Communications to the Editor

Catalysis and Chiral Recognition through Designed Complexation of Transition States in Transacylations of Amino Ester Salts[1]

Sir:

Previous papers demonstrated that chiral macrocyclic polyethers as hosts discriminated in complexation in chloroform between enantiomers of amino ester salts as guests.[2] Diastereomeric association constant ratios as high as 18 were reported.[2c] Complexation constants between *tert*-butylammonium thiocyanate and macrocyclic polyethers exceeded those of their open-chain analogues by factors of from one to four powers of ten.[3] We now describe the effects of designed complexation of transition states on reaction rates in transacylation reactions (thiolysis) between chiral host thiols **1a** and **2** and enantiomeric guest α-amino ester salts. The reactions between **1a** and the esters resemble the transacylations involving the enzyme trypsin in the sense that the binding of host to guest (vs. enzyme to substrate) involves the guest's ammonium ion, and the transacylations involving papain in the sense that the host's sulfhydryl group acts as a nucleophile.

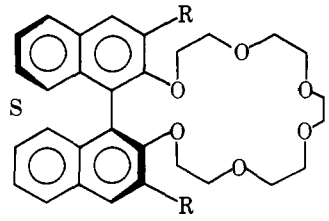
Racemic **1b**[4] mixed with thionyl chloride gave the corresponding chloride,[5,6] which when treated with thiourea followed by morpholine provided racemic **1a**[5,6] (glass). Similarly optically pure (*S*)-**1b**[2b,5-7] (glass) and optically pure (*R*)-**1b**[2b,5-7] (glass) were converted to (*S*)-**1a**[6,7] (glass) and (*R*)-**1a**[6,7] (glass), respectively. Optically pure (*S*)-**2**[6,7] (glass) was prepared by similar reactions from optically pure (*S*)-3,3′-bis(hydroxymethyl)-2,2-dihydroxy-1,1′-binaphthyl[2b]. The *p*-nitrophenyl α-amino esters were purchased as the *N*-carbobenzoxy derivatives and converted to the amine hydrobromides with HBr–AcOH.

Table I records the rate constants and conditions for the liberation of *p*-nitrophenol from six α-amino esters in the absence and presence of cycles **1a** and **1b** and open-chain analogue **2**. Evidence that thioester was formed as an intermediate by the reaction of (*S*)-**1a** with L-phenylalanine ester (2×10^{-2} and 10^{-2} *M*, respectively) was obtained by following changes in polarimetric readings (at 546 nm) in medium A at 25 °C after the rapid initial release of *p*-nitrophenol. Pseudo-first-order kinetics (18 points) were observed with $k = 2 \times 10^{-5}$ s^{-1}. The end point of the reaction after seven half-lives was approximated by an independently prepared solution of L-phenylalanine ethyl ester and (*S*)-**1a** at the same concentrations used in the run. The po-

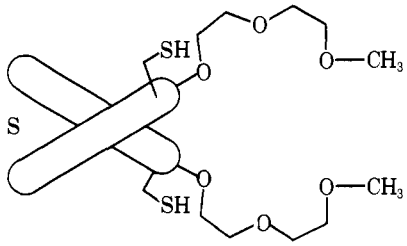
Table I. Rate Comparisons for Liberation of *p*-Nitrophenol from 10^{-4} M Solutions of Amino Acid Ester Salts in the Presence of 5.0×10^{-3} M **1a**, **1b**, or **2** at 25.0 °C

			RC*H(NH_3^+)CO_2Ar			
Run no.	Medium[a]	Polyether present	R	Config	$10^3 k$,[b] s^{-1}	Rate factors
1	A	None	H	—	2.6	1
2	A	**1a**	H	—	>702	>270
3	A	**2**	H	—	5.5	2.1
4	A	**1b**	H	—	7.3	2.8
5	A	18-Crown-6	H	—	8.1	3.1
6	A	(*S*)-**1a**	Prolyl	L	16	0.8
7	A	(*S*)-**2**	Prolyl	L	21	
8	A	(*S*)-**1a**	H	L	>700	>130
9	A	(*S*)-**2**	H	L	5.4	
10	A	(*S*)-**1a**	CH_3	L	≳700	≳130
11	A	(*S*)-**2**	CH_3	L	5.4	
12	A	(*S*)-**1a**	$(CH_3)_2CH$	L	13	160
13	A	(*S*)-**2**	$(CH_3)_2CH$	L	0.08	
14	A	(*S*)-**1a**	$C_6H_5CH_2$	L	200	500
15	A	(*S*)-**2**	$C_6H_5CH_2$	L	0.41	
16	A	(*S*)-**1a**	$(CH_3)_2CHCH_2$	L	≳700	≳1100
17	A	(*S*)-**2**	$(CH_3)_2CHCH_2$	L	~0.6	
18	A	(*S*)-**1a**	$C_6H_5CH_2$	D	25	69
19	A	(*S*)-**2**	$C_6H_5CH_2$	D	0.36	
20	B	(*S*)-**1a**	CH_3	L	70	1
21	B	(*R*)-**1a**	CH_3	L	70	
22	B	(*S*)-**1a**	$(CH_3)_2CHCH_2$	L	~70	~6
23	B	(*R*)-**1a**	$(CH_3)_2CHCH_2$	L	11	
24	B	(*S*)-**1a**	$C_6H_5CH_2$	L	340	8.3
25	B	(*R*)-**1a**	$C_6H_5CH_2$	L	41	
26	B	(*R*)-**1a**	$C_6H_5CH_2$	D	340	8.1
27	B	(*S*)-**1a**	$C_6H_5CH_2$	D	42	
28	B	(*S*)-**1a**	$(CH_3)_2CH$	L	22	9.2
29	B	(*R*)-**1a**	$(CH_3)_2CH$	L	2.4	
30	C	(*S*)-**1a**	H	—	110	20
31	C	(*S*)-**2**	H	—	5.4	
32	C	(*S*)-**1a**	$C_6H_5CH_2$	L	18	8
33	C	(*S*)-**2**	$C_6H_5CH_2$	L	2.2	

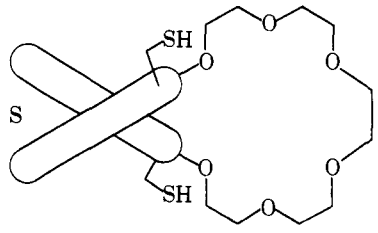
[a] A 20% EtOH in CH_2Cl_2 (v) buffered with 0.2 M AcOH and 0.1 M $(CH_3)_4N^+$ $^-$OAc; B 20% EtOH in CH_2Cl_2 (v) buffered with 0.3 M AcOH and 0.1 M $(CH_3)_4N^+$ $^-$OAc; C 40% H_2O in CH_3CN (v) buffered with 0.2 M AcOH and 0.2 M NaOAc. These buffers in water give pH 4.8. [b] Pseudo-first-order rate constants, corrected for buffer solvolysis, made in triplicate runs of at least 14 points each, and followed for appearance of *p*-$NO_2C_6H_4OH$ at 345 nm.



(*S*)-**1a**, R = CH_2SH
(*S*)-**1b**, R = CH_2OH
(*S*)-**1c**, R = H[2a]



(*S*)-**2**

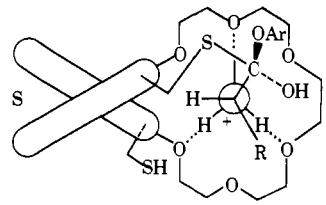


(*S*)-**1a** (cross section)

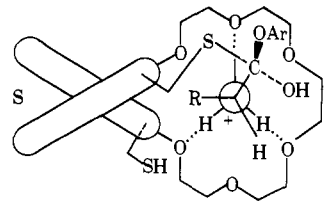
larimetric rate was $\sim 10^4$ times slower than the spectrophotometric rate for the release of *p*-nitrophenol.

Striking generalizations and conclusions emerge from these data. (1) In the more lipophilic medium A (20% C_2H_5OH-CH_2Cl_2), L-amino ester salts that contain NH_3^+ groups react with cyclic dithiol ((*S*)-**1a**) at rates about two to three powers of ten faster than with open-chain dithiol ((*S*)-**2**) (see runs 8-21). With L-proline ester salt which contains an NH_2^+ group, the cyclic and open-chain dithiols react at about the same rates (runs 6 and 7). These results indicate that the free energy of the rate-limiting transition state for reaction is lowered by complexation that is dependent on the host being cyclic and the guest possessing three hydrogen bonding protons. (2) In the more hydrophilic medium (40% H_2O-CH_3CN), these rate factors decrease to about one power of ten (runs 30-33). In this medium, the host-guest complex is probably less structured and therefore less stabilized due to water's ability to hydrogen bond the NH_3^+ protons competitively with the host's ether oxygens. The ground state complexation constants have not been measured, but probably are higher valued in the more lipophilic media (A and B). (3) Unlike the open-chain dithiols (compare runs 15 and 19), the cyclic (*S*)-dithiol reacts in the more lipophilic medium with the L-amino ester salts faster than does the cyclic (*R*)-dithiol by factors that depend on the sizes of the groups attached to the α-carbon of the amino ester (runs 22-29). For $(CH_3)_2CH$ the factor is 9.2; for $C_6H_5CH_2$, 8.2; for $(CH_3)_2CHCH_2$, ~6; for CH_3, ~1.

An examination in advance of experiment of Corey-Pauling-Koltun molecular models of the hypothetical diastereomeric tetrahedral intermediates **4** and **5** led to the prediction that the L to *S* configurational relationship of guest to host is sterically more compatible than the L to *R* (or D to *S*) relationship. The larger the size of the group attached to the α-carbon of the guest, the greater the difference in energy of the transition states involved. The *S* to L steric relationships are depicted in **4**. The α-hydrogen is directed toward the chiral barrier in **4**, whereas in the diastereomeric structure **5** with the *S* to D relationship (same in energy as the *R* to L), the α-R group is directed toward the barrier. This is the first example of an enzyme model whose stereospecificity in catalysis can be rationalized by a predicted complementary fit of guest to host. We anticipate being able to obtain much larger catalytic and stereospecificity factors with more highly designed systems, particularly with those hosts that not only collect and orient the reactants but also provide for all the proton transfers.



4, (*S*) to (*L*) relationships, more stable



5, (*S*) to (*D*) relationships, less stable

Other groups of investigators have developed models for enzyme systems that involved host-guest complexation of rate-limiting transition states in transacylations. Most of the results involve cyclodextrin cavities as the complexing agent and their rims of hydroxyl groups as nucleophiles in aqueous media. The results of Cramer, Bender, Breslow, and van Hooidonk and others have been thoroughly reviewed.[9] Stereospecificity was observed by Kaiser et al.[10] and van Hooidonk[9a] in acylations and phosphorylations of cyclodextrin systems, respectively. An imidazole-substituted α-cyclodextrin accelerated deacylation of *p*-nitrophenyl acetate a factor of 6 more than a 1:1 mixture of α-cyclodextrin and histamine.[11] A completely synthetic complexing carbomacrocyclic hydroxamic acid was used as host and nucleophile to give dramatic rate enhancements in a transacylation.[12]

References and Notes

(1) This work was supported by U.S. Public Health Service Research Grant No. GM 12640-11, from the Department of Health, Education and Welfare, and by a grant from the National Science Foundation, GP 33533X.
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(5) We warmly thank Dr. R. C. Helgeson who first developed these reactions.
(6) Carbon and hydrogen analyses were within 0.30% of theory, and ^1H NMR and mass spectra were as expected.
(7) Rotations were taken in $CHCl_3$: (*S*)-**1a**, $[\alpha]^{25}_{578}$ +11°, $[\alpha]^{25}_{546}$ +13°, $[\alpha]^{25}_{436}$ +19° (*c* 1.7); (*R*)-**1a**, $[\alpha]^{25}_{578}$ −11°, $[\alpha^{25}_{546}$ −12°, $[\alpha]^{25}_{436}$ −20° (*c* 1.8); (*S*)-**2**, $[\alpha]^{25}_{578}$ +105° (*c* 1.7).
(8) In water at 25.0 °C, the pseudo-first-order rate constant for the reaction of $^-Br\ H_3{}^+NCH_2CO_2C_6H_4NO_2$-*p* (0.0001 M) with $HSCH_2CH_2OH$ (0.050 M) at 0.5 ionic strength (NaCl) at pH 4.8 (NaOAc–HOAc) showed a zero-order dependence on buffer concentration from 0.07–0.45 M concentration, and a first-order dependence on OH^- concentration from 0.3×10^{-9} to 2.5×10^{-9}. Similar results were obtained in 20% C_2H_5OH-CH_2Cl_2 buffered with $(CH_3)_4N^+{}^-OAc$–HOAc using the buffer ratio (OAc^-)/(HOAc) as a measure of the basicity of the media. These facts indicate no general acid or base catalysis, and suggest RS^- attack on C=O is

rate limiting (see W. P. Jencks, "Catalysis in Chemistry and Enzymology", McGraw-Hill, New York, N.Y., 1969, p 551.
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Received September 29, 1975

Reaction of Singlet Oxygen with α-Ketocarboxylic Acids. Oxidative Decarboxylation and Peroxyacid Formation

Sir:

An important class of monooxygenases are those which require α-ketoglutarate as cofactor.[1] Biological oxidation is catalyzed by the metalloenzyme so that hydroxylation of a substrate (SH) is effected by half a mole of molecular oxygen, while the other half is taken up by α-ketoglutarate which acts as reductant (Scheme I). The details of the general scheme are presently not known.[2] However, the ingenious and mechanistically plausible suggestion has been made that α-ketoglutaric acid (**1**) is converted by oxygen to persuccinic acid (**3**) which subsequently brings about oxidation of the substrate (Scheme II).[3] Direct reaction of singlet α-keto acid and triplet oxygen is spin-forbidden and in fact does not take place. Consequently, the role of transition metal complexation has been invoked to render molecular oxygen acceptable to the α-keto acid function.[3] However, it occurred to us that the plausibility of this idea depends largely on whether singlet oxygen itself is reactive towards α-ketocarboxylic acids.[4] We now report the first examples of this new reaction.

A selected range of α-keto acids and similar structures was submitted to photogenetic singlet oxygen[6] (Table I). For those acceptors which possess a ketonic carbonyl group, singlet oxygen was consumed steadily, carbon dioxide was evolved, and the corresponding carboxylic acids were obtained (entries 1, 2, 3, 4, 5, 12; Table I). Singlet oxygen appeared to be the reagent responsible as omission of any one

Scheme I

$$\underset{\mathbf{1}}{SH + O_2 + HO_2C(CH_2)_2COCO_2H} \xrightarrow[\text{ascorbic acid}]{\text{enzyme}, Fe^{2+}} \underset{\mathbf{2}}{SOH + HO_2C(CH_2)_2CO_2H + CO_2}$$

Scheme II

$$\underset{\mathbf{3}}{1 + O_2 \longrightarrow HO_2C(CH_2)_2CO_3H} + CO_2$$

$$3 + SH \longrightarrow SOH + \mathbf{2}$$

of the three components, light, oxygen, or dye, stopped the reaction. The addition of DABCO unexpectedly did not dampen the reaction, but accelerated it.[7] This was attributed to the greater reactivity of the carboxylate anion, which was confirmed by the similar behavior of the sodium salt (entries 3, 4; Table I). On the other hand, progressive addition of β-carotene slowed, but did not halt the reaction.[8]

Reactivity depends on electronic effects which are as yet difficult to completely evaluate. Electron withdrawing groups attached to the α-carbonyl group manifestly stabilize the α-keto acid. Moreover, oxalic acid and its derivatives are inert. The stability of phenylglyoxalic acid (entries 10 and 11) seems to be electronic in origin and not simply due to the absence of a β-hydrogen atom, as *tert*-butylglyoxalic acid is extremely reactive (entry 12).

Although the signs were there, namely the coloration of starch-potassium iodide paper, it was not possible to isolate peracids even at temperatures as low as −78 °C. We believe that as fast as the peracid was formed, it was decomposed by further reaction with the parent α-ketocarboxylic acid.[9] Indeed, the mixing of equimolar amounts of perbenzoic and α-ketovaleric (**4**) acids resulted in *instantaneous* decarboxylation to give butyric acid (**5**) in quantitative yield (Scheme III). Phenylglyoxalic acid behaved similarly with perbenzoic acid. We decided to take advantage of the latter reaction to demonstrate the intermediacy of singlet-oxygen-generated peracid. Phenylglyoxalic acid (**7**) (3.34 mM) and α-ketovaleric acid (**4**) (3.9 mM) in 30 ml of acetonitrile were photooxygenated at 5 °C for 24 h. Carbon dioxide was evolved in 45% yield. The reaction mixture was then methylated with excess diazomethane in ether, and analyzed.[11] In addition to starting material, methyl benzoate and butyr-

Table I. Reaction of Some α-Ketocarboxylic Acids and Related Compounds with Singlet Oxygen[a]

Entry no.	Acceptor	Exptl conditions[b]	Reaction time (h)	% CO_2 evolved[c]	Products[c,d] (%)
1	$HO_2C(CH_2)_2COCO_2H$	A	19	45	$HO_2C(CH_2)_2CO_2H$ (45)
2	$CH_3(CH_2)_2COCO_2H$	A	40	51	$CH_3(CH_2)_2CO_2H$ (45)
3	$CH_3(CH_2)_2COCO_2H$[e]	A	8	35	$CH_3(CH_2)_2CO_2H$ (40)
4	$CH_3(CH_2)_2COCO_2Na$	B	23	30	$CH_3(CH_2)_2CO_2Na$ (29)
5	$HO_2CCH_2COCO_2H$	A	19	32	$HO_2CCH_2CO_2H$ (8)[f]
6	HO_2CCO_2H	A	19	0	None[g]
7	HO_2CCO_2H	C	19	0	None
8	$CH_3O_2CCO_2H$	A	19	0	None
9	NaO_2CCO_2Na	C	19	6	—[h]
10	$PhCOCO_2H$	A	19	0	None
11	$PhCOCO_2Na$	C	4	0	None
12	t-$BuCOCO_2H$	A	23	100	t-$BuCO_2H$ (95)
13	$CH_3(CH_2)_2(C{=}NOH)CO_2H$	A	24	0	None
14	$CH_2{=}CHCO_2H$	A	19	0	None

[a] Generated as previously described (ref 6). [b] 3 mM of acceptor and 5% methylene blue were dissolved in different solvents and photooxygenated at 5 °C: A = 30 ml acetonitrile; B = 30 ml methanol; C = 50 ml water and 25 ml acetonitrile. [c] Percentage yield based on acceptor. [d] Except for entry 5, in all cases the balance of material recovered is acceptor. [e] One equivalent of DABCO (1,4-diazabicyclo[2.2.2]octane) added. [f] Low yield of product due to cleavage via the presumed dioxetane of the enol form of the reactant; estimated as 60% present in the equilibrium mixture. The cleavage products were not identified. [g] None means no reaction of acceptor. [h] Very slight decomposition.