2422 J. Am. Chem. Soc. 1991, 113, 2422–2425

Electrostatic Catalysis of Oxidation Reactions by Metal Cations: An ab Initio Study

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Received April 10, 1990

Abstract: UMP4SDTQ/6-31G*//6-31G* calculations indicate that complexation of the oxidant with alkali metal cations provides both a strong catalysis of the forward reaction and a thermodynamic stabilization of the products in hydrogen atom abstraction reactions of triplet dioxygen and the hydroperoxy radical with methane, which was used as a model carbon-centered hydrogen atom donor. This effect, which is expected to be general for metal monocations, is based on purely electrostatic interactions, as is shown by the dependence of the calculated activation and reaction energies on the ionic radius of the metal and on the polarization of the $^3O_2$ and by model calculations using only 1 s orbital as the basis set for Li^+.

Triplet oxygen, $^3O_2$, is usually considered to be kinetically inactive.[1] Catalytic activation of $^3O_2$ has therefore been a subject of considerable interest in enzyme chemistry,[2] industrial oxidation reactions,[3] and methane activation.[4] Our theoretical studies on radical reactions have uncovered a general mechanism in which complexation with metal ions catalyzes open-shell reactions.[5,6] This effect has also been observed experimentally.[7] We were recently able to demonstrate that the epoxidation of ethylene by $^3O_2$ is catalyzed in the same way,[8] confirming the generality of the catalytic effect for open-shell reactions. We now report ab initio calculations[9] on the alkali metal ion catalysis of hydrogen atom abstraction reactions by $^3O_2$ and the hydroperoxy radical, $HOO^\bullet$.

The two reactions considered are the oxidation of methane by $^3O_2$

$$^3O_2 + CH_4 \rightarrow CH_3^\bullet + HOO^\bullet \qquad (1)$$

and the corresponding reaction of the hydroperoxy radical

$$HOO^\bullet + CH_4 \rightarrow CH_3^\bullet + H_2O_2 \qquad (2)$$

Both reactions are endothermic in the absence of metal cations,[10] as shown in Table I. There is also a moderate activation barrier in both cases. Complexation with metal cations has two major effects, as shown below by using Li^+ as an example. The complexes of $^3O_2$, $HOO^\bullet$, and H_2O_2 with Li^+ (**1**, **2**, and **3**) have calculated binding energies of −5.0, −27.2, and −40.2 kcal mol^{-1}, respectively. This increasing stability with increasing number of OH bonds in the substrate is due to the $H^{\delta+}$–$O^{\delta-}$–Li^+ polarization within the complex. It leads to a strong relative thermodynamic preference for the OH products in reactions 1 and 2 when complexed to metal ions.

This thermodynamic effect is, however, augmented by the preferential stabilization of the transition state expected[11] from the charge effect on the stabilities of odd-electron bonds. The calculations are, however, less reliable in this respect. Although transition states are found for reactions 1 and 2 both with and without metal cation complexation at UHF/6-31G*, they are strongly stabilized by the inclusion of the Mϕller–Plesset corrections for electron correlation, so that some UMP4sdtq/6-31G*//6-31G* energies for the transition states lie below those of the products when the zero-point energies are included (see Table I). Although the MP4 calculations without the zero-point energy corrections give small barriers, UMP2/6-31G* optimizations would probably give reactions without activation energies in some cases and are in progress. For this reason, however, the calculated activation energies should be regarded as upper limits. This does not alter the qualitative conclusions reached below but suggests that the quantitative data should be treated with caution. Spin contamination is negligible for reaction 1. All $\langle S^2 \rangle$ values lie below 2.06. For reaction 2, $\langle S^2 \rangle$ for **6** is 0.794; otherwise, all $\langle S^2 \rangle$ values are around 0.76.

However, as shown in Table I, each alkali metal provides a very significant thermodynamic and kinetic preference for hydrogen abstraction from methane, both for the triplet reaction 1 and for the radical reaction 2. The structures of the transition states for the Li^+-complexed reactions (shown in Scheme I) show the geometry changes expected on the basis of the thermodynamic changes induced by Li^+ complexation. These effects are predominantly electrostatic in nature and should therefore be observed for all closed-shell metal ions, irrespective of their orbital characteristics. Figure 1 emphasizes this point by showing a plot of the calculated activation and reaction energies for reaction 1 vs the reciprocal of the radius of the metal monocations.[12] The two quantities are clearly related, although the straight lines shown

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(1) See, for instance: Hamilton, G. A. In *Molecular Mechanism of Oxygen Activation*; Hayaishi, O., Ed.; Academic Press: New York, 1974; pp 405–451.

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(9) All calculations used the Convex versions of Cadpac 4.0 (Amos, R. D.; Rice, J. E. *CADPAC: The Cambridge Analytical Derivatives Package*, Issue 4.0; Cambridge University: Cambridge, U.K., 1987) and Gaussian 88 (Frisch, M. J.; Head-Gordon, M.; Schlegel, H. B.; Raghavachari, K.; Binkley, J. S.; Gonzalez, C.; DeFrees, D. J.; Fox, D. J.; Whiteside, R. A.; Seeger, R.; Melius, C. F.; Baker, J.; Kahn, L. R.; Stewart, J. J. P.; Fluder, E. M.; Topiol, S.; Pople, J. A. Gaussian Inc., Pittsburgh, PA, 1988) with the 6-31G* basis set (Hariharan, P. C.; Pople, J. A. *Theor. Chim. Acta* **1973**, *28*, 213.) except for K and Rb, for which Huzinaga 43321/431 and 433321/4331/4 basis sets (Huzinaga, S.; Andzelm, J.; Klobubowski, E.; Radzio-Enzelm, E.; Sakai, Y.; Tatewaki, H. *Gaussian Basis Sets for Molecular Calculations*; Elsevier: Amsterdam, 1984) were used. Optimizations used the unrestricted Hartree–Fock (UHF) formalism, and the optimized structures were characterized as minima or transition states by diagonalization of the UHF/6-31G* force constant matrix. The energies given in the text and in the scheme refer to UMP4SDTQ/6-31G* (Mϕller, C.; Plesset, M. S. *Phys. Rev.* **1934**, *46*, 678. Binkley, J. S.; Pople, J. A. *Int. J. Quantum Chem.* **1975**, *9*, 229. Pople, J. A.; Binkley, J. S.; Seeger, R. *Int. J. Quantum Chem. Suppl.* **1976**, *10*, 1. Frisch, M. J.; Krishnan, R.; Pople, J. A. *Chem. Phys. Lett.* **1980**, *75*, 66) single points on the UHF/6-31G* optimized geometries. Nonvalence orbitals were included in the Mϕller–Plesset correction calculations for reaction 1 because the sodium and potassium results are unreliable when the frozen core approximation is used (Hofmann, H.; Hänsele, E.; Clark, T. *J. Comput. Chem.* **1990**, *11*, 1147). The MP energies for reaction 2 were calculated by using the frozen core approximation.

(10) The energies of reactions 1 and 2 calculated from the heats of formation given by Benson, S. W. (*Thermochemical Kinetics*, 2nd ed.; Wiley: New York, 1976) and the heat of formation (2.5 kcal mol^{-1}) of $HOO^\bullet$ given by Howard, C. J. (*J. Am. Chem. Soc.* **1980**, *102*, 6937) are 55.2 and 17.6 kcal mol^{-1}, respectively.

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Table I. UMP4sdtq/6-31G*//6-31G* Total,[a] Zero-Point, and Relative Energies

species	NIMAG[b]	no M^+	M = Li^+	M = Na^+	M = K^+	M = Rb^+	M = Cs^+
1 + CH_4		−190.320 77	−197.573 89	−351.992 83	−788.702 18	−3125.923 04	−7738.185 67
ZPE[c]		32.8	33.4	33.1	33.0	33.0	33.0
rel energy[d]		0.0	0.0	0.0	0.0	0.0	0.0
4	1	−190.220 10	−197.514 84	−351.924 14	−788.623 04	−3125.841 53	−7738.097 21
ZPE[c]		29.0	30.4	29.9	29.7	29.6	29.5
rel energy[d]		59.4	34.1	39.8	46.3	47.8	52.1
5	0	−190.224 44	−197.516 48	−351.927 82	−788.627 82	−3125.846 32	−7738.103 78
ZPE[c]		30.9	32.6	32.2	32.0	31.9	31.8
rel energy[d]		58.5	35.3	39.9	45.6	47.0	50.2
2 + $CH_3^\bullet$		−190.218 66	−197.500 17	−351.914 25	−788.616 47	−3125.835 67	−7738.098 24
ZPE[c]		29.3	30.4	30.2	30.1	30.0	30.0
rel energy[d]		60.5	43.3	46.4	50.8	51.9	51.9
2 + CH_4		−190.875 41	−198.155 86				
ZPE[c]		39.8	40.9				
rel energy[d]		0.0	0.0				
6	1	−190.821 80	−198.129 94				
ZPE[c]		37.5	38.9				
rel energy[d]		31.1	14.3				
7	0	−190.839 79	−198.148 45				
ZPE[c]		39.2	41.5				
rel energy[d]		21.7	5.2				
3 + $CH_3^\bullet$		−190.835 28	−198.135 78				
ZPE[c]		37.8	39.5				
rel energy[d]		23.2	11.2				

[a] The MP4-calculations for reaction 1 included the core orbitals; those for reaction 2 used the frozen-core approximation.[9] [b] The number of calculated imaginary vibrations. [c] UHF/6-31G*//6-31G* calculated zero-point energies (kcal mol^{-1}). [d] MP4-energies corrected for zero-point energies (kcal mol^{-1}).

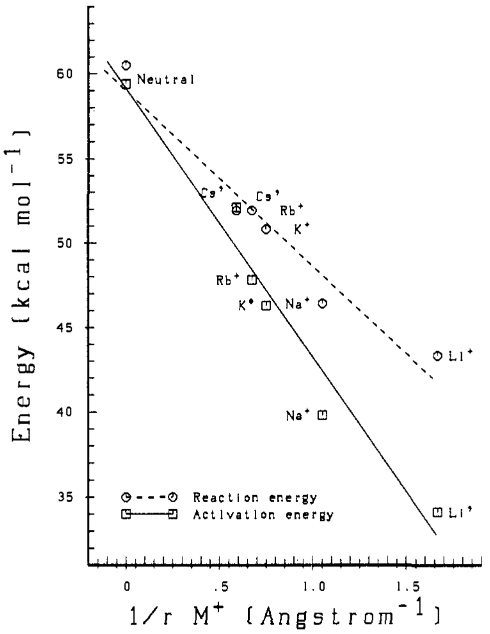

Figure 1. Calculated activation and reaction energies for reaction 1 plotted against the reciprocal of the Pauling ionic radius,[12] *r*, of the metal.

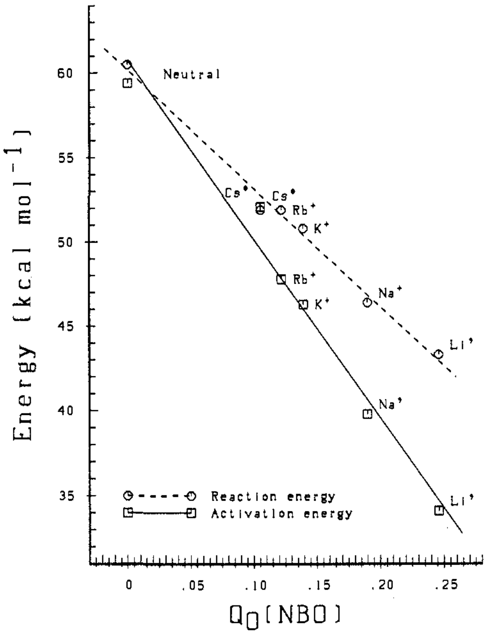

Figure 2. Calculated activation and reaction energies for reaction 1 plotted against the calculated (UHF) charge on the remote oxygen (Q_O) in the complexes **1**.

in the plot should perhaps not be taken too seriously.

The electrostatic nature of the catalysis is also shown by Figure 2, in which the NBO[13] charge on the oxygen not directly bonded to M^+ in **1** is plotted against the calculated energies. Once again, adequate linear correlations are found. A similarly good correlation is found if Mulliken charges are used, although these are generally lower than the NBO charges.

To rule out covalent effects completely, however, reaction 1 was recalculated by using only the 1s orbital from the Li-6-31G* basis set for Li^+. In this way, we are able to "turn off" all interactions involving the lithium 2sp valence shell and calculate species in which lithium interacts exclusively electrostatically.[14] The results of the full and truncated basis set calculations are

Table II. Relative (kcal mol^{-1}) Energies for $Li^{+}\cdot{}^3O_2 + CH_4 \rightarrow Li^{+}\cdot OOH^\bullet + CH_3^\bullet$ (Reaction 1) without Correction for Zero-Point Vibrations and for the Same Reaction without Valence Orbitals on Lithium (in Parentheses)

species	NIMAG[b]	HF[a]	MP2[c]	MP3[c]	MP4sdtq[c]
$Li^{+}\cdot{}^3O_2 + CH_4$	0	0.0	0.0	0.0	0.0
		(0.0)	(0.0)	(0.0)	(0.0)
TS	1	46.1	39.0	38.7	37.1
		(47.7)	(42.5)	(41.8)	(40.4)
minimum	0	30.1	39.3	34.7	36.0
		(31.9)	(43.0)	(38.3)	(40.0)
$Li^{+}\cdot OOH^\bullet + CH_3^\bullet$	0	37.1	49.7	44.5	46.3
		(38.6)	(52.8)	(47.5)	(49.5)

[a] Restricted Hartree-Fock (RHF) for closed-shell systems and unrestricted Hartree-Fock (UHF) for radicals. [b] See Table I. [c] All nonvalence orbitals were included in the Møller-Plesset correction calculations.

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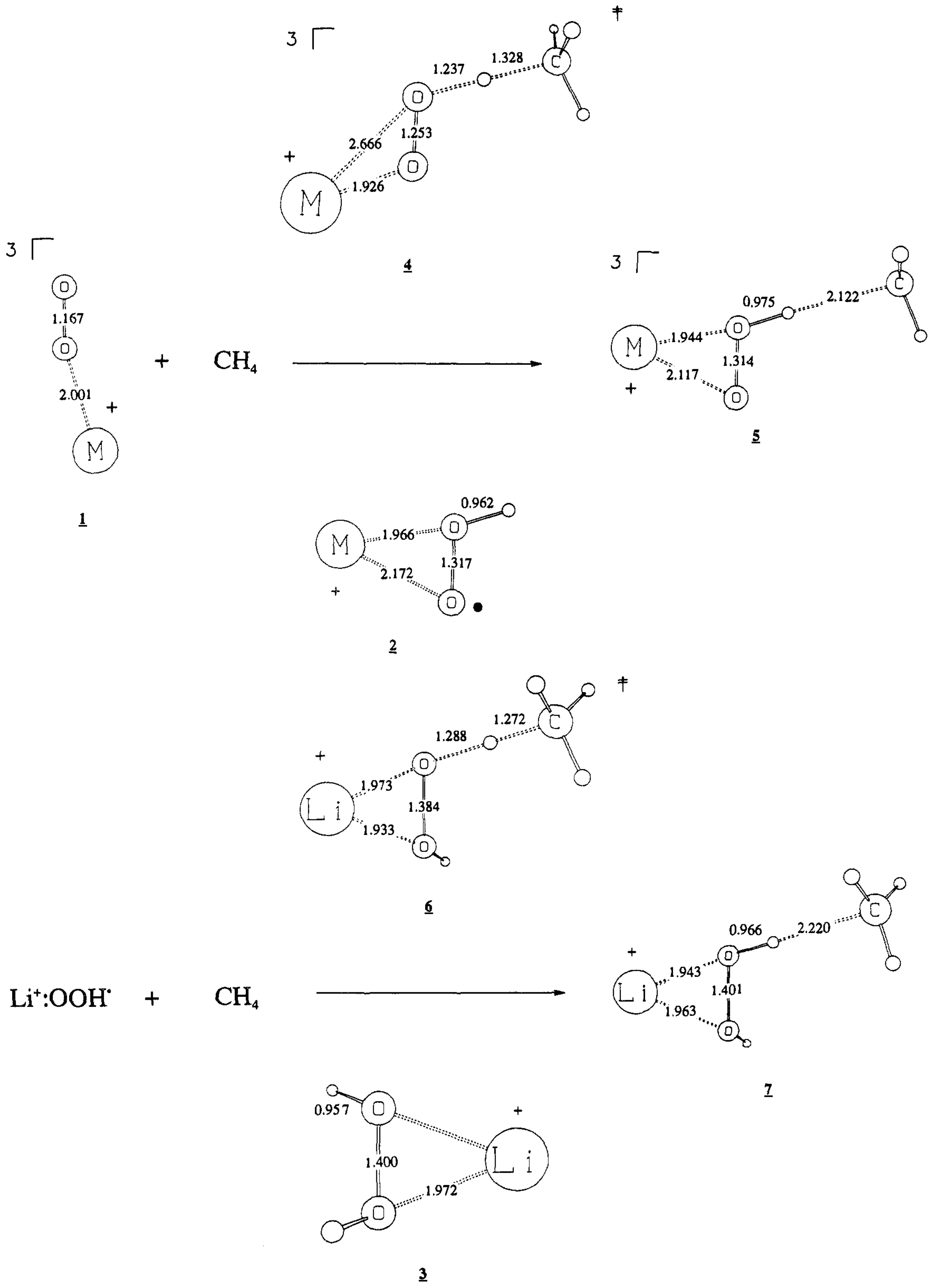
(13) Reed, A. E.; Weinhold, F. *J. Am. Chem. Soc.* **1985**, *107*, 1919.

(14) See, for instance: Clark, T.; Rohde, C.; Schleyer, P. v. R. *Organometallics* **1983**, *2*, 1344, for an example of the use of this technique.

Scheme I



compared in Table II. The deviation between the calculated activation and relative energies between the two series of calculations is at most 4 kcal mol^{-1}. These small deviations arise from BSSE effects because of the inadequacy of the 6-31G* basis for oxygen.[15] The origin of the catalysis is therefore clearly electrostatic.

We are extending our studies to the transition metals to assess the relative importance of electrostatic and orbital effects. A reasonable working picture, however, seems to be that the catalysis is predominantly electrostatic in nature but that the transition metals form stronger complexes to oxygen by virtue of their d orbitals.[16]

Our results, especially those for reaction 2, have important consequences for biological systems. When complexed to Li$^+$, reaction 2 becomes exothermic for more favorable CH donors than methane, such as, for instance, allylic CH bonds or those α to

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heteroatoms. This and the presence of alkali metal counterions in most biological systems make the role of metal ions in reactions of oxygen radicals in biological systems a fascinating new area for further work.

Acknowledgment. This work was supported by the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie, the Volkswagen Stiftung, and the Convex Computer GmbH.

Supplementary Material Available: Gaussian 88 archive entries for the MP4 single points on the reactants, transition states, and products of the uncatalyzed reactions and those with Li^+, Na^+, K^+, Rb^+, and Cs^+ (10 pages). Ordering information is given on any current masthead page.

Aqueous Solvation of *N*-Methylacetamide Conformers: Comparison of Simulations and Integral Equation Theories

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Abstract: The aqueous solvation thermodynamics of *cis*- and *trans*-*N*-methylacetamide is studied by integral equation theories and molecular dynamics simulations and compared with Monte Carlo results (Jorgensen, W. L.; Gao, J. *J. Am. Chem. Soc.* **1988**, *110*, 4212). Although the hypernetted chain (HNC) approximation is generally recommended for polar systems, the solvation free energy derived from the Gaussian fluctuation (GF) approximation gives much better absolute solvation thermodynamics. With the same atomic charges for the two conformers, the difference in solvation free energy between the cis and trans conformers equals 1–2 kcal/mol from the HNC and GF approximations, in approximate agreement with the value of 2.2 kcal/mol from a Monte Carlo simulation with very similar parameters. The simpler superposition approximation introduced by Pettitt and Karplus (*Chem. Phys. Lett.* **1985**, *121*, 194) gives results for the relative solvation thermodynamics (cis versus trans conformers) that compare well with the more exact integral equation theories.

1. Introduction

Biological macromolecules are polymers composed of simple organic monomers;[1] e.g., proteins are composed of 20 different types of amino acids and nucleic acids of 4 different nucleotides. The covalent bonding in the biopolymers is such that the main chain structure is chemically homogeneous. In proteins, the main chain consists of $-(NHC^{\alpha}CO)_n-$, where *n* is the number of amino acids in the sequence; in nucleic acids, the main chain is $-(\text{phosphate–ribose})_n-$, where the ribose is oxy in RNA and deoxy in DNA. The heterogeneity of the polymers results from different amino acid side chains attached to the C^{α} atoms in proteins and the different purine/pyrimidine bases attached to the ribose in nucleic acids. From X-ray and NMR structural studies, it is known that the backbone is flexible due to the presence of soft (ϕ, ψ in proteins; α, β, γ, δ, ϵ in nucleic acids) and hard (ω in proteins) dihedral angle degrees of freedom and can assume a wide range of conformations. The relative stability of these conformations is determined by the intrinsic properties of the backbone, the nature of the monomers, and the solvent environment. For proteins in their native state, the prediction of the ϕ, ψ values expected for a given sequence corresponds to the solution of the *folding* problem, the object of much of the theoretical and computational analyses of these systems. For peptides and denatured proteins, both the main chain and side chain tend to have a high solvent exposure. An analysis of the structural properties of these systems requires a detailed understanding of the effect of solvent on the stability of different conformations.

Recent computational and theoretical developments have made it feasible to focus on the effects of solvent on the structural, dynamical, and thermodynamic properties of biological macromolecules.[2,3] For example, the stochastic boundary simulation method[4] was introduced to study the active site dynamics of proteins in the presence of solvent.[5,6] Such simulation methods,[7,8] although very useful, require extensive computational resources with the explicit inclusion of solvent being the most time-consuming element. An alternative is to use integral equation theories to describe the effect of solvation.[9,10] Although approximate, the results have been shown to be meaningful for pure liquids and solutions.[9–20] To apply integral equation theory in a simple form that is consistent with standard molecular mechanics/dynamics potentials,[2] a superposition approximation has been developed to decompose the solvation corrections into pairwise additive contributions.[21,22] It has been employed to study the effect of solvation

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