Selective Aromatic Substitution within a Cyclodextrin Mixed Complex

Sir:

The selectivity of enzyme-catalyzed reactions is due to the formation of an enzyme–substrate complex. Within such a complex, only certain substrate atoms are sterically accessible to attack. Organic reactions, by contrast, generally involve attack by simple reagents on those positions of a substrate which are intrinsically reactive. The most obvious difference is that biochemical reagents (enzymes) are almost always larger and more complex than the substrates, while the reverse is generally true in organic chemistry. However, a number of studies have been made of the hydrophobic binding of small molecules into the cavities of cyclodextrins (cycloamyloses).[1] Furthermore, these cyclic sugars have been shown to catalyze the hydrolysis of some phosphate[2] and carboxylic esters[3] which form mixed complexes. We have examined the possibility of directing the course of an aromatic substitution by carrying it out within the cyclodextrin cavity on a cyclodextrin–substrate complex. The results indicate not only that the cyclodextrin blocks all but one aromatic ring position to substitution, but also that it actively catalyzes substitution at the unblocked position.

Anisole, 10^{-4} *M* in H_2O, was treated for 12 hr at room temperature with 10^{-2} *M* HOCl (unbuffered, initial pH 4.7) in the presence of varying amounts of cyclohexaamylose (α-cyclodextrin). The relative yields of *o*-chloro- and *p*-chloroanisole were determined by vpc analysis and are listed in Table I. We have also determined the anisole–cyclodextrin dissociation constant to be $(3.72 \pm 0.5) \times 10^{-3}$ *M* at 25°, using the method of Cramer[1] and a Hildebrand–Benesi plot[4] (isosbestic points at 276 and 265 nm). The per cent of anisole bound at the various cyclodextrin concentrations is listed in Table I. From these data it can be seen that *para* chlorination becomes essentially the exclusive process in the presence of sufficient cyclodextrin, although in controls maltose had no effect on the product ratio. Models show that the anisole can fit into the cyclodextrin cavity as shown in Figure 1, so that the *ortho* positions are blocked but the *para* position is free and accessible to cyclodextrin hydroxyl groups.

Table I

Cyclohexaamylose, $M \times 10^3$	Chloroanisole product ratio, *p*:*o*	% anisole bound
0	1.48	0
0.933	3.43	20
1.686	5.49	33
2.80	7.42	43
4.68	11.3	56
6.56	15.4	64
9.39	21.6	72

However, this cannot be the whole story, since with only 72% of the anisole complexed, substitution is almost exclusively *para*. The data in Table I are fully consistent with a kinetic scheme in which the partial rate factor $k_{ortho\ \text{complex}}$ is zero, and $k_{para\ \text{complex}}/k_{para\ \text{free}}$ is 5.6 ± 0.8 (the error reflects uncertainty in the dissociation constant, and the least squares kinetic plot has only 3% deviation). The increase in rate within the nonpolar cyclodextrin cavity for a process in which charge develops in the transition state is not expected. The most obvious explanation is that the hydroxyl groups which rim the cavity are participating catalytically, perhaps by reaction with HOCl to form intracomplex hypochlorite groups which act as the true donors.

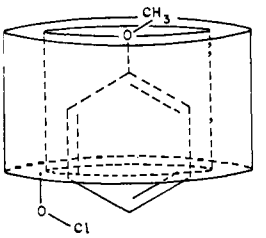

Figure 1. Schematic representation of an anisole molecule in the cavity of cyclohexaamylose. Eighteen hydroxyl groups (not shown) ring the mouths of the cavity, one of which is written as its hypochlorite ester to indicate a mechanism by which the increased rate of chlorination in the complex may be explained.

It is interesting that enzymatic chlorination of anisole shows no such increased specificity[5] as we have observed in our enzyme model but is instead apparently occurring with uncomplexed substrate. However, our system is a good model for more typical highly specific enzymatic reactions, and it may also represent a useful approach to specificity in synthetic chemistry.[6]

(1) F. Cramer, W. Saenger, and H.-Ch. Spatz, *J. Am. Chem. Soc.*, **89**, 14 (1967), and references therein.
(2) N. Hennrich and F. Cramer, *ibid.*, **87**, 1121 (1965).
(3) R. L. Van Etten, J. F. Sebastian, G. A. Clowes, and M. L. Bender, *ibid.*, **89**, 3242 (1967); R. L. Van Etten, G. A. Clowes, J. F. Sebastian, and M. L. Bender, *ibid.*, **89**, 3253 (1967).
(4) H. A. Benesi and J. H. Hildebrand, *ibid.*, **71**, 2703 (1949).
(5) F. S. Brown and L. P. Hager, *ibid.*, **89**, 719 (1967).
(6) Support of this work by the National Institutes of Health is gratefully acknowledged.
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Solvent Effects on a Probable Charge-Transfer Reaction. Inter- and Intramolecular Photoreactions of Tertiary Amines with Ketones

Sir:

Interest in the photoreduction of ketones by amines has very recently evolved into quantitative studies.[1-6] Specific bimolecular rate constants for interaction of ketone triplets with triethylamine have been estimated to exceed 10^8 M^{-1} sec^{-1} for benzophenone[1,4b] and to lie in the range 10^7–10^8 M^{-1} sec^{-1} for fluorenone[3,5] and *p*-aminobenzophenone.[2] The latter two ketones possess π,π^* lowest triplets, and the rate constants with

(1) (a) S. G. Cohen and R. J. Baumgarten, *J. Am. Chem. Soc.*, **89**, 3741 (1967); (b) S. G. Cohen and H. M. Chao, *ibid.*, **90**, 165 (1968); (c) S. G. Cohen, N. Stein, and H. M. Chao, *ibid.*, **90**, 521 (1968).
(2) S. G. Cohen and J. I. Cohen, *J. Phys. Chem.*, **72**, 3782 (1968).
(3) S. G. Cohen and J. B. Guttenplan, *Tetrahedron Letters*, 5353 (1968).
(4) (a) R. S. Davidson and P. F. Lambeth, *Chem. Commun.*, 1265 (1967); (b) R. S. Davidson and P. F. Lambeth, *ibid.*, 511 (1968).
(5) G. A. Davis, *et al.*, *J. Am. Chem. Soc.*, **91**, 2264 (1969).
(6) N. J. Turro and R. Engel, *Mol. Photochem.*, **1**, 143 (1969).

Table I. Quantum Yields and Quenching Parameters for Type II Photoelimination of γ-DMAB[a]

Solvent	Φ_{II}	$k_q\tau$, M^{-1}	k_q, 10^9 M^{-1}sec^{-1} [b]	$1/\tau$, 10^9 sec^{-1}
Benzene	0.025	0.60	5.0	8.3
Acetonitrile	0.05	1.5	10.0	7.7
Methanol	0.25	4.5	15.0	0.8
Methanol (HCl)[c]	0.009	720	15.0	0.005

[a] Irradiations performed at 25°, 3130 A, on 0.1 *M* ketone. Conversions were kept below 5%. [b] P. J. Wagner and I. Kochevar, *J. Am. Chem. Soc.*, **90**, 2232 (1968). [c] γ-DMAB-HCl.

rises to 0.64 in the presence of 0.8 *M* triethylamine. Table II lists the Stern–Volmer quenching slopes for both the amines and 2,5-dimethyl-2,4-hexadiene, as well as the lifetimes and rate constants calculated therefrom. *The efficiencies with which triethylamine (TEA) and dimethyl-t-butylamine (DMBA) quench triplet valerophenone are almost identical in all three solvents.*

Several aspects of these results are particularly noteworthy.

(1) In even the most rapid free-radical hydrogen abstraction processes, secondary C–H bonds are

Table II. Quenching of Valerophenone Photoelimination[a]

Solvent	Quencher	Φ^0_{II}	$k_q\tau$, M^{-1}	k_q, 10^9 M^{-1} sec^{-1}	$1/\tau$, 10^9 sec^{-1}
Benzene	Diene	0.33	36	5.0	0.14
	TEA	0.33	25	3.5	0.14
	DMBA	0.33	25	3.5	0.14
Acetonitrile	Diene	0.85	68	10.0[b]	0.15
	TEA	0.85	25	3.8	0.15
	DMBA	0.85	22	3.3	0.15
Methanol	Diene	0.88	100	15.0[b]	0.15
	TEA	0.88	5.5	0.8	0.15
	DMBA	0.88	3.5	0.5	0.15

[a] Same conditions as in Table I. [b] See footnote *b*, Table I.

which they abstract hydrogen atoms from tributylstannane are only 10^5–10^6 M^{-1} sec^{-1}.[5,7] Cohen has proposed that the great reactivity of amines may be associated with a process other than simple α-hydrogen atom abstraction, namely charge transfer or electron transfer followed by proton transfer.[1,2] Such a hypothesis is especially appealing as an explanation for the reaction with the π,π* ketone triplets, since amines are thought to quench π,π* singlets by charge-transfer interactions.[8–10] However, no compelling evidence in support of this hypothesis for n,π* triplets has yet been reported. This article reports (1) some results inconsistent with the possibility of direct hydrogen atom abstraction from trialkylamines by the n,π* triplets of phenyl alkyl ketones, and (2) some solvent effects *opposite* to those expected for an electron-transfer process.

We have studied the type II photoelimination of γ-dimethylaminobutyrophenone (γ-DMAB) as well as the photoreduction of valerophenone by two tertiary aliphatic amines in benzene, acetonitrile, and methanol. Upon irradiation, γ-DMAB yields acetophenone almost quantitatively.[11] Quantum yields were measured as a function of 1,3-pentadiene concentration. Triplet lifetimes in the three solvents were ascertained from the slopes of the resulting linear Stern–Volmer plots. All the pertinent results are collected in Table I, together with those on the hydrochloride of γ-DMAB in methanol.

Amines quench acetophenone formation from valerophenone. That this quenching corresponds to photoreduction of valerophenone is indicated by the fact that the quantum yield for its disappearance in benzene

(7) G. S. Hammond and P. A. Leermakers, *J. Am. Chem. Soc.*, **84**, 207 (1962).
(8) A. H. Weller and H. Leonhard, *Ber. Bunseges Physik. Chem.*, **67**, 791 (1963).
(9) W. R. Ware and H. P. Richter, *J. Chem. Phys.*, **48**, 1595 (1968).
(10) N. Mataga and K. Ezumi, *Bull. Chem. Soc. Japan.*, **40**, 1355 (1967).
(11) A small percentage of cyclobutanol is also formed. The olefin fragment is an enamine; its fate will be reported later.

significantly more reactive than primary C–H bonds. Therefore, the lack of any difference between TEA and DMBA in the rates at which they react with triplet valerophenone indicates that the primary process is something other than hydrogen atom abstraction. It must be stressed that this conclusion cannot be reached by a simple comparison of photoreduction quantum yields.[4]

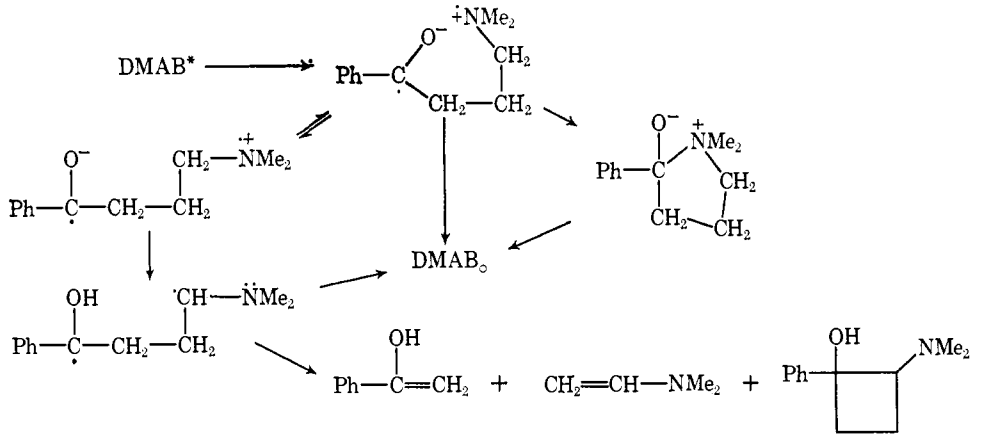
(2) The solvent effects on both inter- and intramolecular rate constants for amine–triplet ketone interactions are the same: essentially no difference between benzene and acetonitrile, with an order of magnitude *decrease* in methanol. Ground-state reactions which proceed by electron transfer demonstrate tremendous rate enhancements in acetonitrile relative to benzene.[12] Even more important, fluorescence quenching involving electron transfer from amines proceeds considerably faster in methanol and acetonitrile than in benzene.[8,9,13]

(3) A comparison of the $1/\tau$ values in Table I with the amine k_q values in Table II reveals that the amino ketone serves almost quantitatively as a model for a bimolecular solution encounter between amine and valerophenone. The $1/\tau$ values for γ-DMAB in benzene and acetonitrile almost equal the diffusion rate in those solvents so that the bimolecular interactions proceed at close to the diffusion-controlled limit. In methanol, the intramolecular rate is very much smaller than the diffusion rate and equals the intermolecular rate constant.[14] For known cases of hydrogen atom abstraction, the intramolecular rate constant is 10^2–10^3 times faster than the bimolecular rate constant.[15]

(4) The inverse relationship between quantum efficiency and triplet-state reactivity in type II

(12) E. M. Kosower and M. Mohammad, *J. Am. Chem. Soc.*, **90**, 3271 (1968).
(13) K. Kaneta and M. Koizumi, *Bull. Chem. Soc. Japan*, **40**, 2254 (1967).
(14) Whether they are actually equal depends on the value of k_q assumed for the quenching of valerophenone by the diene.
(15) C. Walling and A. Padwa, *J. Am. Chem. Soc.*, **85**, 1597 (1963).

Scheme I



processes[16] is especially marked for γ-DMAB. In benzene, the quantum yield of acetophenone formation is only 8% that from valerophenone, while the triplet decay rate is 60 times faster. *There is no such correspondingly low quantum yield for bimolecular photoreduction of ketones by tertiary amines.*[1b,c] Moreover, both α-dimethylamino-[17a] and α-dibenzylaminoacetophenone[17b] undergo type II photoelimination in respectable quantum yields (~0.16). We have already presented considerable evidence that quantum yields of type II processes are low in hydrocarbon solvents because of the disproportionation of biradical intermediates,[16] which reaction is prevented by polar solvents.[18] Acetonitrile does double Φ_{II} for γ-DMAB, and we shall assume that this increase accounts for all the biradicals. Consequently, 95% of the γ-DMAB triplets in benzene or acetonitrile and 75% in methanol probably do not yield a biradical. Revertible[19] electron transfer has been suggested by Cohen as the cause of the moderate quantum efficiencies in amine–ketone photoreactions.[1,2] However, something further must prevent the supposed γ-DMAB zwitterionic intermediate from proceeding on to biradical. One possibility is that in nonpolar and aprotic solvents, the positive and negative ends of the zwitterion do not separate sufficiently for a γ proton to approach the negative oxygen. It is also possible that the zwitterion cyclizes, as shown in Scheme I.

(5) Transannular interactions have been reported for cyclic amino ketones.[20] There is no evidence in the uv, ir, or nmr spectra of γ-DMAB for ground-state interactions between the amino and carbonyl functions. The phosphorescence spectrum[21] of γ-DMAB looks very much like that of valerophenone, with the important exception that the emission from γ-DMAB is much longer lived. This phenomenon will be reported separately and is mentioned here simply to emphasize that a significant interaction between the amino group and the *excited* carbonyl can be detected spectroscopically.

(6) Tetraethylammonium bromide does not quench valerophenone. Protonation of the amino group of γ-DMAB increases its triplet lifetime substantially. The quantum yield of γ-DMAB–HCl disappearance is eight times greater than that of acetophenone formation, so that photoreduction by solvent must be the main reaction. We estimate that the γ hydrogens in γ-DMAB–HCl are $< 1/100$ as reactive as those on valerophenone and $< 1/4000$ as reactive as those on γ-DMAB.

In summary, the data in Table II and the very low type II quantum yield of γ-DMAB are inconsistent with simple hydrogen atom abstraction being the primary process between amines and ketone triplets. However, the solvent effects on rates are seemingly inconsistent with an actual electron-transfer process. Consequently, we conclude that the formation of some sort of charge-transfer complex between tertiary amines and ketones must occur. This complex can then proceed on to actual radical ion pairs or transfer hydrogen to the carbonyl oxygen directly. Since the CT process merely creates a large dipole and not necessarily free charge, solvent effects can be expected to differ from those observed in electron-transfer processes. Koizumi has recognized this possibility in his fluorescence quenching studies.[13] In particular, the reorganized solvation of the CT complex may not be sufficient to offset the decreased availability of a hydrogen-bonded amine lone pair.[22]

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(17) (a) P. J. Wagner, unpublished work; (b) A. Padwa, W. A. Eisenhardt, R. Gruber, and D. Pashayan, *J. Am. Chem. Soc.*, **91**, 1857 (1969).

(18) P. J. Wagner, *ibid.*, **89**, 5898 (1967).

(19) This term is preferable to "reversible" since the latter, taken strictly, would imply that excited ketone is re-formed. Moreover, one connotation of "revert" is "return to an ancestral form."

(20) N. J. Leonard, D. F. Morrow, and M. T. Rogers, *J. Am. Chem. Soc.*, **79**, 5476 (1957), and preceding papers.

(21) We thank David Graber and Professor Alfred Haug of the Michigan State University AEC Plant Radiation Laboratory for the emission spectra.

Loss of Neutral Metal Fluorides in the Mass Spectra of Tris(1,1,1,5,5,5-hexafluoro-2,4-pentanedionato)metal Complexes

Sir:

In several recent mass spectral studies of the metal chelates of acetylacetone and its derivatives, a large body of indirect evidence has been accumulated to