497. The Kinetics of Hydrogen Isotope Exchange Reactions. Part X.* The Acid-catalysed Detritiation of [o-³H]p-Cresol in Water and in Deuterium Oxide.

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The loss of tritium from [o-³H]p-cresol has been studied kinetically in aqueous hydrochloric acid in the approximate concentration range 3·5—6·5N. The reaction velocity has the same dependence on acidity as the previously investigated exchange of [o-²H]p-cresol. At the same acidity, detritiation is 2—3 times slower than dedeuteration. The detritiation occurs 1·6₂ times faster in deuterium oxide than in protium oxide solutions of 4N-hydrochloric acid. The velocity in mixtures of deuterium oxide and water follows the predictions of the Gross–Butler theory. The mechanism of aromatic hydrogen exchange is discussed.

IN some of the earlier parts [1] of this series, evidence concerning the mechanism of acid-catalysed hydrogen-isotope exchange in aromatic systems has been obtained by studying the dependence of the exchange velocity on the acidity of the medium. In the course of our discussion of these earlier results we indicated [1a] that comparative studies of deuterium and tritium exchange might provide further information about the mechanism. Experiments of this kind have now been carried out. The rate of loss of tritium from [o-³H]p-cresol to aqueous hydrochloric acid has been studied, and the result compared with the rate of the previously studied [1c] analogous reaction of [o-²H]p-cresol, in order to establish the effect of the isotopic mass of the leaving atom. The effect of varying the nature of the entering isotope has been examined by following the rate of loss of tritium from this compound in deuterium oxide, in water, and in mixtures of the two as solvents.

EXPERIMENTAL

Materials and Equipment.—Tritium was supplied (as THO), by the Atomic Energy Authority, in ampoules of 1 ml. with a nominal activity of 0·2 curie/ml. The deuterium oxide was the Norsk Hydro product; that used contained 99·8 wt. % of D_2O. The counting was performed with an Ekco N612 scintillation unit in conjunction with an Ekco N529 B scaler, and an E.H.T. unit 532A supplied by Isotope Developments Ltd. The scintillation solution (to which a sample to be counted was added) contained only Eastman Organic Chemicals' P.P.O. (2,5-diphenyloxazole) dissolved in " AnalaR " toluene. [o-³H]p-Cresol was prepared essentially by Gold and Satchell's method,[1a] active aqueous perchloric acid being used. Two samples were made, m. p. 35°, which exhibited activities corresponding to 21% and 66% of that expected for complete exchange equilibrium.

Procedure for Kinetic Experiments.—The first-order loss of tritium from p-cresol, dissolved in an excess of inactive aqueous acid, was followed by extracting samples of the solute and determining the loss of activity. (Under the conditions used, negligible activity accumulates in the phenolic group.)

Small known amounts of cresol (*ca.* 0·04 g.) were dissolved in acid (10 ml.) contained in flasks fitted with ground-glass stoppers, and having an additional sealing of Apiezon Q compound. The flasks, and contents, were kept at 25° in a thermostat bath. At intervals, 1 ml. samples were withdrawn, run into 5 ml. graduated flasks, neutralised to Methyl Orange with concentrated sodium hydroxide, and then rendered slightly acid by addition of one drop of 2N-hydrochloric acid. " AnalaR " toluene (2 ml.) and water were now added to bring the volume to 5 ml. After shaking, the layers were separated with the aid of a pipette. The aqueous layer was further extracted with one 2 ml. and four 1 ml. portions of toluene. (It was shown that this procedure gave a quantitative extraction.) The toluene extracts were placed

* Part IX, *J.*, 1959, 966.

[1] (a) Gold and Satchell, *J.*, 1955, 3609; (b) *ibid.*, p. 3619; (c) *ibid.*, p. 3622; (d) Satchell, *J.*, 1958, 1927.

in a graduated tube and made up to 8·5 ml. This solution was neutralised and dried with small amounts of barium carbonate and magnesium sulphate, and 5 ml. were then taken for counting. Eight samples were taken for each run. To conserve deuterium oxide, the solvent acid volume was restricted to 5 ml. for solutions rich in deuterium, and 0·5 ml. samples were taken at intervals. In these cases, the concentration of cresol remained similar, but the more active of the two specimens was used to maintain a suitable counting rate. The initial sample (at $t = 0$) had an activity providing *ca.* 80,000 counts/min. The counting time was sufficient to give a statistical accuracy of better than 1%. All the samples for a given run were counted on the same day to minimise instrumental fluctuation, and all the counting solutions for a given run contained the same concentration of cresol, so that any quenching by this solute will have been the same in each. It was also shown that added cresol, in amounts up to 10 times that usually present in the counting mixtures, had little quenching effect.

Composition of the Acid Solvents.—Studies were made in five aqueous hydrogen chloride solutions with molarities varying between 3·5 and 6·7. These were prepared by the dilution of a stock hydrogen chloride solution. Studies were also made with seven different H_2O–D_2O mixtures, each containing 4·0M-hydrogen chloride. Since both the molar and the partial

FIG. 1. *Dependence of exchange velocity on acidity.*
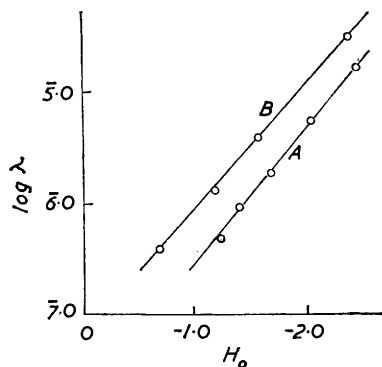
A, *Detritiation (this work).*
B, *Dedeuteration (ref. 1c).*

FIG. 2. *Dependence of exchange velocity on isotopic composition of medium.*
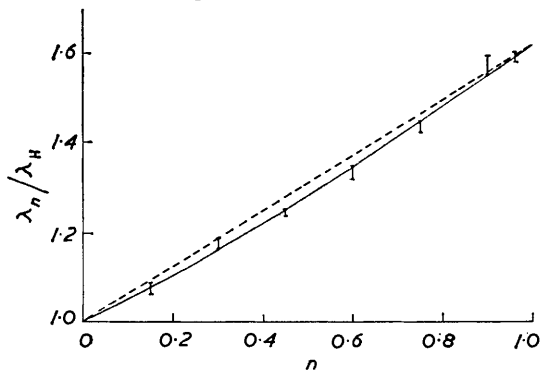
Full curve, calculated for $\lambda_D/\lambda_H = 1·62$.
The broken curve is straight.

molar volumes of water and deuterium oxide are very similar, mixtures of the two may be accurately made up by volume. For the solutions rich in deuterium a 7M-solution of hydrogen chloride in deuterium oxide was prepared and diluted with deuterium oxide (or water) as desired. The greatest atom fraction [D/(D + H)] obtainable for a 4·0M-hydrogen chloride solution, when starting with 99·8% deuterium oxide and protium chloride, is 0·962. This was considered sufficiently close to unity for the present purpose, and no attempt was made to use deuterium chloride. The 7M-stock solution in deuterium oxide was made by absorbing the dry gas under conditions which excluded atmospheric moisture and allowed none of the gas to bubble through the solution and escape—a process which would lead to loss of deuterium. The solutions poor in deuterium were prepared by appropriate addition of deuterium oxide to a stock aqueous hydrogen chloride solution.

Results.—The various rate constants, and others, for comparison, drawn from previous work, are tabulated. The dependence of exchange velocity on acidity and on the isotopic composition of the medium is shown in the Figures.

DISCUSSION

As Fig. 1 shows, the tritium exchange rate increases with acidity in the same manner as the deuterium exchange. Roughly parallel behaviour is required by any mechanism so far considered for this exchange reaction and therefore does not, by itself, provide a new criterion of mechanism. The best straight lines drawn through the two sets of data have slopes of −1·14 for deuterium exchange, and −1·23 for tritium exchange. No reliance is

placed on this small difference in slope, which may perhaps arise from experimental errors affecting the points outside the most convenient part of the velocity range. The experimental data for $[o\text{-}^2\text{H}]p$-cresol are those for which in our earlier paper [1c] we reported a slope of $-1\cdot40$ for the line of log λ against H_0. The changed value is due to a recent revision [2] of the H_0 scale for aqueous hydrochloric acid.

The distance between the lines indicates that deuterium loss is 2—3 times more rapid than tritium loss. This is in approximate agreement with ratios in the range $1\cdot5$—$1\cdot9$ recently reported [3] for somewhat different experimental conditions, *viz.*, heterogeneous exchange between sulphuric acid and isotopically substituted benzene and toluene. An isotope effect of this magnitude is substantial, since we are here comparing the masses 2 and 3, as against the more familiar primary hydrogen isotope effects in which the masses 1 and 2 are concerned.

TABLE 1. *Loss of tritium from* $[o\text{-}^3\text{H}]p$-*cresol to aqueous hydrochloric acid at* $25°$.

HCl (M)	3·50	4·00	4·76	5·72	6·71
$-H_0$	1·23	1·40	1·68	2·03	2·43
$10^7\lambda$ (sec.$^{-1}$)	4·88	9·44	18·7	54·6	164·0

TABLE 2. *Loss of tritium from* $[o\text{-}^3\text{H}]p$-*cresol to water–deuterium oxide mixtures containing* $4\cdot00$M-*hydrochloric acid, at* $25°$.

n = atom fraction of D in solvent; λ_n, λ_n', λ_n'', and λ_n''' are the rate constants for atom fraction n, corresponding respectively to the best lines obtained by inspection, by a least-squares treatment of the first 6 points, by a similar treatment of points 2—6, and by a similar treatment of all 8 points.

n	$10^7\lambda_n$	$10^7\lambda_n'$	$10^7\lambda_n''$	$10^7\lambda_n'''$	n	$10^7\lambda_n$	$10^7\lambda_n'$	$10^7\lambda_n''$	$10^7\lambda_n'''$
0·00	9·55	9·437	9·55	9·77	0·75	13·9	13·45	13·68	14·04
0·15	10·1	10·15	10·21	10·61	0·90	14·9	14·65	15·21	15·12
0·30	11·1	11·02	11·31	11·43	0·96	15·3	15·01	15·10	15·59
0·45	11·9	11·82	11·94	12·19	1·00 *	15·5	15·29	15·47	15·83
0·60	12·8	12·45	12·84	13·04					

* Extrapolated values.

TABLE 3. *Calculated and experimental rate ratios for water–deuterium oxide mixtures.*

k_n'/k_H represents the calculated rate for a solvent of atom fraction n, relative to that in pure water (see text).

n	k_n'/k_H	λ_n/λ_H	λ_n'/λ_H'	λ_n''/λ_H''	$\lambda_n'''/\lambda_H'''$	n	k_n'/k_H	λ_n/λ_H	λ_n'/λ_H'	λ_n''/λ_H''	$\lambda_n'''/\lambda_H'''$
0·00	1	1	1	1	1	0·75	1·450	1·45	1·425	1·432	1·437
0·15	1·078	1·06	1·075	1·070	1·086	0·90	1·553	1·56	1·553	1·593	1·547
0·30	1·162	1·16	1·168	1·185	1·170	0·96	1·594	1·60	1·591	1·581	1·595
0·45	1·252	1·24	1·253	1·251	1·248	1·00 *	1·620	1·62	1·620	1·620	1·620
0·60	1·350	1·34	1·320	1·345	1·335						

* Extrapolated values.

The results in Table 3 and Fig. 2 show that for solutions containing 4N-hydrochloric acid the exchange in deuterium oxide as solvent is $1\cdot6_2$ times faster than in water. The results in water–deuterium oxide mixtures agree with the predictions of the Gross–Butler theory [4] based on this rate ratio. To avoid unconscious bias in the evaluation of rate constants, these were computed by the method of least squares, and the uncertainty of the rate ratios—as revealed by computations based on slightly different assumptions as to the most reliable range of each of the runs—is indicated in the graphs. Although the systematic error of the rate *constants* can be appreciably higher, it is thought that the probable error of the rate *ratios* does not exceed $\pm2\cdot8\%$. The value for deuterium oxide as solvent is based on a short extrapolation from the atom fraction 0·96, which proved to be the highest proportion of deuterium attainable without the use of deuterium chloride in

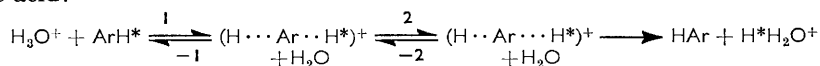[2] Bell, Dowding, and Noble, *J.*, 1955, 3106.
[3] (a) Olsson, *Arkiv Kemi*, 1959, **14**, 85; (b) cf. Melander and Olsson, *Acta Chem. Scand.*, 1956, **10**, 879.
[4] Butler and Orr, *J.*, 1937, 330; Nelson and Butler, *J.*, 1938, 958; Gross *et al.*, *Trans. Faraday Soc.*, 1936, **32**, 877, 879, 883.

the preparation of the acid solutions. The extrapolation does not admit much latitude, and it was verified that small variations of the value of λ_D would not substantially worsen or improve the fit of the curve.

Unfortunately, the agreement of the intermediate rate ratios with the predictions of the Gross–Butler theory cannot be adduced as diagnostic evidence for any particular reaction mechanism, since one of us has recently shown [5] that the result is equivocal in this application (see also later discussion).

We have previously proposed a mechanism for acid-catalysed aromatic hydrogen exchange which involves the rapidly reversible formation of a conjugate acid of the aromatic substrate, in which the entering and departing isotopic hydrogen atoms occupy non-equivalent positions,† and a subsequent rate-determining rearrangement of that conjugate acid:

$$H_3O^+ + ArH^* \underset{-1}{\overset{1}{\rightleftharpoons}} (H \cdots Ar \cdots H^*)^+ \underset{-2}{\overset{2}{\rightleftharpoons}} (H \cdots Ar \cdots H^*)^+ \longrightarrow HAr + H^*H_2O^+$$
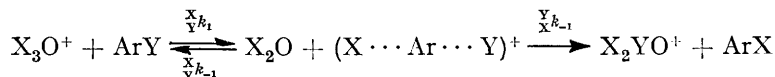$$+H_2O \qquad\qquad +H_2O$$

The isotope effects now observed can be explained on this model as follows: The difference between the dedeuteration and detritiation velocities is due to the loosening of the ejected atom in the formation of the transition state of the slow step. The rate difference between water and deuterium oxide is ascribed to a combination of two opposed effects, *viz.*, the effect on the acid–base pre-equilibrium, which will cause the concentration of the conjugate acid of the substrate to be greater in deuterium oxide solution (perhaps by a factor of 2—3) and a smaller reverse effect of the mass of the entering isotope in the rearrangement step. The present observations are therefore compatible with the model previously put forward. However, they are also compatible with other mechanistic models. For instance, with (*a*) models involving no intermediates, and (*b*) a model involving a symmetrical intermediate, $H \cdots Ar \cdots H^*$.

(*a*) The only hypothesis required to explain the two isotope effects in a model without intermediates concerns the tightness of binding of hydrogen in the aromatic substrate, in the transition state (here assumed to be symmetrical with respect to the hydrogen atoms undergoing exchange), and in the hydroxonium ion. If it is assumed that this binding becomes progressively looser along this series—so that a heavier hydrogen isotope will cause the greatest stabilisation in the aromatic substrate, a smaller one in the transition state, and a slightly smaller one yet in the hydroxonium ion—then the observed isotope effects may be explained.

(*b*) An exchange mechanism involving a symmetrical intermediate would be analogous to the type of mechanism postulated by Melander [6] in explanation of the isotope effects observed in certain other electrophilic aromatic substitutions, and supported by Zollinger [7] in discussion of his work on isotope effects in diazo-coupling reactions.

In this scheme, there are two potential-energy maxima, one on each side of the intermediate. If it is assumed that the binding of hydrogen at the two maxima is tighter than in the hydroxonium ion but looser than in the intermediate and in the aromatic molecule, then the observed effects may be accounted for. The numerical values, given below, illustrate these qualitative arguments for this particular mechanism, which can be written as follows (X and Y denoting two hydrogen isotopes):

$$X_3O^+ + ArY \underset{{}^X_Y k_{-1}}{\overset{{}^X_Y k_1}{\rightleftharpoons}} X_2O + (X \cdots Ar \cdots Y)^+ \overset{{}^Y_X k_{-1}}{\longrightarrow} X_2YO^+ + ArX$$

In this notation ${}^X_Y\lambda = {}^X_Y k_1 \cdot {}^Y_X k_{-1}/({}^Y_X k_{-1} + {}^X_Y k_{-1})$.

† Other writers have referred to this intermediate as a π-complex, although we were careful to avoid this term.

[5] Gold, *Trans. Faraday Soc.*, 1960, **56**, 255.
[6] Melander, *Arkiv Kemi*, 1950, **2**, 213.
[7] Zollinger, *Experientia*, 1956, **12**, 165.

Thus, for the two effects observed, we have

$$\frac{{}^{H}_{D}\lambda}{{}^{H}_{T}\lambda} = \frac{{}^{H}_{D}k_1}{{}^{H}_{T}k_1} \cdot \frac{{}^{D}_{H}k_{-1}}{{}^{T}_{H}k_{-1}} \cdot \frac{{}^{H}_{T}k_{-1} + {}^{T}_{H}k_{-1}}{{}^{H}_{D}k_{-1} + {}^{D}_{H}k_{-1}} \simeq 2\cdot5$$

$$\frac{{}^{D}_{T}\lambda}{{}^{H}_{T}\lambda} = \frac{{}^{D}_{T}k_1}{{}^{H}_{T}k_1} \cdot \frac{{}^{T}_{D}k_{-1}}{{}^{T}_{H}k_{-1}} \cdot \frac{{}^{H}_{T}k_{-1} + {}^{T}_{H}k_{-1}}{{}^{D}_{T}k_{-1} + {}^{T}_{D}k_{-1}} \simeq 1\cdot6$$

The following set of rate ratios is consistent with these effects:

$${}^{H}_{D}k_1/{}^{H}_{T}k_1 = 2,\quad {}^{D}_{H}k_{-1}/{}^{T}_{H}k_{-1} = 2,\quad {}^{H}_{T}k_{-1}/{}^{T}_{H}k_{-1} = 2\cdot5,\quad {}^{D}_{T}k_1/{}^{H}_{T}k_1 = 1\cdot05,\quad {}^{T}_{D}k_{-1}/{}^{T}_{H}k_{-1} = 1\cdot25$$

It is emphasised that this particular set of values is not the only possible one which fits the results, though rather little latitude exists in the choice of the ratios.

Thus, while the isotope effects we have observed do not refute our mechanism involving an unsymmetrical intermediate, nevertheless they do not support it in any positive sense and it is, perhaps, pertinent to re-examine the whole question of whether the inclusion of such an intermediate is essential to an understanding of the exchange process, for doubts concerning this have been expressed by Long and Paul[8] and by Melander and Myhre.[9]

It is recalled that the proposed mechanism involving unsymmetrical conjugate acids as intermediates was based on the interpretation of the observed linear logarithmic dependence of the exchange velocity on Hammett's acidity function H_0.   It has since been shown that this result is not confined to the aqueous acids first studied, but is also found in other widely differing acidic solvent systems.[10]   The nature of the recent criticism of our proposals by Long and Paul, and by Melander and Myhre, is that a mechanism involving slow proton transfers from solvent acid species might also be expected to show correlations with H_0, and that, therefore, unsymmetrical conjugate acid intermediates are not required by our kinetic observations.   These two sets of authors base their expectations on different grounds, between which it is important to distinguish.

Long and Paul expect a correlation with H_0 even when the bases from which the protons are being transferred participate in the transition state.   As regards transfers from the hydroxonium ion, they remark that the water molecule in the transition state will be a " solvation molecule," and imply that its presence, or absence, in the transition state will not, therefore, affect the activity coefficient of the latter.   It has, however, been pointed out that the only available experimental measurements do not support this suggestion.[11]   In addition, there are further difficulties for this particular reaction model.

Gold and Satchell[1a] observed the exchange rate to follow H_0 over the approximate composition range 10—85% sulphuric acid by weight in mixtures with water.   Over this range the hydrogen ion is not the only Brønsted acid in the system since the presence of H_2SO_4 molecules is experimentally established[12] above 66%.   A rate-determining proton transfer, of the type accepted by Long and Paul, would be expected to involve additive contributions from the various acids (after the manner of general acid catalysis), in particular from H_3O^+ and the stronger acid H_2SO_4, although no other example of this kinetic behaviour is known with certainty.   Accordingly, the rate constant of exchange would be expected to be given by

$$\lambda = k_{H_3O^+}[H_3O^+]\, f_{ArH}\, f_{H_3O^+}/f^{\ddagger}_1 + k_{H_2SO_4}[H_2SO_4]\, f_{ArH}\, f_{H_2SO_4}/f^{\ddagger}_2$$

where the activity coefficients $f^{\ddagger}_1$ and $f^{\ddagger}_2$ refer to the transition states for proton transfer from H_3O^+ and H_2SO_4 respectively, and square brackets denote concentration. Proportionality between λ and h_0 is compatible with this mechanism only if certain obvious

[8] Long and Paul, *Chem. Rev.*, 1957, **57**, 935.
[9] Melander and Myhre, *Arkiv Kemi*, 1959, **13**, 507.
[10] (*a*) Satchell, *J.*, 1956, 3911; (*b*) *ibid.*, 1958, 1927, 3910; (*c*) Mackor, Smit, and van der Waals, *Trans. Faraday Soc.*, 1957, **53**, 1309.
[11] Kresge and Satchell, *Chem. and Ind.*, 1958, 1328.
[12] Young, *Record of Chem. Progress*, 1951, 81.

assumptions are made concerning the values of the various terms in the above equation. We do not feel that these assumptions are probable ones, and it was our reluctance to base an interpretation on such assumptions which led us to abandon our preconception that exchange in acidic media involves a slow proton transfer and to put forward what seemed to be more straightforward mechanistic proposals.   The more recently discovered fact [10a] that deuterium exchange of anisole occurs at similar speeds in sulphuric acid–water and sulphuric acid–acetic acid mixtures of the same H_0 value (*i.e.*, in media where different carriers of the proton must be present) is in full agreement with our mechanism, but requires *ad hoc* postulates if there is a slow proton transfer in which the conjugate base of the solvent acid becomes part of the transition state.   It therefore seems most probable to us that an acceptable mechanism should involve a transition state containing only the aromatic substrate and a proton.

Besides our solution of this problem, two others have been put forward.   One of these is the " freer proton " theory of de la Mare, Hughes, Ingold, and Pocker.[13]   We have previously given reasons for disfavouring this model.   The other solution is that of Melander and Myhre,[9] who have recently pointed out, in effect, that the unsymmetrical " structure " of composition SH^+ postulated by Gold and Satchell *need* not correspond to a potential minimum along the reaction co-ordinate.   No experimental criterion based on kinetic analysis is known at the moment by which to detect the presence or absence of a slight potential minimum preceding the transition state.   In particular, the Gross–Butler test [4] could not distinguish between a mechanism involving structures of SH^+ which are intermediates in the generally accepted sense, and a mechanism involving similar structures which do not correspond to a stable configuration (quite apart from the equivocal status of this procedure as a test of the *composition* of the transition state [5]).

Among other discussions of the exchange mechanism is the suggestion [14] that the slow step may involve an isomerisation from $Ar\begin{smallmatrix}D\\H-S\end{smallmatrix}$ to $Ar\begin{smallmatrix}D-S\\H\end{smallmatrix}$, where H–S is an acid species. Such a scheme would not be expected to lead to the dependence on H_0 which is commonly observed.

Finally, the recent discovery [15] of exchange in 1,3,5-trimethoxybenzene under the catalytic influence of acetic acid molecules in aqueous solution suggests that under these conditions it is possible to realise the general acid catalysis which we have failed to detect in the strong acids and on the absence of which our mechanism was based.   The results are very significant to the exchange mechanism in dilute aqueous solution with a strongly basic substance such as 1,3,5-trimethoxybenzene and imply that in these reactions the conjugate base of the catalyst remains part of the transition state.   It is not certain how far one may generalise this conclusion.   It seems quite likely that a drastic change in reactivity of the exchanging substrate would stabilise the symmetrical intermediate HArH* so that the transition state for proton detachment requires the presence of a base. This would in turn require the transition state for formation of HArH* to involve the whole catalyst acid molecule and hence give rise to general acid catalysis.   Similar ideas were expressed by Gold and Long [16] in relation to hydrogen exchange in the strongly basic aromatic molecule, anthracene.   For this molecule the high stability of the symmetrical ion $(ArH_2)^+$ had been established by spectroscopic studies.[17]

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[13] de la Mare, Hughes, Ingold, and Pocker, *J.*, 1954, 2930.
[14] Dallinga, Verrijn Stuart, Smit, and Mackor, *Z. Elektrochem.*, 1957, **61**, 1019.
[15] Kresge and Chiang, *J. Amer. Chem. Soc.*, 1959, **81**, 5509.
[16] Gold and Long, *J. Amer. Chem. Soc.*, 1953, **75**, 4543.
[17] Gold and Tye, *J.*, 1952, 2172.