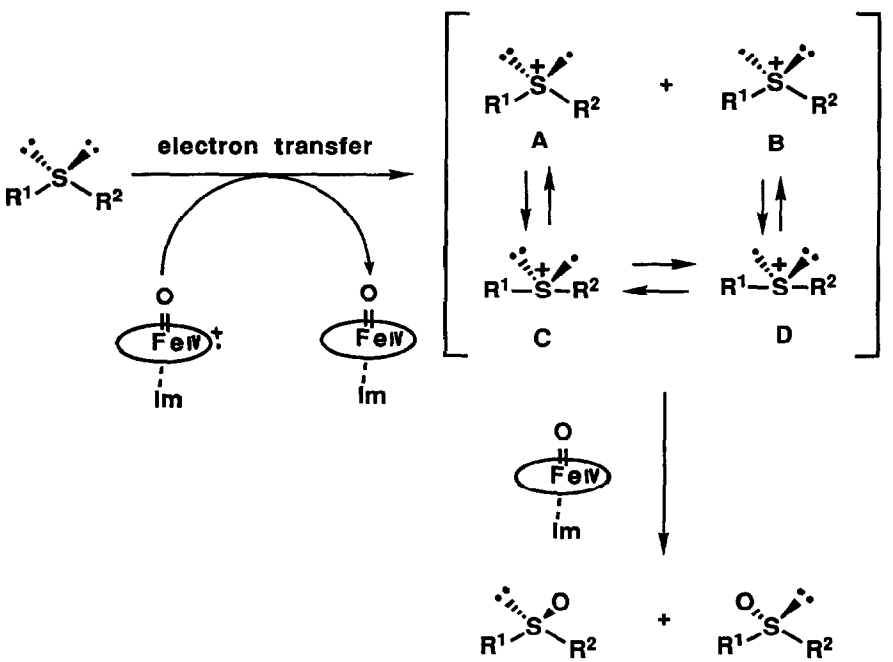
For the clarification of the origin of asymmetric induction, we examined the oxidation with various kind of substituted aryl methyl sulfides. Substituents on the aryl moieties, however, did not show significant effect on e.e.; e.g. in XC_6H_4SMe series, X=H (46% e.e.), 2-NO_2 (24% e.e.), 4-NO_2 (53% e.e.), 4-Me (54% e.e.) and 4-OMe (42 % e.e.). Moreover, we tried a competitive reaction between thioanisole and ethyl phenyl sulfide under the standard reaction conditions (Scheme 2), and found that methyl phenyl sulfoxide was produced preferentially in 89% selectivity. These results imply that steric effect of the substutuents on the sulfur atom works more significantly for the reaction than the electronic one.

Scheme 2.



Watanabe et. al.[14] suggested that monooxygenation of sulfides catalyzed by iron porphyrin proceeds via single electron transfer and cation radical formation was observed in the both cases of P-450 enzymes and and the model complex (Scheme 3). The present system implies this oxidation also proceeds via single electron transfer process. For three kind of *para*-substituted aryl methyl sulfides, their relative rates $\log(k_X/k_H)$ were almost constant ($\rho^+=0$), i.e. 0.34 (X=*p*-Me) and 0.33 (X=*p*-NO_2), regardless of the *para*-substituent. This

Scheme 3

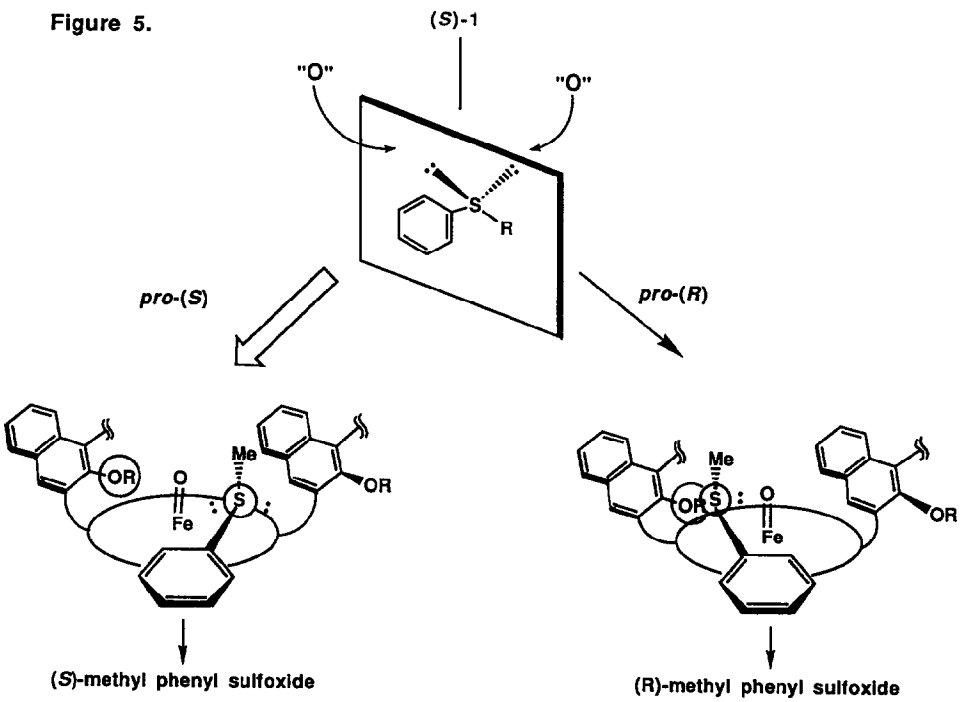


means the rate determining step of this oxidation would not be oxo-transfer stage to sulfides but the formation of high valent iron species. This argument is good accordance with the previous study,[14] where Hammett plot gave very small ρ^+ values (-0.16 and -0.26).

Next, we mention the relation between single electron transfer mechanism and enantioselectivity. The intermediary sulfur cation radicals, **A** and **B**, will very quickly equilibrate through the linear conformers, **C** and **D**, for the sake of decreased electronic repulsion between lone pair electrons (Scheme 3). Such a conformational change in sulfur cation radicals has been confirmed in theoretical and experimental studies for the case of H_2S and H_2S^+.[15] It is likely that the intermediate loses the stereochemical integrity of the initial substrate. Such a stereochemical equilibrating process as mentioned above would also decrease the efficiency of prochiral face recognition. While, rigid fixation of both substrate and intermediate in the vicinity of active site of the catalyst is required for the realization of high enantioselectivity.

A mechanism at the transition state determining absolute configurations of produced sulfoxides, i.e. (*S*)-sulfoxides formed by (*S*)-**1**, can be understood according to the following pictures, by mainly considering the steric interaction between the molecular appendages of the catalyst and substrate (Figure 5). Based on an examination using CPK models, such a mechanism would be most reasonable that an aryl methyl sulfide molecule approaches to the putative oxo iron center from the side opening of the molecular crefts keeping the benzene ring out of the cavity to minimize steric interaction. In the geometry (A) (*pro*-(*S*) addition), sulfur atom can smoothly approach to the oxygen center. In the geometry (B) (*pro*-(*R*) addition), on the other hand, the steric repulsion between the sulfur and the inside methoxy group can not be avoided. Hence, the oxygen addition favorably occurs from the *pro*-(*S*) face of the substrates leading to the formation of the (*S*)-sulfoxides as major enantiomers.

Figure 5.



These results are in remarkable contrast to those of the oxidation of the styrene derivatives catalyzed by the same iron porphyrin complexes, in which case the substituent σ^+ values closely correlated with the observed e.e. of the epoxides produced.[8] Higher optical yields were recorded in the oxidation of electron-deficient styrene derivatives than in that of electron-rich ones. The integrity of optical purity of the epoxides were dependent upon the lifetimes of the intermediate (cation radical centered at C_α) and the extent of the prochiral face recognition, both of which were mainly governed by the electronic character of the substrates. It is noteworthy that the prochiral face recognition would be promoted by π-π intreraction between an electron-deficient phenyl ring of a styrene derivative and the the electron-donating naphthalene ring of the catalyst which is electron rich on account of both the methoxy and the methylene groups.

In the oxidation of sulfides, such a CT type π-π interaction could not occur at the oxo transfer step (*vide supra*). Since sulfide substrate containing an internal sulfur atom has to penetrate more deeply into the cavity than for the case of terminal alkenes at the oxo transfer stage, π-system of aryl sulfides should be located outside of the cavity and could not take an appropriate position enough to develop this CT type π-π interaction with the naphthalene moiety.

From the results with various kind of sulfides in steric and electronic sense, we can conclude that the steric hindrance around the sulfur atom of the substrates rather than the electronic character of the substituents is dominant for the recognition of their prochiral face on the catalyst at the transition state of oxygen transfer.

Acknowledgement

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Experimental

Apparatus

400 MHz ^{1}H NMR spectra were recorded on a JEOL JNM-GX400. UV-vis absorption spectra were measured on a Shimadzu UV-3000 spectrometer. Gas chromatography was performed on a Shimadzu GC-8A using a Shimadzu capillary column CBP-1-520-050 (0.33mmx25m) and a FID detector. The reaction temperature was controlled by a NESLAB RTE-110.

Materials

All reagents were of the commercial reagent grade and were used without further purification except with noted. Dry dichloromethane was obtained by refluxing and distilling from CaH_2 and bubbling through argon gas. Sulfides (**4~11**) were prepared from the corresponding thiophenols by alkylation with DBU and iodomethane.[16] Sulfides (**12~14**) were obtained according to the method from the corresponding *trans*-β-bromostyrenes.[17] Iodosobenzene was obtained by the basic hydrolysis of iodosobenzene diacetate[18] and stored at -20°C. All compounds exhibited spectral and physical properties consistent with their structures.

The detailed synthesis and characterization of the iron complexes (**1** and **2**) will be reported elsewhere.[8]

Catalytic Oxidation of Thioanisole by 1 and Iodosobenzene

To a mixture of the catalyst (1 μmol), thioanisole (62 mg, 500 μmol), 1-chlorooctane (10 mg, 70 μmol) as a GLC internal standard and 1-methylimidazole (8.2 mg, 100 μmol) in deaerated dry dichloromethane (1 ml), solid iodosobenzene (44 mg, 200 μmol) was added at once. The reaction mixture was stirred at a constant

revolution under an argon atmosphere at -15°C in the dark. Aliquots (5 μl) were taken with some intervals and quenched quickly with a CH_2Cl_2 solution of triphenylphosphine (1 μmol). The formation of the oxide was monitored by GLC, and the isolation was accomplished by silica-gel flash column chromatography. After evaporation of the solvent, the residue was suspended in hexane and deposited on a column. The remaining sulfide, the GLC standard and iodobenzene were first eluted with hexane-CH_2Cl_2 (4 : 1, v/v), and next, the sulfoxide with hexane-CH_2Cl_2 (1 : 4, v/v), weighed and characterized by means of ^1H NMR. Determination of the optical yield was done as follows: the protons of the methyl groups showed their signals at δ2.7 of singlet in $CDCl_3$. When ca. 1 equivalent of chiral 1,1'-bi-2-naphthol was added, the signal separated into two signals of unequal intensity. Integrated values of these separated signals were used to measure the e.e.

Oxidation and analysis of other sulfides were done in the same manner with exception noted in the text and Table 1.

References and Notes

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