Kinetic Isotope Effect Study of Reductions of Benzophenone with Complex Metal Hydrides

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Abstract: Carbon-14 and deuterium kinetic isotope effects were determined for reductions of benzophenone with $NaBH_4$, $LiBH_4$, and $LiAlH_4$ at 25.0 °C. The observed $^{12}k/^{14}k$ at the carbonyl carbon and k_{H4}/k_{D4} of the reducing agents were 1.066 and 0.75, 1.043 and 1.089, and 1.024 and 1.10, respectively, for $NaBH_4$, $LiBH_4$, and $LiAlH_4$ reductions. Kinetic isotope effect calculations with various transition-state models suggested that the extent of hydride transfer from Al or B to the carbonyl carbon is increasing in the order $LiAlH_4$ (0.35) < $LiBH_4$ (0.55) < $NaBH_4$ (0.75). Nucleophilic solvent participation to the BH_4 moiety is weak if present for the SBH reduction.

Sodium borohydride (SBH) and lithium aluminum hydride (LAH) are the most common reducing agents in organic syntheses, but they differ in many respects both in mechanistic and practical viewpoints.[1] LAH rapidly reacts with hydroxylic groups and should be used in aprotic solvents, while SBH is usually utilized in protic solvents; in fact a hydroxylic group has been shown to be important to the action of SBH.[2] Many mechanistic studies have been carried out for the LAH and in particular the SBH reductions.

The role of solvents and metal ions is well recognized in these reductions.[1] Furthermore, it has been proposed that the transition state (TS) of the SBH reduction is product-like, while the LAH reduction involves a reactant-like TS; the position of TS along the reaction coordinate has been assumed to be in the range of 0.6–0.7 for the former and 0.25–0.4 for the latter based primarily on the comparison of Hammett ρ values in the reduction of aromatic ketones, although these figures involve much uncertainty.[3,4] However, there is still no consensus as to the detailed mechanism and the TS structure of the hydride-transfer process of these reactions.

In the present paper, we report the results of a kinetic isotope effect (KIE) study of SBH, lithium borohydride (LBH), and LAH reductions of benzophenone. Possible TS structures and their variations with the reducing agents are presented based on the comparison of theoretically calculated KIEs with the experimental values. The usefulness of this combined experimental–theoretical KIE technique has been demonstrated for other types of reactions such as elimination,[5] molecular rearrangement,[6,7] and solvolysis.[8]

Experimental Results and Model Calculations

Carbon-14 KIEs at the carbonyl carbon were measured by running the reaction of labeled benzophenone with preset amounts of standardized solutions of reducing agents. After standing overnight in a constant-temperature bath, the reaction solutions were worked up, and the product benzhydrol and unreacted benzophenone were separated by TLC and purified by repeated recrystallizations. Radioactivities were measured by a liquid scintillation counter. KIEs were calculated according to the method of Yankwich.[9] Deuterium KIEs were measured by direct

Scheme I
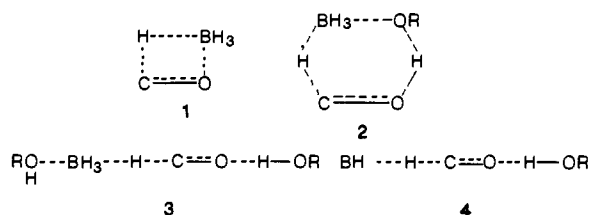
rate measurements (SBH) and/or competitive methods[10] (SBH, LBH, and LAH). Deuterium KIE for the SBH reduction determined by the competitive method was in agreement with that obtained by direct rate measurements. Table I summarizes the experimental KIEs determined in the present study.

Deuterium KIEs determined for SBH and LAH reductions are consistent with those reported in the literature; k_H/k_D values are normal for LAH[11] and inverse for SBH.[12] The magnitude of the carbon-14 KIE is greater for SBH than for LAH. The results tentatively suggest larger bonding change and thus a product-like TS for the SBH reduction.

Model KIE calculations[13,14] were carried out to investigate what variations in the nature and the structure of TS are responsible to the observed variations in KIEs. Wigfield et al. have performed brief calculations of deuterium KIEs in the reduction of ketones with lithium tri-*tert*-butoxyaluminum hydride in which Al–H and H–C bond orders were changed with other parameters fixed and found a substantial inverse KIE in the latter part of the reaction coordinate.[15] This is consistent with the replacement of a weaker Al–H bond by a stronger C–H bond. The present calculations are much more extensive; ^{14}C and D KIEs were calculated with both TS geometry and reaction coordinate (RC) parameters changed. General computational details are the same as reported before.[16] The geometrical model and equations relating geometrical parameters are shown in Figure 1. As can be seen in Figure 1, n_{CH} is the only independent parameter to determine the geometry. Configuration at the metal atom changes from tetrahedral to planar and that at the carbonyl carbon changes from planar to tetrahedral when n_{CH} increases from 0 to 1. Force constants for the reacting bonds were related to the bond orders as described earlier.[16] Standard force constants were the same as before[16] except for the following: $F_{B-H}^0 = 2.75$ mdyn Å^{-1},

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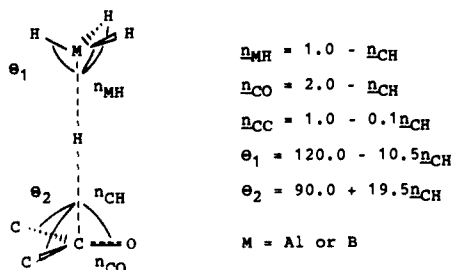
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Table I. Kinetic Isotope Effects in Reduction of Benzophenone at 25.0 ± 0.1 °C[a]

reagent/solvent	R_o, R_r, R_p	f, R_o, R_r	f, R_o, R_p	f, R_r, R_p	$^{12}k/^{14}k$ (av)	k_{H4}/k_{D4}
LiAlH$_4$/Et$_2$O	1.024 ± 0.003	1.022 ± 0.002	1.027 ± 0.004	1.023 ± 0.002	1.024 ± 0.003	1.10 ± 0.01[b]
LiBH$_4$/Et$_2$O	1.041 ± 0.007	1.047 ± 0.007	1.039 ± 0.008	1.043 ± 0.006	1.043 ± 0.007	1.09 ± 0.03[c]
NaBH$_4$/2-PrOH	1.065 ± 0.003	1.071 ± 0.005	1.060 ± 0.013	1.069 ± 0.004	1.066 ± 0.004	0.72 ± 0.03[b]
						0.77 ± 0.01[d]

[a] Listed carbon-14 KIEs are averages from five to six runs whose fractions of reaction are in the range 30–70%. For definitions of R_o, R_r, R_p, and f, see the Experimental Section. Errors for the carbon-14 and deuterium KIEs are the standard deviations from the averages for multiple measurements. [b] Determined by GC/MS. [c] Determined by NMR. [d] Determined by direct rate measurements: $k_2 = (2.23 ± 0.01) \times 10^{-3}$ L mol^{-1} s^{-1} (NaBH$_4$), $k_2 = (2.90 ± 0.05) \times 10^{-3}$ L mol^{-1} s^{-1} (NaBD$_4$).

$$n_{MH} = 1.0 - n_{CH}$$
$$n_{CO} = 2.0 - n_{CH}$$
$$n_{CC} = 1.0 - 0.1 n_{CH}$$
$$\theta_1 = 120.0 - 10.5 n_{CH}$$
$$\theta_2 = 90.0 + 19.5 n_{CH}$$
M = Al or B

Figure 1. Transition-state geometrical model and equations relating geometrical parameters.
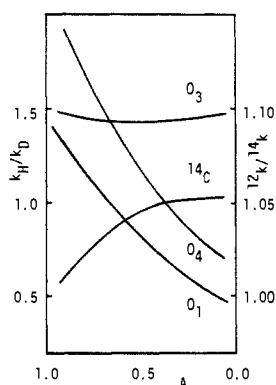
Figure 2. Variations of calculated D$_1$, D$_3$, D$_4$, and ^{14}C KIEs vs. RC in the reduction of ketone with BH$_4^-$. $D = 1 - A^2 - B^2 = -0.01$, and $n_{CH} = 0.6$.
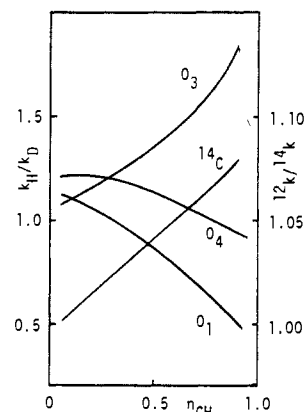
$F_{H-B-H}{}^0 = 0.48$ mdyn Å rad^{-2}, $F_{Al-H}{}^0 = 1.80$ mdyn Å^{-1}, and $F_{H-Al-H}{}^0 = 0.27$ mdyn Å rad^{-2}. These force constants were determined to reproduce the experimentally observed vibrational frequencies of BH$_4^-$ and AlH$_4^-$.[17] Lengths of the C–H, C–O, and C–C bonds were taken from the standard sources, and those of B–H (1.225 Å) and Al–H (1.547 Å) were taken from the literature.[17] Two RC parameters, A and B, were used to generate RC. Parameter A is the interaction constant between the M–H and H–C stretching modes in the TS force-constant matrix and generates an H$^-$-transfer motion from M to C as a part of the RC. Parameter B is the interaction constant between the H–C and C–O stretching modes. This generates an addition of H$^-$ to C=O as a part of the RC. Some of the results are illustrated in Figures 2–4.

Discussion

Four different mechanisms have been proposed as shown in Scheme I. Among these, Wigfield and Gowland have ruled out the four-center mechanism (1) by showing that (RO)$_4$B produced has alkoxy groups exclusively derived from solvent under such conditions that the exchange of alkoxy groups on boron is extremely slow.[18] An alternative cyclic mechanism involving a molecule of hydroxylic solvent (2) has also been eliminated on the basis of kinetic results[12] and of hydrogen-exchange experiments.[19] Wigfield suggested an acyclic TS, 3.[1] On the other

Figure 3. Variations of calculated D$_1$, D$_3$, D$_4$, and ^{14}C KIEs vs. n_{CH} in the reduction of ketone with BH$_4^-$. $A = 0.45$, $B = 0.8986$, and $D = -0.01$.
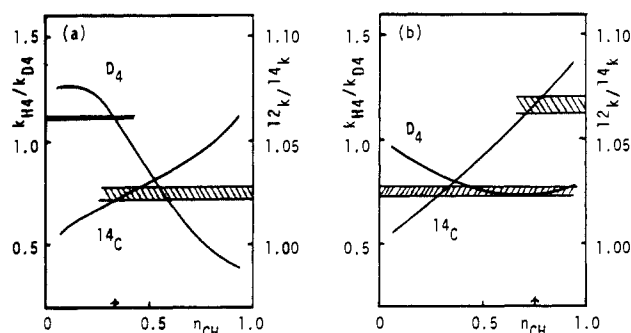
Figure 4. Variations of calculated D$_4$ and ^{14}C KIEs vs. n_{CH}. Shaded areas represent the regions of experimental KIEs. (a) LiAlH$_4$, $A = 0.65$, $B = 0.7665$. (b) NaBH$_4$, $A = 0.10$, $B = 1.00$.

hand, on the basis of an isotope tracer experiment, Gold proposed a two-step mechanism (4) in which BH$_3$ is formed as a discrete species before forming a boron–oxygen bond.[19] Recently, Ashby et al. also suggested the formation of AlH$_3$ during the reduction of RX by LAH in an ethereal solvent.[20] Thus, it is likely that after the H$^-$ transfer step, BH$_3$ or AlH$_3$ forms in a solvent cage which rapidly reacts with nucleophilic solvent (in the case of SBH in ROH) or the alkoxide derived from the ketone (in the case of the LAH reduction of ketones in ethereal solvents), although there is no strong evidence that the TS structure for the LAH reduction of ketone is acyclic.

Eisenstein et al. have performed ab initio MO calculations for the SBH reduction of formaldehyde in the gas phase.[21] They obtained the TS structure, 5, in which the hydride transfer is almost completed while the new BO bond is not yet formed. The BH$_3$ is nearly planar in the TS. The Pauling bond orders calculated by eq 1,[22] in which r represents the bond lengths in the

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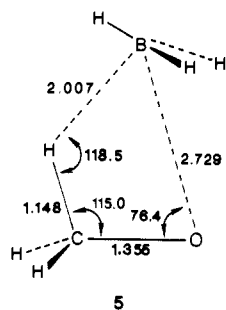
$$n = \exp[(r_0 - r)/0.3] \qquad (1)$$

TS and r_0 represents those of the relevant stable species, are 0.83, 0.08, and 0.02, respectively, for the CH, BH, and BO bonds. When a water molecule was added to form a hydrogen bond to the oxygen atom of formaldehyde, the BO bond became further weaker ($n = 0.01$) and the BHC angle was calculated to be slightly larger. Although one molecule of water does not represent the whole effect of the solvent, these calculations suggest that the B---O interaction is not important in protic solvent and that the reaction may have the TS as illustrated in **3** or **4**.

Figures 2–4 illustrate some of the results calculated by using model **4**. Here, D_1 and D_3 represent deuterium KIEs of the transferring hydrogen and of the nontransferring hydrogens, respectively, and D_4 represents the overall deuterium KIE of the four hydrogens. Figure 2 shows how the magnitudes of the KIEs depend on the RC parameters for a fixed TS geometry. It is interesting to note that the secondary D_3 KIE is almost constant regardless of the RC, while the primary D_1 and ^{14}C KIEs are very sensitive to the RC; the magnitude of the D_1 KIE becomes smaller while the ^{14}C KIE becomes larger when A becomes smaller (B becomes larger). These results are consistent with the idea that primary KIEs are large when the isotopic atoms are involved in the RC. Figure 3 shows the variations of the calculated KIEs with the change in TS geometry for given RC parameters. The primary D_1 KIE becomes smaller while the carbon KIE becomes larger for a more product-like TS. The inverse D_1 KIE for a late TS is consistent with the earlier observation by Wigfield et al.[15] The secondary D_3 KIE becomes larger because of decreased HB---H bending frequencies for a product-like TS.

A series of calculations were carried out for different values of n_{CH} and A/B in order to determine the position of the TS and the nature of the RC in the benzophenone reductions.[23] Selected results are illustrated in Figure 4; here calculated KIEs are compared with the experimental values (shown as shaded areas) in the LAH (Figure 4a) and the SBH (Figure 4b) reduction. As Figure 4a shows, simultaneous matching of the calculated D_4 and ^{14}C KIEs with the experimental values was observed only when $A = 0.65$, $B = 0.7665$, and $n_{CH} = 0.35$ for the LAH reduction. Similarly, matching was achieved when $A = 0.10$, $B = 1.00$, and $n_{CH} = 0.75$ for the SBH reduction. Thus, the TS is reactant-like for LAH and product-like for SBH. The n_{CH} value for LBH was determined as 0.55 in a similar way. It should be noted here that not only the central metal but also the countercation and solvent are different for the LAH and SBH reductions, while only the central metal is different for the LAH and LBH reductions. Therefore, the present results indicate that the change in metal atoms from Al to B shifts the TS from reactant-like to central and that the change in cation (from Li to Na) and solvent (from diethyl ether to 2-propanol) further makes the TS product-like.

The role of hydroxylic solvent in the SBH reduction of ketone was investigated by Wigfield et al.,[2] who showed that the kinetic order of 2-propanol in the reduction of cyclohexanone in diglyme is 3/2, suggesting that more than one 2-propanol molecule is involved in the TS. It is reasonable to assume that the role of the first molecule is to stabilize the TS by hydrogen bonding to

the carbonyl oxygen. Although the 2-propanol molecule is not explicitly considered in the present model, the effect of the hydrogen bond on the deuterium and carbon KIEs should be small and can be regarded to virtually be incorporated in the model through the CO bond order. The other role of 2-propanol may be to interact nucleophilically with the boron atom, assisting the transfer of hydride in a push–pull sense as shown in TS **3**. This may cause large influence on deuterium KIEs. Therefore, some calculations were carried out to test the possibility of the concerted nucleophilic attack of hydroxylic solvent in the SBH reduction. As can easily be anticipated from the analogy of the α-CD$_3$ KIE in methyl-transfer reactions, the secondary BD$_3$ KIE for the push–pull model was very small and less than unity. This made the overall BD$_4$ KIE substantially smaller than that for model **4**. The carbonyl carbon KIE is not affected at all by the inclusion of the solvent molecule. It was impossible to reproduce both carbon and deuterium KIEs simultaneously with the push–pull model. Therefore, it can be concluded from the present calculations that the extent of the bond formation between 2-propanol and BH$_3$ in the TS should be very small if present as suggested by the earlier kinetic study.[2]

Experimental Section

Materials. 2-Propanol was dried over and distilled from calcium hydride. Diethyl ether was dried over LAH and distilled before use. SBH and sodium borodeuteride (Merck Sharp & Dohme) were recrystallized from diglyme.[24] LBH and lithium borodeuteride were prepared according to the literature.[25] LAH and lithium aluminum deuteride (Merck Sharp & Dohme) were used as received. All glasswares were flame-dried, and the solution of the reducing agents was handled under nitrogen by using Schlenk tube techniques. The hydride activity of the SBH solution was determined by titration.[26] Other hydride solutions were analyzed by methods described in the literature.[27] Benzophenone labeled with ^{14}C at the carbonyl carbon was prepared by the Friedel–Crafts benzoylation of benzene with benzoyl chloride-^{14}C, which was obtained by chlorination of benzoic acid-7-^{14}C (NEN) with thionyl chloride.

Determination of Deuterium Kinetic Isotope Effects. Deuterium KIE in reduction of benzophenone was determined by direct rate measurements and/or the competitive technique.[10] Rate constants for the SBH reduction were determined by a UV (Hitachi 100–60 UV spectrometer) method in which the absorbance of benzophenone at 325 nm was used to follow the reaction. The temperature of the UV cell was maintained constant by circulating water (25.0 ± 0.1 °C) from a Lauda RM-3 constant-temperature bath. The initial concentration of benzophenone was 5.6 mM and that of the hydride was about 40-fold in excess. Reactions showed good pseudo-first-order rate plots with correlation coefficients better than 0.999 96. The second-order rate constant determined for the SBH reduction was in agreement with the value reported in the literature ($k_2 = (2.04 \sim 2.31) \times 10^{-3}$ L mol^{-1} s^{-1}).[26] The deuterium KIE was obtained as the ratio of the rate constants for the protio and deuterio runs. The competitive measurements of deuterium KIEs were carried out for all reducing agents. The typical procedure was as follows. The solutions of labeled and unlabeled reducing agents were prepared separately and mixed to give a solution of ca. 50% deuterium content. Six reaction samples were then made; 1–3 contain 0.49 mmol of the mixed reducing agent (1.96 mmol in hydride) and 98 μmol of benzophenone in 5.25 mL of solvent (fraction of reaction would be 5% with respect to the reducing agent), and 4–6 contain 24.5 μmol of the reducing agent (98 μmol in hydride) and 1.96 mmol of benzophenone in 5.25 mL of solvent (fraction of reaction should be 100% with respect to the reducing agent). The samples were allowed to react in a constant-temperature bath (25.0 ± 0.1 °C) overnight and worked up as usual. Crude benzhydrol thus obtained was treated with trifluoroacetic acid–trifluoroacetic anhydride (2:3) to give trifluoroacetate, which was subjected to GC/MS analysis. The analysis was performed with JMS-DX300 (EI 75 eV) connected with a JMA-3100 data processor; GC separation was made with silicon OV-1 at 120 °C. The peaks at m/z 280, 281, and 282 were used to calculate the deuterium content. It was found that the relative intensities

(23) Calculations were carried out under the constraint of $D = 1 - A^2 - B^2 = -0.01$ which generates the RC frequency of as large as 100i cm^{-1}. A set of RC parameters which yield a larger RC frequency give qualitatively the same conclusions.

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of these peaks vary depending on the position of the GC peak subjected to the MS analysis due probably to different GC retention time for the protio and deuterio compounds. The reproducible intensity at each m/z value was obtained by adopting a summation procedure in which the sample gas from GC was continuously introduced into MS, and the intensity of each m/z value was integrated for the whole GC peak. Deuterium KIEs were calculated by compring the deuterium contents of 1–3 and 4–6 samples.[10] Analysis of the deuterium content for the LBH reduction was carried out with NMR (Bruker-WM 360) instead of GC/MS. In this case, crude benzhydrol was separated from unreacted benzophenone if necessary by preparative TLC and purified by recrystallization from hexane. The relative intensity of the methine proton of benzhydrol to that of the aromatic protons was used to calculate the deuterium content.

Determination of Carbon-14 Kinetic Isotope Effects. A solution of benzophenone labeled with ^{14}C at the carbonyl carbon (1.0 M, 10 mL) was divided into five parts and transferred with a stainless steel needle into flame-dried test tubes capped with rubber septa. To these solutions preset amounts of standardized solutions of reducing agents were added; the molar ratio of active hydride to ketone was in the range 0.3–0.7. After standing overnight in a constant-temperature bath at 25.0 ± 0.1 °C, the reaction solutions were worked up, and the actual fractions of reaction were determined by GLC (PEG HT, 2-m glass column at 190 °C). The product benzhydrol and the unreacted benzophenone were separated by preparative TLC and purified by repeated recrystallizations from hexane. Radioactivities were determined by a liquid scintillation counter (Beckman LS 9000) as reported previously.[8] KIEs were calculated for each fraction of reaction by using four equations of Tong and Yankwich.[9] These equations allows KIE calculations in four ways by using any three of the measured parameters, fraction of reaction, f, radioactivity of the starting ketone, R_0, activity of the recovered ketone, R_r, and activity of the product alcohol, R_p. Agreement among the KIEs calculated by the four different equations was excellent in all cases, and the isotope effects thus obtained showed no trend with the fraction of reaction. These facts indicate the high reliability of the results.

Supplementary Material Available: Tables of calculated MMI, EXC, ZPE, VP, imaginary frequencies, KIE, and EIE for each model (1 page). Ordering information is given on any current masthead page.

Kinetics of Ozonation. 4. Reactions of Ozone with α-Tocopherol and Oleate and Linoleate Esters in Carbon Tetrachloride and in Aqueous Micellar Solvents

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Abstract: Vitamin E (α-tocopherol; α-T) is known to protect animals against the deleterious effects of ozone in polluted air; one such effect is the ozone-initiated autoxidation of polyunsaturated fatty acids (PUFA) that occur in membranes. In order to assess the possibility of a direct reaction of ozone with α-T competing with the very fast ozone–PUFA reaction, we have measured the rates of reaction of ozone with α-T, oleic acid, and linoleic acid. In CCl$_4$ as solvent, α-T reacts with ozone with a rate constant of about 5500 M^{-1} s^{-1}; methyl oleate and methyl linoleate react 2 orders of magnitude faster. In aqueous micellar solutions the rate constants for α-T and the fatty acids are more similar. The k for the ozone/α-T reaction is about 1×10^6 M^{-1} s^{-1} at pH 7, but decreases as the solution becomes more acidic; the k's for oleic acid and linoleic acid are ca. 1×10^6 M^{-1} s^{-1} and exhibit no significant pH dependence. Since the ratio of fatty acids to α-T in membranes is typically at least 100–1000 to 1, we conclude that the direct reaction of ozone with α-T is unlikely. Thus, the protection that vitamin E provides to animals breathing ozone-containing air must result from vitamin E acting as a free radical scavenger. We have also detected the α-tocopheroxyl radical as an intermediate from the reaction of ozone with α-T both in CCl$_4$ and aqueous micelles using electron spin resonance spectroscopy. We suggest that the observation of this intermediate is consistent with an initial electron transfer from α-T to ozone.

Ozone is among the most important of atmospheric oxidants, causing damage to a wide variety of biological target molecules in vivo.[1-3] In particular, when ozone in polluted air reacts with polyunsaturated fatty acids (PUFA) in pulmonary lipids, free radical intermediates are produced and autoxidation is initiated.[2] We have shown from studies of PUFA autoxidation[2c,3] and by spin-trapping techniques[4] that free radicals are produced from the reaction of ozone with PUFA or simple olefins in vitro. Evidence for the in vivo production of free radicals includes observations of increased production of conjugated dienes via lipid peroxidation,[5] expiration of ethane and pentane in the breath of animals exposed to ozone,[6,7] and the decreased sensitivity to the

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