Micellar Catalysis of the Basic Hydrolysis of Amides. 4. Substituted N,N-Diphenylbenzamides[1]

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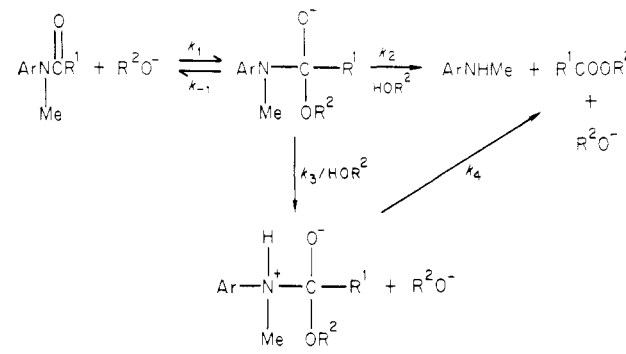
The catalysis of the basic hydrolysis of a series of *N*-aryl-*N*-phenylbenzamides (1) and a series of substituted *N,N*-diphenylbenzamides (2) by micelles of cetyltrimethylammonium bromide (ctab) has been studied. On the basis of the effects of substituents on the aromatic ring attached to the nitrogen atom, a mechanistic change on transfer from water to a micellar environment is proposed. In water the mechanism involves rate-determining solvent-assisted carbon–nitrogen bond breaking (mechanism B), while in the presence of micelles of ctab, a rate-determining attack of hydroxide ion (mechanism C) is proposed. Reasons for the mechanistic change are discussed.

The mechanism of basic hydrolysis and methanolysis of anilides is of current interest.[2-5] Recent work has shown that these reactions occur by an addition–elimination mechanism ($B_{AC}2$) involving an intermediate complex (Scheme I). Within this mechanistic framework, however, three different pathways have been found. Their occurrence depends primarily on the substituents on the aromatic ring[2,4] but also on the solvent.[6,7] With very poor amine leaving groups $k_2 \ll k_{-1}$, and a rate-determining protonation (k_3) of the nitrogen atom in the intermediate complex is necessary before C–N bond breaking (k_4, fast) can occur (mechanism A, $k_1 - k_3 - k_4$). For better amine leaving groups, solvent-assisted C–N bond breaking is the rate-determining step [mechanism B; $k_1 - k_2$ (rds)]. In the extreme case where the amine is a better leaving group than methoxide/hydroxide the rate-determining step becomes bond forming (mechanism C; k_1 (rds) $- k_2$).

One of the probes used to study the mechanism in a particular case is the use of Hammett plots of substituent effects on rate for a series of anilides substituted on the aromatic ring attached to the N atom. It has been found that the Hammett ρ value depends on the mechanism of reaction.[2,4-6] Typically, for methanolysis, mechanism A is characterized by a very small ρ value ($\sim$0) while mechanisms B ($\rho \simeq 3$) and C (ρ = 1.5–2.0) have substantial ρ values.

Of particular interest in this case is the possible occurrence of mechanism C. The operation of mechanism C in a particular case requires that $k_2 > k_{-1}$, i.e., that loss of amine anion is faster than loss of methoxide/hydroxide ion from the intermediate complex. One of the factors which governs the relative magnitude of k_2 and k_{-1} is the basicity of the two leaving groups. Thus the operation of mechanism C should be favored for anilides derived from weakly basic amines. With this in mind, the mechanism of the basic methanolysis of a series of *N*-aryl-*N*-phenylbenzamides was studied.[8] Surprisingly, the basic methanolysis of the *N*-aryl-*N*-phenylbenzamides was found to occur by mechanism B (ρ = 2.82). The operation of mechanism B for anilides in which the amine anion should be less basic than the leaving methoxide ion was explained by the presence of steric effects in the intermediate complex.[8] Inspection of space-filling molecular models shows that the nigrogen atom of the amine anion leaving group is very effectively buried in the intermediate complex. On the other hand, the oxygen of the methoxide leaving group is exposed to the solvent. Consequently, loss of methoxide ion from the intermediate complex (k_{-1}) can occur with solvent assistance whereas for the loss of the amine anion at least some degree of carbon–nitrogen bond breaking must occur without the assistance of the solvent. Thus the effect of solvent assistance to k_{-1} but not to k_2 results in $k_{-1} > k_2$ and the operation of mechanism B for the reaction in methanol.

Scheme I[a]



[a] R^2 = H or Me.

It was decided to look at the basic hydrolysis of some *N,N*-diphenylbenzamides (1 and 2) in the presence of micelles of cetyltrimethylammonium bromide (ctab). Micellar catalysis of anilide hydrolysis has been observed in a number of cases.[1,9-13] Furthermore, the observation of a micelle-induced mechanistic change (mechanism A to mechanism B) has been reported for the hydrolysis of some substituted toluanilides.[11] Hydrolysis of *N,N*-diphenylbenzamides in water would most likely occurs by mechanism B (cf MeOH). However, in the presence of micelles the operation of mechanism C may be favored by the positive electrostatic field of the micelle.

Results and Discussion

Rate constants for the basic hydrolysis of *N*-aryl-*N*-phenylbenzamides **1a–l** and substituted, *N,N*-diphenylbenzamides **2a–e** in the presence of micelles of ctab are

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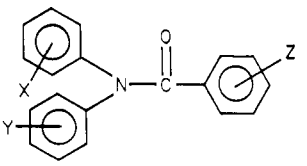

	X	Y	Z
1a,	4-OMe	H	H
b,	3-Me	H	H
c,	H	H	H
d,	4-F	H	H
e,	4-Cl	H	H
f,	3-F	H	H
g,	3-Cl	H	H
h,	3-CF_3	H	H
i,	3-NO_2	H	H
j,	4-NO_2	H	H
k,	3-Cl	3-Cl	H
l,	3,5-Cl_2	H	H
2a,	H	H	4-Cl
b,	H	H	3-Br
c,	H	H	4-CF_3
d,	H	H	3-NO_2
e,	H	H	*a*

[a] C_6H_4Z is replaced by 3-pyridyl.

given in Table I. Rate constants in the absence of ctab ($k_{2,w}$) are included for comparison purposes. Typical rate–[ctab] profiles are obtained from the data for these compounds.[14] The rate increases to a maximum ($k_{2,max}$) as the concentration of ctab is increased. This corresponds to the amount of ctab required to completely solubilize the substrate molecules. Bunton and others[15-18] have shown that the micellar catalysis of bimolecular reactions is mainly due to concentration of the reagents in the micellar pseudophase. Consequently, the addition of further detergent after complete solubilization has been achieved and the consequent dilution of the reagents in the micellar pseudophase result in a decrease in rate.

For one compound, **1b**, there is some doubt about the concentration of detergent required to give the maximum catalysis due to experimental error and a broad maximum in the rate–[ctab] profile. Consequently, an average value of the observed rate in the range 2–5 mM ctab was taken as $k_{2,max}$.

The rate–[ctab] profiles for compounds **1** and **2** show a very steep increase from $k_{2,w}$ to $k_{2,max}$, probably a result of the hydrophobicity of the bulky organic molecule. Problems with solubility of the reactants and/or the products were obtained for many compounds at [ctab] less than 2 mM. In fact, reactions in the absence of ctab had to be carried out in the presence of 20% methanol, with half the normal concentration of amide, to maintain the solubility of the reactants and products.

To get some indication of the kinetic effect of the addition of 20% methanol to the solvent, the rate of the basic hydrolysis of *N*-(4-nitrophenyl)-*N*-methyl-4-methylbenzamide (3) at 65.5 °C was determined in the presence of 0.5% (8.39×10^{-3} L mol^{-1} s^{-1}), 10% (1.69×10^{-2} L mol^{-1} s^{-1}), and 20% (1.78×10^{-2} L mol^{-1} s^{-1}) methanol by volume. Thus for compound **3**, the addition of 20% methanol to

Table I. Second-Order Rate Constants, k_2, for the Basic Hydrolysis of Some Substituted *N*,*N*-Diphenylbenzamides **1** and **2** in the Presence of ctab[d]

	10^3k_2, L mol^{-1} s^{-1} for [ctab] (mM) of														
compd	0[a]	1	1.5	1.8	2	2.5	3	3.5	4	4.5	5	6	7	8	10	15
1a					4.07		4.38		4.97		5.3[b]	4.8	4.42	3.74	3.73	3.21
1b	0.059				7.03[c]	6.65[c]	7.23[c]	7.20[c]	7.63[c]		6.95[c]	6.11		5.84	5.39	
1c	0.099				9.67	14.9[b]	14.4	12.9	13.5	12.5	11.4	11.7	12.2			
1d	0.173				23.0	28.2[b]	27.8	26.8	24.7	26.8	26.6	26.0				
1e	0.514	5.46			55.9	68.6[b]	60.9		60.4		58.4	52.3	47.5			
1f	0.749				55.1	53.4	58.4[b]	55.7	54.5	51.6	54.6	53.5	48.7			
1g	1.10	43		62.9	81.9	86.3[b]	86.1	82.5	80.3		78	71	64	64.2		
1h	1.45				105	116[b]	111	105	101		95.7	83.9	80.2	77.6		
1i	8.51	16.5			327		374	397	422[b]	372	375	353	313	302		
1j	50.6	84.1			1528		1625	1875[b]	1764	1684	1465					
1k	6.11		286		319[b]	305	274		266		244	217	195	194		
1l	8.07		404		443[b]	414	388		364		335	295	279	258		
2a	0.236				39.9	42.7[b]	40.8	36.7	36.4		32.3	29.9	29.8	27.5		
2b	0.386		48.5		59[b]	57.2	56.2		53.2		44.6	43.7	39.7			
2c					103	122[b]	107	109	96.2		90.3	81	75.4			
2d	2.0				178	202	210	214[b]	203		183	161	169	160		
2e	1.26															

[a] Rate constants in the absence of ctab, i.e., $k_{2,w}$. [Substrate] = 2.5×10^{-5} M; [NaOH] = 0.01–0.15 M. The solvent contains 20% MeOH (by volume). [b] Maximum observed rate, i.e., $k_{2,max}$. [c] The average of these results is taken as $k_{2,max}$, i.e., 7.12×10^{-3} L mol^{-1} s^{-1}. [d] At 65.5 °C; [substrate] = 5×10^{-5} M; [$Ba(OH)_2$] = 1.5×10^{-3} M.

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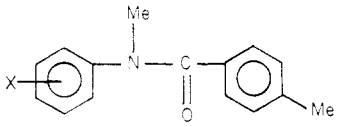
the solvent results in an approximate doubling of the rate of hydrolysis.

Hammett Correlations. (a) Effects of Substituents on the *N*-Aryl Ring. The effects of substituents on the *N*-aryl ring (i.e., X and Y, compounds **1a–l**) correlated well with Hammett σ values, except for the 4-nitro substituent for which a value intermediate between σ and σ^- was required (1.02). Such intermediate σ values for the 4-nitro substituent are common,[19] and experimental values ranging from 0.76 to 1.70[19] have been reported. Correlation of the rates of uncatalyzed hydrolysis gave $\rho = 2.63$ (correlation coefficient $r = 0.997$), while the rates of catalyzed hydrolysis ($k_{2,max}$) gave $\rho = 1.99$ ($r = 0.986$).

The mechanistic conclusions that can be drawn from these results are that the uncatalyzed reaction occurs by mechanism B ($\rho \simeq 3$) while the ctab-catalyzed reaction occurs by mechanism C ($\rho \simeq 1.5$–2.0). This change of mechanism is further substantiated by the observation that for reactions occurring by the same mechanism in both water and in a micelle, the ρ value in the micelle is greater than in water.

The reasons for an increase in the Hammett ρ values for reactions on transfer from water to a micelle were first proposed by Cordes[20] for the acid-catalyzed hydrolysis of substituted methyl orthobenzoates in the presence of sodium lauryl sulfate. More recently this was applied to the basic hydrolysis of amides in the presence of ctab.[1] On the basis of the Hammond postulate, the transfer of a reaction from water to a micellar environment leads to a more product-like transition state, and this is reflected in the larger ρ value for the catalyzed than for the uncatalyzed reaction. For the acid-catalyzed hydrolysis of substituted benzaldehyde diethyl acetals[21] $\rho_{H_2O} = -3.3$ and $\rho_{micelle} = -4.1$ while for the acid-catalyzed hydrolysis of substituted methyl orthobenzoates[20] $\rho_{H_2O} = -2.0$ and $\rho_{micelle} = -2.5$.

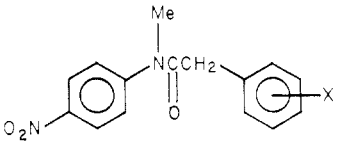
In the case of the basic hydrolysis of amides, hydrolysis of substituted *N*-aryl-*N*-methyl-4-methylbenzamides (**3**)



3, X = 3-Cl, 3-NO_2, 3-Cl-5-NO_2, or 3,5-$(NO_2)_2$

occurs by mechanism B both in water and in the presence of ctab. An increase in the Hammett ρ value on transfer from water (2.1) to ctab (2.4) was observed.[11]

The basic hydrolysis of a number of substituted *N*-methyl-*N*-(4-nitrophenyl)acetamides (**4**) occurs by mech-



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anism C both in water and in the presence of ctab. An increase in the Hammett ρ value on transfer from water (0.41) to ctab (0.74) was observed.[1] The rather small Hammett ρ values obtained in series **4** are a result of the substituent being on the acid ring rather than on the amine ring and also of the insulating effect of the methylene group between the reaction center and the substituent.

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Thus in bona fide examples of reactions which have mechanisms B and C in both aqueous and micellar media, the magnitude of the Hammett ρ value is increased on transfer from water to micellar solution. The basic hydrolysis of compounds **1a–l** (substituents on the amine ring) and compounds **2a–e** (substituents on the acid ring) constitute the first examples of a decrease in the magnitude of ρ on transfer from water to a micellar environment. Thus we conclude that the mechanism of hydrolysis of compounds **1** and **2** changes on transfer from water (mechanism B) to a micellar environment (mechanism C).

The results for compounds **1g,k,l** provide a comparison between compounds containing one chlorine substituent in the meta position (**1g**) and those containing two chlorine substituents in meta positions (**1k,l**). For both the catalyzed and uncatalyzed reactions the kinetic data for the monochloro compound (**1g**) fits well on the Hammett plot with the normal σ value for 3-Cl, i.e., 0.37. For the 3,5-dichloro-substituted compound **1l** (both chloro groups on the same aromatic ring), the kinetic data fits well on both Hammett plots with a σ of 0.74 (i.e., 2 × 0.37).

However, compound **1k**, with one *m*-chloro substituent on each aromatic ring, reacted approximately 25% slower than compound **1l**, and consequently the point for this compound lies below the line in both of the Hammett plots. The data for compound **1k** was not used in the statistical analysis of the substituent effects in this series.

The difference between the 3,5-Cl_2 compound **1l** and the 3,3′-Cl_2 compound **1k** may be rationalized after inspection of space-filling molecular models. Steric crowding in both the reactant and especially in the intermediate complex results in twisting of the aromatic rings attached to the nitrogen atom out of the plane of the N–C–O group. When both substituents are present on the same ring (**1l**), a conformation in which both chloro atoms are equidistant from the negative charge on the oxygen is possible. This is very similar to the situation for the monochloro compound **1g**. Hence a net doubling of the σ values for a *m*-chloro substituent is observed.

When the two chloro substituents are on different aromatic rings (**1k**), the conformation with both chloro atoms equidistant from the oxygen is not energetically favorable. Thus a nonadditive effect of the two *m*-chloro substituents is observed in this case.

(b) Effects of Substituents on the Benzoyl Ring. The effects of substituents on the benzoyl ring (i.e., Z in compounds **1c** and **2a–e**) also correlated well with σ. For the uncatalyzed reaction, solubility problems were encountered with the 4-CF_3-substituted compound, **2c**, and this compound was deleted. The (*N*,*N*-diphenyl-3-carbamoylphenyl)pyridine compound **2e** was used in its place. This compound was not used for the catalyzed reaction because of doubts about the effect of the hydrophilic azanitrogen atom on the solubilization of the substrate by the micelle. Previous studies[10] have shown that *N*-(4-pyridinyl)-*N*-methylbenzamide is not as efficiently solubilized as other amides which do not contain heterocyclic aromatic rings and also that the catalysis of this compound was significantly less. Fortunately, for the catalyzed reaction the 4-CF_3 compound **2c** could be used since the presence of ctab overcame the solubility problems.

Correlation of the rate of uncatalyzed hydrolysis with σ gave $\rho = 1.79$ ($r = 0.995$) while for the catalyzed reaction $\rho = 1.62$ ($r = 0.994$). Thus as for the effects of substituents on the *N*-aryl ring, the magnitude of ρ was less for the catalyzed reaction than for the uncatalyzed reaction.

Mechanistic Conclusions. From changes in the Hammett ρ value for substituents on the *N*-aryl ring on

transfer from water to a micellar solution it appears that reaction in water occurs by mechanism B whereas reaction in the micelle occurs by mechanism C. The similarity in the Hammett ρ value for basic methanolysis[8] and for the uncatalyzed hydrolysis (methanolysis, $\rho_{N\text{-aryl}} = 2.82$; $\rho_{\text{benzoyl}} = 1.95$; hydrolysis, $\rho_{N\text{-aryl}} = 2.63$; $\rho_{\text{benzoyl}} = 1.79$) lends strong support to the same mechanism occurring for both reactions. The reasons for the operation of mechanism B for basic methanolysis have been extensively discussed.[8] It would seem reasonable that the same factors apply in the basic hydrolysis.

Reaction in the presence of micelles of ctab, however, appears to occur by mechanism C, i.e., $k_2 > k_{-1}$. Basicity considerations[8] suggest that the basic methanolysis of amides of diarylamines containing substituents of equal or greater electron-withdrawing capacity than *p*-bromo should occur by mechanism C. However, basic methanolysis of these compounds has been shown to occur by mechanism B. This has been attributed to steric restrictions in the intermediate complex, i.e., loss of methoxide ion (k_{-1}) can occur with solvent assistance since the oxygen atom is exposed to the solvent, while loss of amine anion (k_2) cannot occur with solvent assistance since the nitrogen atom is very effectively buried.

In a micelle, the breakdown of the intermediate complex can be assisted by the positive electrostatic field of the micelle. This electrostatic field is not subject to steric approach arguments and consequently can affect both hydroxide ion and amine anion loss equally. Thus, in a micelle we expect to see the reactivity related to the basicity of the two nucleofuges without any complications caused by steric arguments. Thus the loss of the amide anions is favored over loss of hydroxide ion, $k_2 > k_{-1}$, and mechanism C is observed.

In fact, mechanism C is observed for the catalyzed reaction of all compounds in series **1**, i.e., 4-OMe to 4-NO_2, not just for those with electron-withdrawing substituents equal or better than 4-bromo. The changeover at the 4-bromo compound was predicted for basic methanolysis where k_{-1} involves loss of methoxide ion. In basic hydrolysis, however, k_{-1} involves loss of hydroxide ion. In dilute solution (0.2 M) hydroxide ions in water are more basic (H_- = 13.3) than methoxide ions in methanol (H_- = 12.9).[22] At a 1 M concentration both hydroxide in water and methoxide in methanol have almost identical basicity (H_- = 14.01 ± 0.02). The difference in basicity thus increases in more dilute solution. The kinetics of the ctab-catalyzed basic hydrolysis were carried out at 3 mM hydroxide ion and the basic methanolysis at 2–80 mM methoxide ion.[8]

The operation of mechanism C for the ctab-catalyzed hydrolysis of all compounds in series **1**, including the *p*-methoxy-substituted compound ($\sigma = -0.27$),[23] thus occurs because hydroxide ion is a stronger base (lower k_{-1}) than methoxide ion, and thus $k_2 > k_{-1}$ for all compounds in the basic hydrolysis.

Experimental Section

Materials. Compound **1a–c,e,g,i,j,2a,d** were available from previous work.[8]

Compounds **1d,f,l** were prepared by the Chapman rearrangement[24] by heating the aryl *N*-phenylbenzimidate[25] in a sealed tube at 250–300 °C. Recrystallization from EtOH afforded white crystals which were shown to be pure by TLC analysis (SiO_2/CH_2Cl_2). Compound **1k** was prepared as an oil, pure by TLC analysis, by the Chapman rearrangement by heating 3-chlorophenyl *N*-(3-chlorophenyl)benzimidate in a sealed tube at 250 °C. The following data were obtained. **1d**, mp 162–164 °C. Anal. Calcd for $C_{19}H_{14}FNO$: mol wt 291.1059. Found: mol wt 291.1059 (high-resolution mass spectrometry). **1f**, mp 117–118 °C. Anal. Calcd for $C_{19}H_{14}FNO$: mol wt 291.1059. Found: mol wt 291.1059 (high-resolution mass spectrometry). **1l**, mp 112–113 °C (lit.[26] mp 107–109 °C). The molecular weight determination for **1k** gave the following results. Anal. Calcd for $C_{19}H_{13}Cl_2NO$: mol wt 341.0374. Found: mol wt 341.0377 (high-resolution mass spectrometry).

Compounds **2b,c,e** were prepared by the reaction of diphenylamine with the appropriate substituted benzoyl chloride in pyridine.[27] Recrystallization from EtOH gave colorless crystals that were shown to be pure by TLC analysis. The following data were obtained. **2b**, mp 97.5–98.5 °C. Anal. Calcd for $C_{19}H_{14}BrNO$: mol wt 351.0259. Found: mol wt 351.0255 (high-resolution mass spectrometry). **2c**, mp 149–150 °C. Anal. Calcd for $C_{20}H_{14}F_3NO$: mol wt 341.1028. Found: mol wt 341.1029 (high-resolution mass spectrometry). **2e**, mp 146.5–147 °C (lit.[28] mp 147–148 °C).

Compound **1h** was prepared by the reaction of phenyl [3-(trifluoromethyl)phenyl]amine with benzoyl chloride in pyridine.[27] Phenyl[3-(trifluoromethyl)phenyl]amine was prepared by the method of Smith.[29] Crude **1h** was purified by preparative TLC (SiO_2, CH_2Cl_2) to give an oil which was pure by TLC. Anal. Calcd for $C_{20}H_{14}F_3NO$: mol wt 341.1028. Found: mol wt 341.1029 (high-resolution mass spectrometry).

Distilled water was further purified by a Millipore system. The ctab was purified by the method of Mukerjee and Mysels.[30]

Kinetics. Rate constants for the basic hydrolysis of compounds **1** and **2** at 65.5 °C were determined by using a thermostated Varian 635 ultraviolet–visible spectrophotometer.

Stock solutions of amide, barium hydroxide (or sodium hydroxide), and ctab were prepared in purified water. For slow reactions ($t_{1/2}$ >30 min) the required volumes of amide, hydroxide, and ctab stock solutions were pipetted into a 50-mL volumetric flask and then diluted to the mark with water. This solution was then placed in the curvette. The solution was allowed 15 min to reach temperature equilibrium, and then the recorder was started. The rate of production of the amine product was monitored for at least 75% reaction. The infinity value was calculated by a computer program designed to give the best linear regression analysis of the $\log_{10}$ form of the data. Good agreement was obtained between rate constants obtained by this method and those obtained by following the reaction for 10 half-lives to get an experimental infinity measurement.

Faster reactions were studied by pipetting the required volumes of hydroxide and ctab stock solutions into a 50-mL volumetric flask and diluting to the mark with water. A 3-mL sample of this solution was then pipetted into the cuvette which was then placed in the thermostated cell holder for 15 min. The reaction was initiated by the addition of 18 μL of a 1×10^{-2} M solution of the amide in methanol.

Reactions were carried out under pseudo-first-order conditions, $[OH^-] \gg$ [amide], and second-order rate constants were obtained from the observed pseudo-first-order rate constants by using eq 1.

$$k_2 = k_1/[OH^-] \quad (1)$$

Electron-impact mass spectra were carried out by using a JEOL-JMS-D100 mass spectrometer.

Registry No. **1a**, 73333-81-0; **1b**, 73333-80-9; **1c**, 4051-56-3; **1d**, 77826-08-5; **1e**, 23938-23-0; **1f**, 77826-09-6; **1g**, 73347-61-2; **1h**, 77826-10-9; **1i**, 73333-85-4; **1j**, 73333-79-6; **1k**, 77826-11-0; **1l**, 77826-12-1; **2a**, 15732-27-1; **2b**, 77826-13-2; **2c**, 77826-14-3; **2d**, 73333-82-1; **2e**, 77826-15-4; ctab, 57-09-0.

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