On the Viability of Oxametallacyclic Intermediates in the (salen)Mn-Catalyzed Asymmetric Epoxidation**

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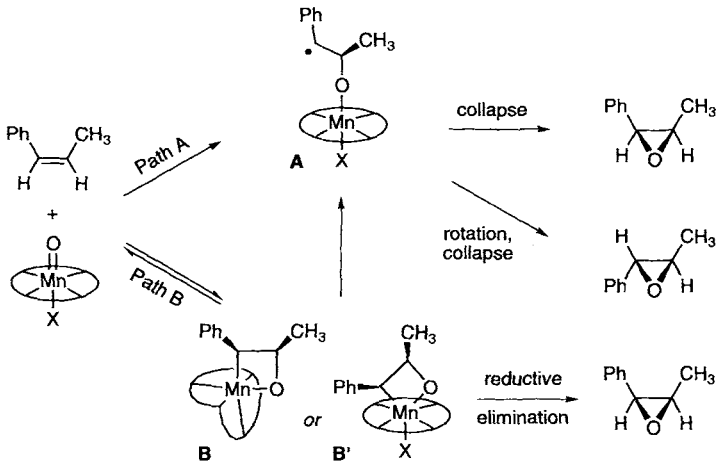
The mechanism of oxygen-atom transfer from high-valent oxometal intermediates to organic substrates has stimulated great interest as a result of its relevance to a wide range of important synthetic and biological catalytic pathways.[1] Two fundamentally different proposals have been considered: direct substrate attack at the oxo ligand with concerted or sequential C–O bond formation, and substrate attack at both the metal and oxo centers to generate an oxametallacyclic intermediate.[2] For the epoxidation of conjugated olefins catalyzed by (salen)M and M porphyrin complexes (salen = *N*,*N*′-bis(salicylidene)-ethylenediamine dianion; M = Cr, Fe, Mn), a substantial body of evidence has been accumulated that supports direct attack of olefin at the oxometal (Scheme 1, path A). This model has



Scheme 1.

been refined on the basis of stereoselectivity data to entail a side-on approach of the olefin at the oxo center to generate a radical intermediate, which in turn partitions between collapse and rotation–collapse processes to provide the observed mixture of *cis* and *trans* epoxides.[3] Recent computational[4] and experimental[5] studies purporting to substantiate the intermediacy of oxametallacycles (path B) in the (salen)Mn-catalyzed epoxidation warrant careful scrutiny, particularly since this reaction currently stands as the most effective method for the generation of optically active epoxides by oxo transfer.[1e, 6]

Here we assess the viability of such intermediates based on an analysis of the (salen)Mn coordination environment, the observed substrate scope, a computational study of representative diastereomeric radical intermediates, and the temperature dependence of enantioselection. We conclude that the radical path A remains the simplest mechanism that is consistent with all of the available data. In contrast, the oxametallacyclic mechanism fails to accomodate several crucial experimental observations, and remains both unsubstantiated and unnecessarily complicated.

The two mechanisms in question place very different constraints on the coordination environment of the manganese center throughout the catalytic cycle. Whereas the formation of a radical intermediate requires only the presence of the apical oxo ligand, formation of the proposed oxametallacycle requires that a coordination site is available for formation of the Mn–C bond, and that this coordination site is adjacent to the oxo ligand. Two critical issues are whether the (salen)Mn intermediates possess such an open coordination site during the oxo transfer steps, as required for formation of **B**, and, if not, whether the formation of oxametallacycles can be accomodated by a 7-coordinate ligand environment as in **B′**.

The first of these questions may be addressed by analyzing the effect of amine *N*-oxide additives, which have a dramatic impact on the outcome of the epoxidation reaction. Additives such as pyridine *N*-oxide influence the rate, yield, *cis*/*trans* ratio, and enantioselectivity of the (salen)Mn-catalyzed epoxidation with a range of terminal oxidants.[7] As illustrated with *cis*-β-methylstyrene addition of *N*-oxide can more than double the *cis*/*trans*-epoxide ratio, and significantly increase the chemical yield and degree of asymmetric induction (Table 1). This clearly indicates

Table 1. Epoxidation of *cis*-β-methylstyrene with various oxidants and (*S*,*S*)-**6** as catalyst.

Oxidant	Additive [e] (equiv)	*t*[h]	Conversion [%][a]	Yield [%][a]	*cis*/*trans* ratio	ee_{fac} [%][b,c]
NaOCl(aq)	4-PPNO (0.2)	0.5	100	98	19	81
NaOCl(aq)	–	2	78	62	18	71
PhIO	4-PPNO (0.2)	8.5	81	76	3	72
PhIO	–	8.5	54	2	2	69
oxone(aq)	4-PPNO (0.4)	2	98	93	15	80
oxone(aq)	–	2	18	13	10	58
oxone/K_2CO_3	NMO (2.0)	17	100	99	27	82
oxone/K_2CO_3	–	41	24	11	4	40
*m*CPBA/K_2CO_3	NMO (10.0)	0.5	100	91	16	82
*m*CPBA/K_2CO_3	–	0.5	97	41[d]	5	7

[a] Conversion, yield, and enantiomeric excess were determined by GC (see *Experimental Section*). [b] The absolute configuration of the major *cis*-β-methylstyrene oxide enantiomer is (*1S*,*2R*), and that of the major *trans*-β-methylstyrene oxide enantiomer is (*1R*,*2R*) [3h]. [c] $ee_{fac} = (x_{cis} \times ee_{cis}) + (x_{trans} \times ee_{trans})$; x = portion of *cis* or *trans* product. [d] No epoxidation was detected under these reaction conditions in the absence of **6**. [e] 4-PPNO = 4-phenylpyridine-*N*-oxide, NMO = *N*-methylmorpholine-*N*-oxide.

that the *N*-oxide additive influences the stereoselectivity of both C–O bond forming steps. Furthermore, electrochemical studies show that the presence of *N*-oxide significantly lowers the oxidation potentials for (salen)Mn complexes (Figure 1). Since oxidation to the O=Mn^V(salen) is generally rate limiting,[8] the observed rate acceleration induced by the *N*-oxide can be attributed to association of the additive with the metal center during generation of the reactive oxo intermediate. Similarly, the increase in the turnover numbers of the catalyst in the presence of *N*-oxide was taken as evidence that the additive stabilizes the highly reactive O=Mn^V(salen) by ligation after the initial oxidation.[8]

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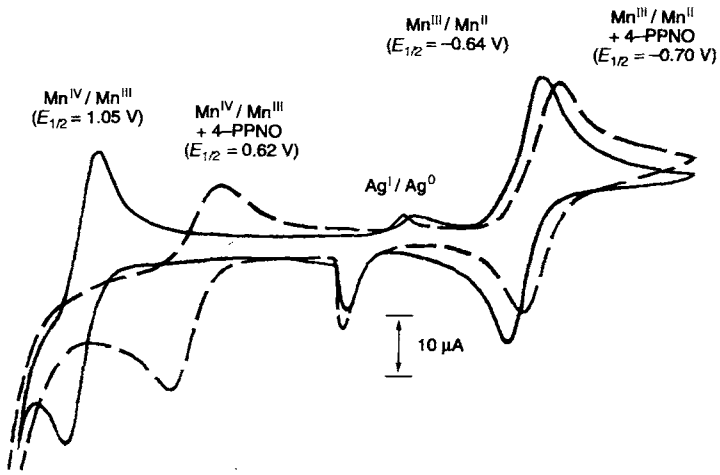


Figure 1. Cyclic voltammograms of (*R*,*R*)-**2** measured in the absence (solid line) and presence (dashed line) of 4-phenylpyridine *N*-oxide (4-PPNO, 5 equiv). Redox potentials are given relative to the saturated calomel electrode (SCE).

Further evidence that *N*-oxide additives function as axial ligands is provided by a study of catalyst **1** strapped with pyridine *N*-oxide. Figure 2 displays the X-ray crystal structure of **1** in which the tethered *N*-oxide unit is axially coordinated, as predicted, to the nearly planar (salen)Mn unit and is opposite to the chloride counterion.[9] The rate of epoxidations catalyzed by **1** is not influenced by adding 4-phenylpyridine *N*-oxide (4-PPNO; Figure 3).[10,11] For comparison, epoxidations with catalyst **2** proceed with higher conversion and at a faster rate in the presence of 4-PPNO; the combination of **2** and 4-PPNO affords results nearly identical to those obtained with catalyst **1** alone.

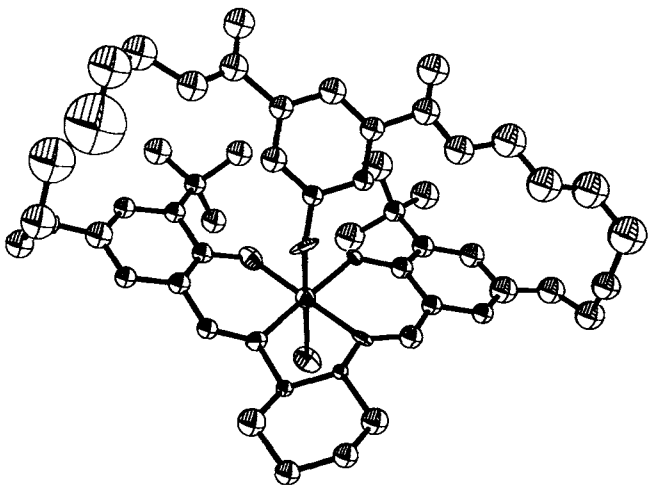


Figure 2. ORTEP representation of (*R*,*R*)-**1** (thermal ellipsoids for 50% probabilities).

These observations support a mechanism in which the *N*-oxide influences the epoxidation by axial ligation to the metal center during every step of the catalytic cycle. As a result, the relevant (salen)Mn intermediates do not possess an available coordination site for distortion of the ligand, as required for formation of intermediate **B**. Furthermore, such distortion of the (salen)Mn ligand from the square-planar disposition observed in every reported X-ray crystal structure of this class of complexes is completely unprecedented,[12] and **B** may therefore be reasonably excluded from further consideration.[13]

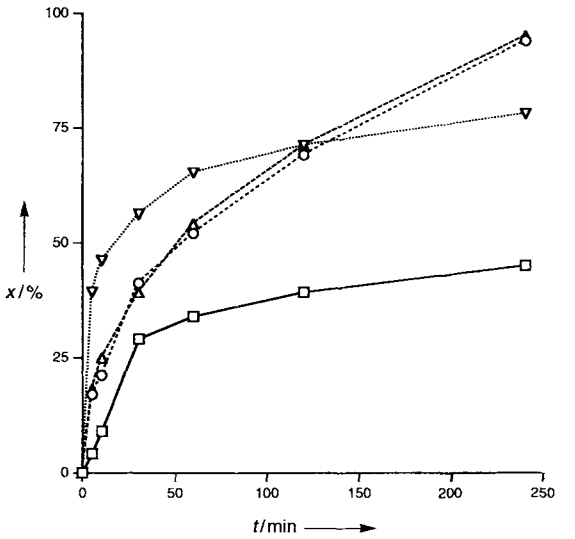
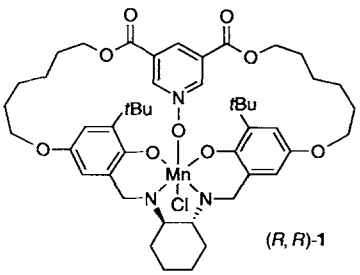
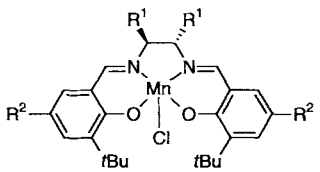


Figure 3. Plot of conversion *x* versus time *t* for the NaOCl epoxidation of styrene catalyzed by (*R*,*R*)-**1** (10 mol%; ○), (*R*,*R*)-**1** (10 mol%) and 4-PPNO (20 mol%; △), (*R*,*R*)-**2** (10 mol%; □), as well as (*R*,*R*)-**2** (10 mol%) and 4-PPNO (20 mol%; ▽).

Even cursory inspection of the alternative 7-coordinate intermediate **B′** reveals severe steric repulsions between the salen ligand and the oxametallacycle. To accomodate the observation that diastereomeric epoxides generated from acyclic *cis* olefins are epimeric at the benzylic position (see Scheme 1), the aryl-substituted olefin terminus would have to bind to the Mn center in closest proximity to the ligand plane. In light of the fact that hindered (salen)Mn catalysts such as **3** are highly active and enantioselective for the epoxidation of tri- and even certain tetrasubstituted olefins,[14] this is simply implausible.[15] The formation of oxametallacycles **B** or **B′** is thus inconsistent with a range of quantitative and qualitative experimental data, and mechanistic schemes invoking these intermediates must be regarded with skepticism.

The only experimental data presented thus far that is inconsistent with the radical mechanism is the recent report of nonlinearity in Eyring plots for the epoxidation of four olefins with a catalyst related to **2**–**5**.[5] This may indicate the presence of a reversibly formed intermediate along the reaction coordinate. However, several features complicate interpretation of this data. First, the variations in enantiomeric excess were quite small (less than 10%), rendering the changes in slope ambiguous. Second, critical experimental details—such as conversion, yield, and terminal-oxidant solubility—were missing.[16] Third, the epoxide for which the greatest effect (in terms of $\Delta\Delta G^{\neq}$) was observed, 1,2-dihydronaphthalene oxide, is known to undergo efficient kinetic resolution by a secondary oxidation pathway.[17]





2: $R^1, R^1 = -(C_4H_8)-$, $R^2 = OCH_3$
3: $R^1, R^1 = -(C_4H_8)-$, $R^2 = tBu$
4: $R^1, R^1 = -(C_4H_8)-$, $R^2 = H$
5: $R^1 = Ph$, $R^2 = CH_3$
6: $R^1 = Ph$, $R^2 = Br$

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In our earlier work on effective, homogenous epoxidation of olefins with *m*-chloro peroxybenzoic acid (*m*CPBA) catalyzed by (salen)Mn complexes,[8b] we observed a linear correlation of enantioselectivity and temperature for the epoxidation of styrene catalyzed by **5** over a wide temperature range. We carried out similar experiments with indene, dihydronaphthalene, and cyclooctadiene; the latter two (with styrene) are also substrates evaluated in the study by Katsuki et al.[5] The Eyring plot for the epoxidation of all four substrates catalyzed by **5** over a range of 100 degrees shows a completely linear correlation between asymmetric induction and temperature (Figure 4). The results from the *homogenous* epoxidation of these four olefins fail to reveal any sort of nonlinear behavior, and thus there is no reliable evidence suggesting existence of any reversibly formed intermediates.

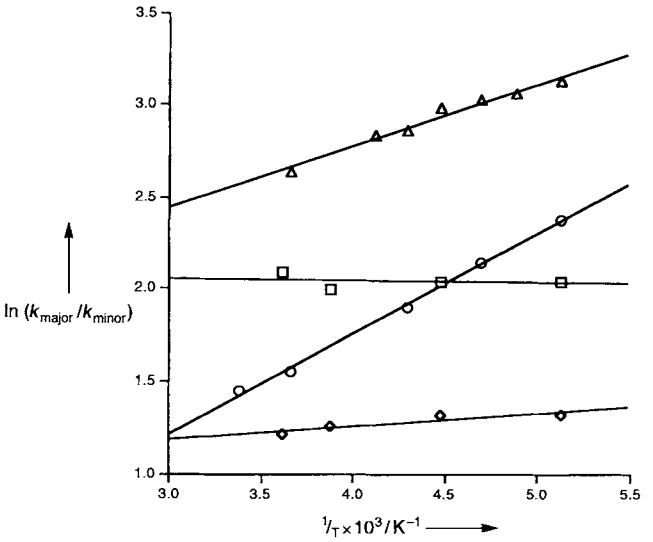

Figure 4. Eyring plots from the epoxidation of dihydronaphthalene (△), indene (□), styrene (○), and cyclooctadiene (◇) with *m*-CPBA catalyzed by (*S*,*S*)-**5**.

The simplest mechanism consistent with the observed data for (salen)Mn-catalyzed epoxidation reactions remains direct attack of olefin on an (oxo)manganese species to generate a radical intermediate, followed by ring closure to form the epoxide products. Besides adequately explaining all of the salient features of the reaction, this mechanism provides the greatest congruity with related sulfoxidation reactions[18] and biomimetic porphyrin oxidations.[3] Whereas more complicated mechanistic schemes—such as *N*-oxide ligand dissociation from the metal center during oxametallacycle formation and reassociation during epoxide formation, or the reaction of different olefins and catalysts proceeding by separate mechanisms—cannot be categorically excluded; there is no experimental evidence to support such possibilities. In what remains a fundamentally experimental discipline, it is essential to adhere to Ockham's Razor: "That which is explained with the assumption of fewer things is explained in vain by the assumption of more things."[19]

Experimental Section

Epoxidations with catalyst (*R*,*R*)-**1** were carried out following the standard biphasic epoxidation procedure [20]. Low-temperature epoxidations were conducted as described [7b], and proceeded with 20–50% conversion within 10 min; the product accounted for more than 95% of the consumed starting material. Conversion, yield, and *cis*/*trans* ratios were determined by capillary gas chromatography. Reported enantiomeric excesses are the average of at least three measurements, and were determined by either chiral capillary GC (Cyclodex-B: styrene oxide, dihydronaphthalene oxide; Gamma-TA: cyclooctadiene monoepoxide) or HPLC (Chiralcel OB: indene oxide).

Electrochemical measurements were performed at a rate of 40 mVs^{-1} on 2 mM solutions of (*R*, *R*)-**2** in CH_3CN (0.1 M Bu_4NPF_6 as the working electrolyte). The employed Pt working, Ag (vycor frit isolated) counter, and Ag/Ag^+ reference electrodes were standardized by in situ measurement of the ferrocene/ferrocenium one-electron oxidation. Redox potentials are reported relative to the saturated calomel electrode (SCE).

The semi-empirical UHF calculations described in ref. [13] were performed using the semi-empirical PM3 (tm) parameters, as implemented by the Spartan interface (Spartan version 4.0, Wavefunction, Inc., Irvine, CA (USA)). The starting catalyst conformation was derived from the crystal structure of **1** by deletion of the apical chloride and the alkyl tethers connecting the pyridine *N*-oxide to the salen aromatic rings. The phenylcyclohexanolyl fragment was appended with a fixed Mn–O bond length of 1.8 Å, and minimizations were carried out from eight different initial values for the O(salen)-Mn-O-C dihedral angle.

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[13] One of the principal difficulties encountered in evaluating the radical mechanism is the question of how an essentially flat ligand system can impart such exquisite levels of enantioselectivity with a wide range of substrates. This has served as the impetus for the proposal by Norrby et al. [4] of the 6-coordinate oxametallacyclic intermediate **B**. Credence was lent to this pathway by calculations based on empirical force-field models, which predicted significant differences in energy between diastereomeric 6-coordinate (salen)Mn oxametallacycles. The documented effect of amine *N*-oxide derivatives on the epoxidation rules out such intermediates. Still, it is worth considering whether a similar computational analysis of the radical mechanism stands up well against available enantioselectivity data. We performed semi-empirical calculations of the diastereomeric radical intermediates for the epoxidation of phenylcyclohexene (PM3 (tm) parameters, Spartan version 4.0). This analysis indicates that the enantioselectivity of the epoxidation reaction may be readily ascribed to energetic differences between diastereomeric radical intermediates, and that the radical mechanism is perfectly consistent with enantioselective epoxide formation.

[14] For example, epoxidation of triphenylethylene catalyzed by **3** provides triphenylethylene oxide in 92% *ee* and 97% yield, and epoxidation of phenylcyclohexene proceeds in 88% *ee* and 67% yield: B. D. Brandes, E. N. Jacobsen, *J. Org. Chem.* **1994**, *59*, 4378. Similarly, epoxidation of 3′-bromo-2,2,3,4-tetramethylchromene employing **5** provides the corresponding chromene oxide in 96% *ee* and 84% yield: B. D. Brandes, E. N. Jacobsen, *Tetrahedron Lett.* **1995**, *36*, 5123.

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Is There a Radical Intermediate in the (salen)Mn-Catalyzed Epoxidation of Alkenes?**

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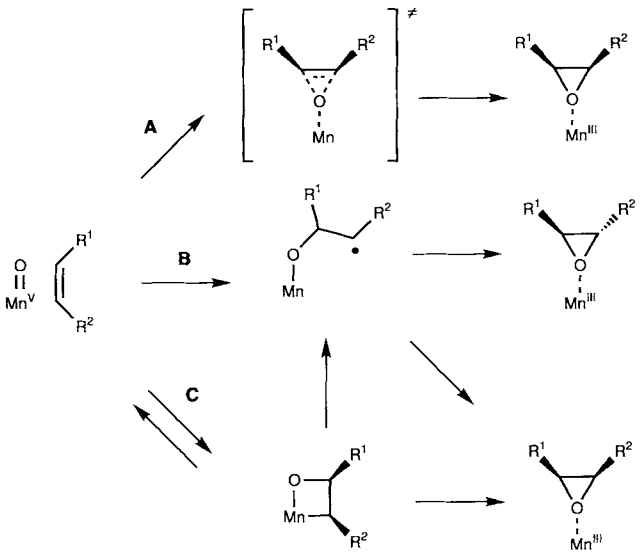
The mechanism for the (salen)Mn-catalyzed epoxidation of alkenes is a topic of great interest (salen = *N*,*N*′-bis(salicylidene)ethylenediamine dianion).[1] The reaction has been proposed to proceed either in a concerted manner,[2] via a radical intermediate,[1, 3] or via a manganaoxetane intermediate[4, 5] (Scheme 1). According to Jacobsen et al.[2] alkyl-substituted alkenes react concertedly (Scheme 1, pathway **A**). The *cis*/*trans* isomerization observed in the epoxidation of conjugated alkenes was taken as evidence for a radical intermediate (Scheme 1, pathway **B**).[6]



Scheme 1. Proposed mechanisms for the (salen)Mn-catalyzed epoxidation: **A**: concerted reaction ($R^1 = R^2$ = alkyl); **B**: reaction via a radical intermediate (R^1 = alkyl, R^2 = aryl, alkenyl, alkynyl); **C**: reaction via an oxetane intermediate (R^1 = alkyl, R^2 = alkyl, aryl, alkenyl, alkynyl).

Recently we suggested that the (salen)Mn-catalyzed epoxidation proceeds by reversible formation of a manganaoxetane, followed by irreversible rearrangement or ring opening, leading to the two diastereomeric products (Scheme 1, pathway **C**).[4, 7] The selectivity in the title reaction could be explained by postulating that epoxidation of conjugated alkenes mainly proceeds through an oxetane in which the conjugated carbon atom is bound to the manganese atom.[4] Katsuki et al.[5c] independently proposed a manganaoxetane intermediate to rationalize the observed nonlinear Eyring plots for relative rates of formation of the enantiomeric epoxides.[8, 9] The absence of alkene isomerization in the reaction mixture in combination with reversible formation of an intermediate suggest that any radical formation by pathway **B** (Scheme 1) is effectively *irreversible*. A concerted pathway such as **A** cannot be reconciled with the nonlinear Eyring behavior.

In the closely related epoxidations utilizing metal porphyrin complexes, strong objections were raised against the proposed metallaoxetane intermediates.[7b, 10] However, it is uncertain whether the arguments are applicable to the (salen)Mn catalysts.[11]

In analogy to the radical-probe experiments of Jacobsen et al.,[2] which were performed in a mechanistic study of the epoxidation of isolated alkenes, we investigated the catalytic epoxidation of substituted styrenes **1a**–**c**[12] to look for benzylic radicals (Scheme 2). If the mechanism of epoxidation involves a radical intermediate **4**, reaction of **1a**–**c** is expected to yield ring-opened products. A similar result is likely if a manganaoxetane intermediate **2** undergoes homolytic cleavage of the Mn–C bond. However, if **2** rearranges directly to epoxide **3** the cyclopropane unit should survive unscathed. Traps **1b** and **1c** give us the additional opportunity to study the effect of *cis*–*trans* isomerization.

For the epoxidation of **1a**–**c**, we used racemic [*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamine]manganese(III) chloride[13] as the catalyst. The reaction was carried out in a two-phase system of CH_2Cl_2 and a buffer solution of

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