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A PRIMARY KINETIC ISOTOPE EFFECT FOR THE O-H INSERTION OF DIMETHOXYCARBENE†

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Summary. The primary kinetic isotope effect for the insertion of dimethoxycarbene into MeOH(D) is 3.3 ± 0.5.

Singlet carbenes "insert" into O-H bonds by several mechanisms: (1) electrophilic attack on an oxygen lone pair with the (possibly reversible) formation of an ylide, that subsequently suffers an O to C proton transfer; (2) direct, 3-center O-H insertion; or (3) carbene protonation, followed by rapid collapse of the resulting carbocation/oxide ion pair.[2] Nucleophilic carbenes, whose reactivity is dominated by lone electron pairs, ought to eschew mechanism (1) in favor of (3) or possibly (2), whereas electrophilic carbenes, where reactivity is centered in the vacant p orbitals, should prefer mechanisms (1) or (2). These qualitative expectations are generally in accord with experiment,[2] although the exclusion of (3) for electrophilic carbenes may not be complete.[2d]

Mechanisms (2) and (3) entail O-H bond stretching in the transition state and, if the latter is not too unsymmetrical, should be attended by significant primary kinetic isotope effects (KIE). In this Letter, we report a **directly** measured KIE of 3.3 ± 0.5 for the insertion of nucleophilic dimethoxycarbene[3] (DMC) into MeOH or MeOD.

Photolysis of 3,3-dimethoxydiazirine in methanol affords >90% of trimethylorthoformate via O-H insertion of DMC.[3] The absolute second order rate constant for this reaction can be determined by laser flash photolysis,[3,4] monitoring the decay of DMC at 255 nm as a function of [MeOH] in pentane at 20°C. In the range $0.08 \le [\mathrm{MeOH}] \le 1.54$ M, the dependence of the pseudo first order rate constant for DMC decay ($\underline{k}_\psi$) is **linear**[5] with [MeOH], affording the second order rate constant $\underline{k}_2{}^H = 6.36 \pm 0.39 \times 10^6\ M^{-1}s^{-1}$ (3 sets of experiments); see Figure 1. In this concentration range, we calculate that oligomeric methanol comprises 34-92% of the bulk MeOH.[6-8] Because oligomeric MeOH is ~2

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† Dedicated to the memory of Professor Jack Hine, pioneer in the chemistry of carbenes.

orders of magnitude more reactive than the monomer toward the highly reactive arylchlorocarbenes,[7] a difference that should be augmented with the much less reactive DMC,[3] we believe that only oligomeric MeOH/DMC reactions significantly contribute to the rate constants in Figure 1.

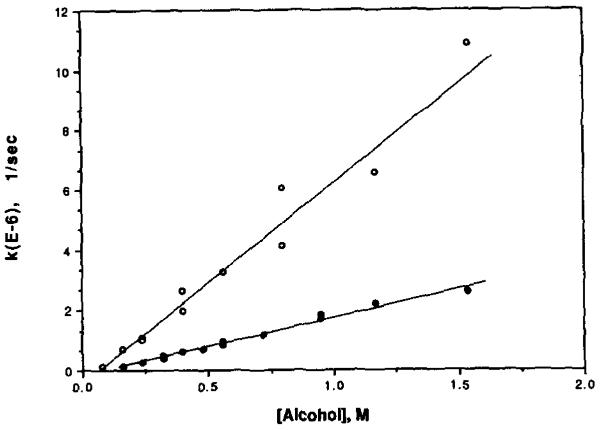
Repetition of these experiments with 0.16-1.54 M (57-92% oligomeric) MeOD gave $k_2^D = 1.95 \pm 0.27 \times 10^6\ M^{-1}s^{-1}$ (3 expts), with the dependence of k_ψ again linear in [MeOD]; see Figure 1. The primary KIE, k_2^H/k_2^D, is thus 3.26 ± 0.49 for the insertion of DMC into MeOH(D).

Laser flash photolytic monitoring of the reactions between DMC and the much more reactive and acidic hydroxylic quenchers AcOH and AcOD gave $k_2^H = 2.91 \pm 0.13_2 \times 10^9\ M^{-1}s^{-1}$ and $k_2^D = 2.84 \times 10^9\ M^{-1}s^{-1}$. Acetic acid was varied from $0.4\text{-}5.3 \times 10^{-3}$ M in pentane at 20°C; and k_ψ was again linear with [AcOH(D)]. The data indicate the absence of a significant KIE in this case, where k_2 approaches diffusion control.[9]

Related observations were made with MeOH/MeOD when the carbene was significantly more reactive than DMC. Both the nucleophilic methylmethoxycarbene[10] (MeCOMe) and the predominantly electrophilic phenylchlorocarbene[7] (PhCCl) react with (oligomeric) MeOH at near diffusion controlled rates, with $k_2 > 10^9\ M^{-1}s^{-1}$ and $k_2^H/k_2^D \sim 1$. Thus, laser flash photolysis[4] of 3-methyl-3-methoxydiazirine at 20°C in pentane gave MeCOMe, whose decay was monitored at 380 nm.[10] Quenching by $0.33\text{-}2.60 \times 10^{-2}$ M MeOH (0.2-8.3% oligomer)[6] or MeOD (0.9-10% oligomer)[6] gave nearly superimposable, curved[7] dependences of k_ψ on [MeOH(D)], indicative of simultaneous reactions with monomeric and oligomeric methanol; see Figure 2.

From these data, $k_2^H = 5.26 \pm 0.83 \times 10^9\ M^{-1}s^{-1}$ and $k_2^D = 4.76 \pm 0.83 \times 10^9\ M^{-1}s^{-1}$ (3 expts. each) could be extracted[7] for reactions of MeCOMe with oligomeric MeOH(D). The KIE is not significantly different from unity. Laser flash photolytic generation of PhCCl in $0.5\text{-}3.8 \times 10^2$ M MeOH(D)/pentane at 23°C[7] gave very similar kinetic results (not illustrated), from which we extract[7] $k_2^H = 2.74 \times 10^9\ M^{-1}s^{-1}$ (lit.[7] $2.9 \pm 0.2 \times 10^9\ M^{-1}s^{-1}$) and $k_2^D = 2.16 \times 10^9\ M^{-1}s^{-1}$ for the reactions with oligomeric methanol. Assuming typical experimental errors, the apparent k_H/k_D (1.27) cannot be far from unity.

The sizeable primary KIE observed in the DMC/MeOH(D) reaction is consistent with either direct insertion or carbene protonation mechanisms (2) or (3).[11] At least in a linear transition state (TS), the magnitude of the primary KIE is largest for the most symmetrical TS, and decreases as the TS more closely resembles the product or reactant states.[12] Therefore, the near diffusion controlled DMC/AcOH(D) and MeCOMe or PhCl/MeOH(D) reactions, with $k_2 > 10^9\ M^{-1}s^{-1}$ and $k_2^H/k_2^D \sim 1$, may each traverse a very reactant-like (or decidedly non-linear[12]) TS.



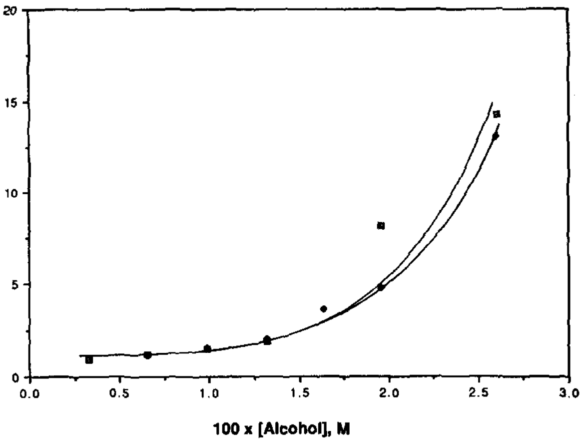


Figure 1 (left). Pseudo first order rate constants ($\times 10^6$, s^{-1}) for the reactions of dimethoxycarbene with methanol as a function of [alcohol]; (o) MeOH, (●) MeOD.
Figure 2 (right). Analogous display of the data for methylmethoxycarbene; (◘) MeOH, (◆) MeOD. The ordinate of Figure 2 is also 10^{-6} $\underline{k}_{\psi}$, s^{-1}.

The DMC/MeOH(D) KIE of 3.3 ± 0.5 is larger than previously encountered primary effects for the intermolecular insertions of singlet carbenes with MeOH(D) in solution.[13] It exceeds the KIE of 2.4 reported for fluorenylidene,[14] and the (product-based) KIE of 2.2 for bicyclo[5.1.0]oct-4-ene-2-ylidene at -78°C (reversible ylide mechanism).[2c] The DMC/MeOH KIE is also larger than typical KIE's for the intermolecular C-H insertion reactions of CCl_2 (~2.5-2.8).[15] We are continuing our studies in these areas.

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(5) An aqueous $NiSO_4$ filter was placed in front of our 1000 W Xe monitoring lamp to block out the 340-450 nm region and prevent adventitious photolysis of the diazirine, thus inhibiting the extraneous generation of DMC that artificially "extends" its lifetime in MeOH and lowers the observed quenching rate constant. Our present k_2 is greater than the previously[3] reported value (2.5×10^6 $M^{-1}s^{-1}$). Additionally, the slight curvature that we observed[3] in k_ψ vs. [MeOH] was not now apparent in 3 independent sets of experiments.

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