BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, VOL. 44, 832—835 (1971)

The Reaction of α-Carbonyl Sulfides with Bases. II. The Effect of Variation in the Nucleophiles

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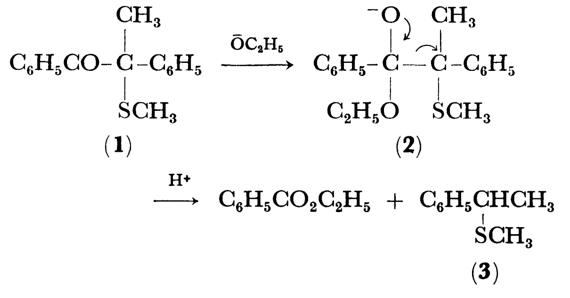
(Received September 29, 1970)

The reactions of α-alkylthio ketones with various nucleophiles were examined. It was found that such "strong bases" as ethoxide did not cause any cleavage of the C–S bond, whereas such "weak bases" as thiourea could cause the cleavage. The phenomena may be explained by the concept of soft-and-hard acids and bases. Discussions are given of some reactions of the nucleophilic attack on sulfur, which have previously been reported, in the light of this new reaction.

Since α-carbonyl sulfides were found to produce the parent keones and esters on treatment with the thiolate anion, it seemed that it would be interesting to study how widely this reaction is applicable. In the preceding paper[1] we have reported that this kind of reactions occurs not only with the α-carbonyl thioethers but also with α-thiocyano ketones and α-mercapto or α-acetylthio ketones. The purpose of this paper is to report on the effect of the kind of nucleophiles on the reaction of α-carbonyl sulfides. As examples of the latter compounds, α-alkylthio ketones were chosen because of their high reactivity.

Results and Discussion

Since thiolate was able to reduce α-alkylthio ketones, it is natural to examine the reaction of the oxygen analogs. Thus sodium ethoxide was allowed to react with α-(ethylthio)acetophenone in boiling ethanol for 1.5 hr. This treatment ended in the recovery of the starting material. One of the reasons for the recovery of this compound could be the enolization of the ketone, which might compete favorably with the nucleophilic attack on the sulfur atom. α-Methyl-α-(methylthio)-deoxybenzoin (**1**) was chosen as an example to be treated with ethoxide, because this compound has no α-hydrogen and the anion expected to be produced should be stable. The formation of the anion should thus be favored.



(**1**) (**2**) (**3**)

However, the products were not the expected α-methyl-

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[1] M. Ōki, W. Funakoshi, and A. Nakamura, This Bulletin, **44**, 828 (1971).

Table 1. The reaction of α-methylthiodeoxybenzoin with various nucleophiles in ethanol

Nucleophile	Heating Period (hr)	Products and Yields	Atmosphere
CN^-	15	$C_6H_5COCH_2C_6H_5$ (78%)	air
SCN^-	25	$C_6H_5COCOC_6H_5$ (trace) $C_6H_5COCH_2C_6H_5$ (trace)	N_2
$(NH_2)_2CS$	35	$C_6H_5COCH_2C_6H_5$ (13%) 85% Recovery	air
Br^-	27	92% Revovery No Product Found	N_2
Br^-	24	92% Revovery $C_6H_5COCOC_6H_5$ (trace) $C_6H_5COCH_2C_6H_5$ (trace)	air
I^-	24	$C_6H_5COCOC_6H_5$ (98%)	air
I^-	48	90% Recovery No Product Found	N_2
I^- [a)]	48	No Reaction	air
$C_2H_5O^-$ [a)]	25	$C_6H_5CH(CH_3)SCH_3$ and $C_6H_5CO_2C_2H_5$ only (vpc)	air
$(C_6H_5)_3P$ [b)]	20	$C_6H_5COCH_2C_6H_5$ (almost quantitative)	air

a) The substrate is α-methyl-α-(methylthio)deoxybenzoin.
b) The substrate is α-(ethylthio)deoxybenzoin.

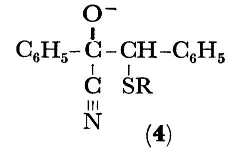
deoxybenzoin and other sulfur compounds; rather, ethyl benzoate and methyl 1-phenylethyl sulfide (**3**) were detected by means of vapor-phase chromatography. Indeed, benzoic acid was isolated after hydrolysis. It is clear that the attack by the ethoxide ion on sulfur is very slow and that the usual ketone cleavage by the base takes place *via* the adduct **2**.

Similarly, α-(methylthio)acetophenone did not give acetophenone on treament with sodium amide, although the amide anion is known to be a stronger base than ethoxide. Thus, it seemed that the capability of causing the C–S scission is not dependent on the base strength expressed by the pK_a values of the conjugate acids. This was experienced in many reactions of carbonium ions[2] and sulfur compounds;[3] the term "thiophilicity" has been proposed to express the nucleophilicity of bases when the site to be attacked is the sulfur atom. Thus, α-(methylthio)deoxybenzoin and its homologs were treated with various bases; the results are given in Table 1.

It can be pointed out that phosphine, cyanide ion, and thiourea are favorable for cleaving the C–S bond to produce deoxybenzoin. Some bases yielded benzil, which must be a product of the simultaneous desulfurization and oxidation; this tendency is clear with the iodide ion. However, in the absence of oxygen, the formation of benzil is not observed, indicating that the reaction is very probably of a radical nature. Support for this idea is given by the reaction of α-methyl-α-(methylthio)deoxybenzoin (**1**), which is not affected under similar conditions. Thus α-hydrogen is necessary to induce the change.

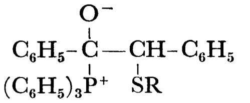
It seems that the higher polarity of the solvents is also a necessary condition for inducing this kind of reaction, for α-(ethylthio)acetophenone failed to give acetophenone when treated with triphenylphosphine in tetrahydrofuran.

The successful cleavage of the C–S bond of α-(alkylthio)deoxybenzoin with the cyanide ion, thiourea, and triphenylphosphine may be taken as support for the direct attack of the nucleophile on the sulfur atom, since, if the adducts **4**, **5**, and **6** are formed, neutral carbon, neutral sulfur which is next to the positive site, or positively-charged phosphorus must be the attacking base. The possibility is, however, very unlikely.



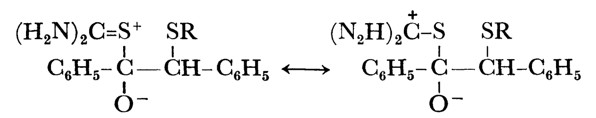
$$C_6H_5\text{-}\underset{\underset{\displaystyle N}{\overset{|||}{C}}}{\overset{\overset{\displaystyle O^-}{|}}{C}}\text{-}\underset{SR}{\underset{|}{CH}}\text{-}C_6H_5$$

(**4**)



$$C_6H_5\text{-}\underset{(C_6H_5)_3P^+}{\underset{|}{\overset{\overset{\displaystyle O^-}{|}}{C}}}\text{—}\underset{SR}{\underset{|}{CH}}\text{-}C_6H_5$$

(**6**)



$$(H_2N)_2C{=}S^+\ \ SR \qquad\qquad (N_2H)_2\overset{+}{C}\text{-}S\ \ SR$$
$$C_6H_5\text{-}\underset{O^-}{\underset{|}{\overset{|}{C}}}\text{—}\overset{|}{CH}\text{-}C_6H_5 \longleftrightarrow C_6H_5\text{-}\underset{O^-}{\underset{|}{\overset{|}{C}}}\text{—}\overset{|}{CH}\text{-}C_6H_5$$

(**5**)

The rough order of the reactivities of the bases is thus obtained as follows:

$$RS^- > C_6H_5S^- \sim (C_6H_5)_3P > CN^- >$$
$$(H_2N)_2C{=}S > SCN^- \sim I^- \sim Br^-$$

Many papers[4,5] have been published dealing with the nucleophilicities of the bases in reactions with polysulfides and disulfides. The main difference between the nucleophilicity of the bases in relation to the polysulfides and that in relation to α-carbonyl sulfides is that hydroxide and ethoxide ions act as effective agents to cleave the S–S bond on the polysulfides, whereas,

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[2] C. G. Swain and C. B. Scott, *J. Amer. Chem. Soc.*, **75**, 141 (1953).

[3] J. O. Edwards and R. G. Pearson, *ibid.*, **84**, 16 (1962).

[4] A. J. Parker and N. Kharasch, *Chem. Rev.*, **59**, 583 (1959).

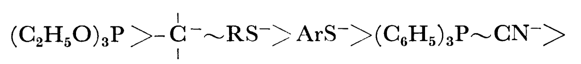
[5] S. Oae and H. Tanaka, *Yukigosei Kagaku Kyokaishi*, **27**, 793 (1969).

they are ineffective in the cleavage of the C–S bond. There have been many attempts to explain the nucleophilicity of the base. Some representative theories will be discussed in an attempt to explain the above results.

Parker and Kharasch obtained the order of nucleophilicity in relation to the bivalent sulfur atom by determining the equilibrium point of the following equation:[4,6)]

$$RSSR + Y^- \rightleftharpoons RS^- + RSY$$

The result was:



$$(C_2H_5O)_3P > -\overset{|}{\underset{|}{C}}{}^- \sim RS^- > ArS^- > (C_6H_5)_3P \sim CN^- >$$
$$SO_3^{2-} > OH^- > S_2O_3^{2-} > (H_2N)_2C{=}S > SCN^- > Br^- > Cl^-$$

An insufficient agreement of this order with the data presented here is, of course, to be expected, since those results were based on the equilibrium point and ours, on the product distribution, which is in turn determined by the one-way reaction rate.

On the other hand, Swain and Scott obtained the following order of nucleophilic constants as a fundamental characteristic of the bases:[2)]

$$S_2O_3^{2-} > SO_3^{2-} \sim SH^- \sim CN^- > I^- >$$
$$SCN^- > OH^- > (H_2N)_2C{=}S$$

It may be pointed out that the placement of thiourea does not explain our results at all.

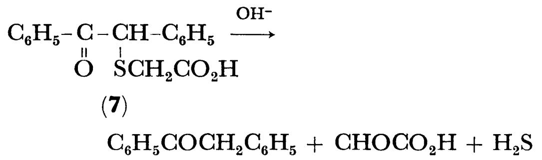
Pearson *et al.* presented the idea of the softness and hardness of the acids and bases and explained some S_N2-type organic reactions by assuming that a soft acid reacts more effectively with the soft bases. The softness is generally understood to express the higher polarizability of the acids and bases and has been obtained from the rates of the reactions of methyl iodide and *trans*-$[Pt(py)_2Cl_2]$ with various bases.[7)] The order of softness thus obtained with the platinum complex is as follows:

$$(C_2H_5O)_3P > (C_6H_5)_3P \gg S_2O_3^{2-} > C_6H_5S^- \sim (H_2N)_2C{=}S >$$
$$(CH_3O)_3P > CN^- \gg SCN^- > I^- > Br^- > CH_3O^-$$

In this view of soft-and-hard acids and bases, sulfur of thioether must be one of the softest acids. Therefore, the cleavage of the C–S bond in α-carbonyl thioethers must be fast with the soft bases. The results presented here may be said to be generally in agreement with Pearson's theory, but the theory cannot explain some of the detailed results; for example, triphenylphosphine is much less reactive than predicted, and the reactivity of thiourea is less than that expected.

It may be necessary to modify the presently-proposed theories or to invent another theory to explain the results obtained with the α-carbonyl sulfides. This is also a rather expected results, since the orders of the rates of reactions of the bases with methyl iodide and the platinum complex do not agree with each other in some details.[7)]

In view of the above-mentioned results, some of the points in the literature are worthy of comment. It was found that the treatment of α-(carboxymethylthio)-deoxybenzoin (**7**) with the hydroxide ion gave deoxybenzoin and glyoxylic acid in addition to hydrogen sulfide.

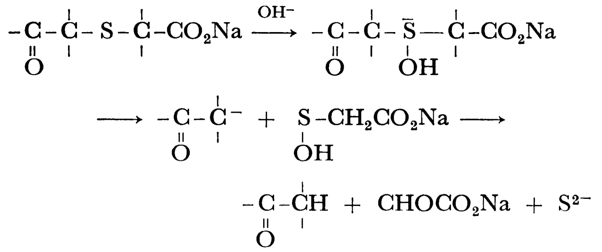


$$C_6H_5\text{-}\underset{\overset{\|}{O}}{C}\text{-}\underset{\overset{|}{SCH_2CO_2H}}{CH}\text{-}C_6H_5 \xrightarrow{OH^-}$$

(**7**)

$$C_6H_5COCH_2C_6H_5 + CHOCO_2H + H_2S$$

In order to explain these results, Iskander *et al.*[8)] have assumed an attack by the hydroxide ion on sulfur, followed by cleavage to carbanion and sulfenic acid; finally, there was decomposition to glycolic acid and hydrogen sulfide.

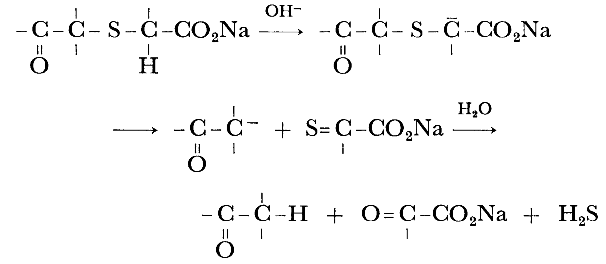


$$-\underset{\overset{\|}{O}}{C}-\overset{|}{\underset{|}{C}}-S-\overset{|}{\underset{|}{C}}-CO_2Na \xrightarrow{OH^-} -\underset{\overset{\|}{O}}{C}-\overset{|}{\underset{|}{C}}-\underset{\overset{|}{OH}}{\bar{S}}-\overset{|}{\underset{|}{C}}-CO_2Na$$

$$\longrightarrow -\underset{\overset{\|}{O}}{C}-\overset{|}{\underset{|}{C}}{}^- + \underset{\overset{|}{OH}}{S}-CH_2CO_2Na \longrightarrow$$

$$-\underset{\overset{\|}{O}}{C}-\overset{|}{\underset{|}{C}}H + CHOCO_2Na + S^{2-}$$

However, these mechanisms involve some points which are still to be clarified; especially, it is very hard to explain why carboxymethanesulfenic acid changes to glyoxylic acid and hydrogen sulfide. Since, in our experiments, proton abstraction occurs with the ethoxide, and, since the hydroxide ion is known to be a typical hard base, we favor the route of the formation of carbanion which has been proposed by Teich and Curtin:[9)]

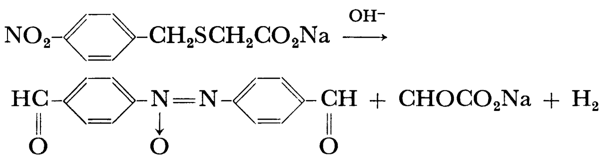


$$-\underset{\overset{\|}{O}}{C}-\overset{|}{\underset{|}{C}}-S-\overset{|}{\underset{\overset{|}{H}}{C}}-CO_2Na \xrightarrow{OH^-} -\underset{\overset{\|}{O}}{C}-\overset{|}{\underset{|}{C}}-S-\underset{|}{\bar{C}}-CO_2Na$$

$$\longrightarrow -\underset{\overset{\|}{O}}{C}-\overset{|}{\underset{|}{C}}{}^- + S{=}\underset{|}{C}-CO_2Na \xrightarrow{H_2O}$$

$$-\underset{\overset{\|}{O}}{C}-\overset{|}{\underset{|}{C}}-H + O{=}\underset{|}{C}-CO_2Na + H_2S$$

We believe the similar reaction of *p*-nitrobenzylthioacetic acid in an alkaline solution reported by Schönberg and Iskander[10)] can be similarly explained instead of considering the hydroxide attack on sulfur:



Experimental

The general procedure for the reaction was essentially the same as that reported in the preceding paper.[1)] The pertinent

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[6)] A. J. Parker and N. Kharasch, *J. Amer. Chem. Soc.*, **82**, 3071 (1960).

[7)] J. O. Edwards and R. G. Pearson, *ibid.*, **90**, 319 (1968), and earlier papers.

[8)] Y. Iskander, Y. Riad, and R. Tewfik, *J. Chem. Soc.*, **1961**, 2402, and earlier papers.

[9)] S. Teich and D. Y. Curtin, *J. Amer. Chem. Soc.*, **72**, 2481 (1950).

[10)] A. Schönberg and Y. Iskander, *J. Chem. Soc.*, **1942**, 90.

data are given in Table 1.

α-Methyl-α-(methylthio)deoxybenzoin. To a solution of 12 g (0.05 mol) of α-(methylthio)deoxybenzoin in 200 m*l* of tetrahydrofuran, 25 g (0.5 mol) of 50% sodium hydride suspension in petroleum was added, with 50 m*l* of tetrahydrofuran, over a period of 30 min. After having been stirred for 30 min at room temperature, the mixture was treated with 8 g (0.06 mol) of methyl iodide in 50 m*l* of tetrahydrofuran with ice-salt cooling. After the completion of the reaction (2 hr), the mixture was quenched with ethanol, poured into water, and extracted with ether. The extract, after evaporation and recrystallization from ethanol, afforded the desired product, mp 83—84°C. Found: C, 75.17; H, 6.06%. Calcd for $C_{16}H_{16}SO$: C, 74.96; H, 6.29%.