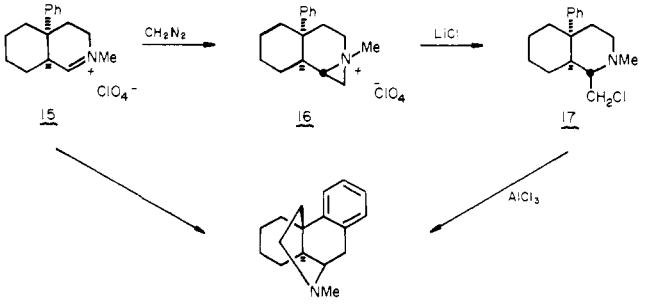
trans-fused immonium perchlorate **14** (X = ClO_4) as an oil. The structure of **14** was established by reduction ($NaBH_4$, MeOH) to **12** (**12**:**13** ≥ 95:5). Alternatively, if the kinetically generated salt **14** was dissolved in ethanol, after several days the cis-fused perchlorate **15** (X = ClO_4) gradually crystallized from solution (mp 162–163 °C) in 95% yield. As previously described, borohydride reduction of **15** afforded **13** in 95% yield (**13**:**12** ≥ 95:5). We have further shown that the conversion of **14** to **15** as described above is *not* a consequence of lattice-energy effects and the selective crystallization of a small equilibrium concentration of **15**. Methylene chloride solutions of **14** (X = Cl) likewise equilibrate (25 °C, 48 h) to **15** (K_{eq} = 32.3).[11] These results correlate well with the dramatic solvent effects noted above in the reduction of the bicyclic enamine **11**. It is concluded that **11** is the direct precursor to the trans-fused perhydroisoquinoline **12** in hydrogenations carried out in ethanol while the thermodynamic cis-fused immonium salt **15** (X = OAc) is the species reduced in acetic acid.[11] This general approach to 4a-phenyldecahydroisoquinolines **12** and **13** is noteworthy for its brevity in comparison with other published syntheses.[8]

By inspection, the morphinan and octahydroisoquinoline ring systems differ only by a crucial methylene bridge, and in principle, immonium salts such as **14** or **15** in conjunction with methylene equivalents could lead *directly* to the morphinan skeleton. In conjunction with testing this hypothesis, it was found that upon addition of diazomethane to **15** (X = ClO_4)[12] in methylene chloride



15 16 17

18

at 0 °C followed by solvent removal a crystalline solid was obtained which upon recrystallization (benzene–acetone) was shown to be the aziridinium perchlorate **16** (mp 164–166 °C)[4] whose stereochemistry was established by subsequent transformations (vide infra). The high degree of stereoselection in this addition process was anticipated, based upon ample precedent established in related nucleophilic addition reactions observed in this ring system during the course of this study.[13] Unfortunately, the relevant stereochemical control elements (stereoelectronic[14] vs. steric) in this immonium ion addition reaction are obscured by the two available half-chair conformations accessible to **15**. Regiospecific cleavage of the highly labile aziridinium ring with lithium chloride (3 equiv, 25 °C, MeCN) afforded the crystalline chloro amine **17** (mp 68–70 °C) in 98% yield. Final ring closure of **17** to *N*-methyl-14α-morphinan (**18**) was readily accomplished with $AlCl_3$[15] (6 equiv, C_6H_6, 80 °C, 2 h) in 60% (from **15**) yield.[4,16] It is worth noting that careful scrutiny of the reaction of immonium salt **15** with diazomethane revealed that a 15% yield (30% in acetone) of the morphinan **18** was produced directly in competition with aziridinium ion formation![16]

This general approach to the synthesis of morphine-based analgesics embodies the inherent flexibility not only for the efficient construction of analogues but also for the synthesis of the primary morphine alkaloids. Investigations directed toward this latter objective will be reported in due course.

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(11) The solution equilibration of **14** ⇄ **15** was conveniently followed by ^{13}C NMR. The approximate half-lives of 2 M solutions of **14** as a function of counterion X at 25 °C in methanol follow: X = ClO_4, $T_{1/2}$ = 16 h; X = Cl, $T_{1/2}$ = 2 h; X = OAc, $T_{1/2} \leq 5$ min.

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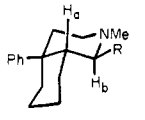
(13) We have observed that the addition of other nucleophiles such as MeMgI and MeNC to **15** proceeds in a highly stereoselective fashion from the convex face of the bicyclic ring system. The assignment of stereochemistry in these systems was deduced from the vicinal coupling between H_a and H_b; in both cases (*R* = Me, CONHME), J_{ab} = 10–11 Hz, suggesting that conformation **i** is preferred.



i

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(15) For a related cyclization, see: Stella, L.; Raynier, B.; Surzur, J. *Tetrahedron Lett.* **1977**, 2721.

(16) Gates, M.; Woodward, R. B.; Newhall, W. F.; Künzli, M. *J. Am. Chem. Soc.* **1950**, *72*, 1141. These workers have prepared **18** as well as its pricrate and methiodide salts. Our melting points were found to be identical with those reported.

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Cation–Medium Control of Hydride Transfer between Carbonyl Groups

Sir:

We report a dramatic demonstration that hydride transfer between two carbonyl groups, as exemplified by the Meerwein–Ponndorf–Verley/Oppenauer (MPV/O) reactions, can be affected in diametrically opposed ways by the cation/base employed, depending on whether or not the transition state allows complexation of both oxygen atoms by a single cation; both trends have been observed simultaneously at the carbonyl group of a single compound.

The experimentally convenient 4-hydroxycyclohexanone **1** undergoes both intra- and intermolecular hydride transfer.[1] In a series of comparative experiments with constant *i*-PrO^-/*i*-PrOH medium, the rate of the *inter*molecular hydride transfer from *i*-PrO–M to **1** (→**4** only) increases with increasing Lewis acidity of the cation ($Al^{3+} > Li^+ > Ba^{2+} > Na^+ > K^+$; see Table I), and therefore decreases with increasing effective basicity of the medium, as expected for the accepted cyclic transition state **12** for MPV/O reactions.[2-4]

However, concurrently in the same medium, the rate of the *intra*molecular process (→**2**) increased in the reverse cationic order of increasing metal–oxygen basic character ($Ba^{2+} > K^+ > Na^+ > Li^+ > Al^{3+}$; see Table I), except for Ba^{2+} being out of order. Moreover, for constant K^+ cation, the rate of the intramolecular hydride shift was found to increase with increasing basicity of the medium (*t*-AmOK/benzene > *t*-AmOK/*t*-AmOH > *i*-PrOK/*i*-PrOH > EtOK/EtOH > MeOK/MeOH; see Table II). In agreement, the addition of 18-crown-6 ether or [2.2.2]cryptand to either the *i*-PrOK/*i*-PrOH or the *t*-AmOK/benzene reaction

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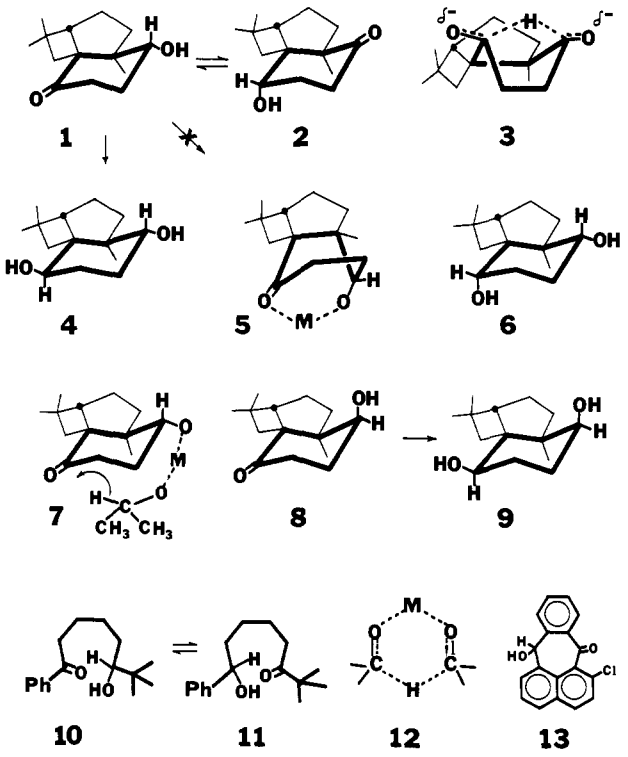

increased the rate 5–10-fold. In practical terms, for *i*-PrO⁻/*i*-PrOH with Ba^{2+} or K^+, intramolecular hydride shift **1** ⇌ **2** reaches equilibrium (K = 0.5) long before any intermolecular transfer occurs, but with Al^{3+} only intermolecular reduction (**1** → **4**) is observed even when the reaction is carried to complete consumption of **1**.[5]

The decrease in rate of intramolecular transfer with increase in Lewis acidity of the cation cannot be attributed to binding of **1** into a conformation (**5**) unsuitable for hydride shift. Were this so, reduction of **5** (M = Al^{3+}) by Na/*t*-BuOH would have yielded **6** whereas the product was found to be 96% of **4** with no more than 4% of **6**. Nor can the decrease in intramolecular transfer be attributed merely to facilitation of intermolecular (at the expense of intramolecular) transfer via complexed isopropoxide (**7**) for the following reasons. Although **1** and **2** give diol configurations in agreement with this possibility (i.e., **1** → **4**), the hydroxyl epimers of **1** and **2** do not give diols of the configuration predicted by this idea (i.e., **8** → **9**). More convincingly, neither **1** nor its hydroxyl epimer **8** undergoes any intramolecular hydride transfer with (*t*-BuO)$_3$Al/*t*-BuOH at 100 °C for 95 h.[6] Consequently, for the intramolecular process, these results strongly indicate an ionic transition state **3**, which must be central for reasons of symmetry as well as experiment[7] and theory.[8]

The contrariness of these results is not intrinsic to the intra- or intermolecularity of the hydride transfer because the acyclic ketol **10**, mp 48–50 °C, does undergo *intra*molecular hydride shift (→**11**) with (*t*-BuO)$_3$Al/*t*-BuOH even at room temperature. In fact, with **10**, the (*t*-BuO)$_3$Al/*t*-BuOH reaction is much faster than the *t*-BuOK/*t*-BuOH reaction, thus giving the same cation order noted for the *inter*molecular reaction of **1** with *i*-PrOM/*i*-PrOH. Furthermore, with (*i*-PrO)$_3$Al/*i*-PrOH, **10** undergoes intra- and intermolecular hydride transfer at very nearly the same rate.

We are forced to conclude that the reversal of the rate order must be a function of how the oxygen atoms are incorporated into the transition state for hydride transfer. If a cyclic transition state **12** is possible (interreaction with **1** and **10**, intrareaction with **10**), then the reaction catalyzed by the better Lewis acid will be favored whether intra- or intermolecular, but if a cation-linked cyclic transition state is stereochemically prohibited (intrareaction with **1**), then hydride transfer is favored by greater negative charge buildup on the oxygen atoms, i.e., by the poorer Lewis acid and the stronger base.[9] Gratifyingly, this latter cation order parallels the effect found for group I cations on intramolecular hydride shift in the dihydropleiadenone **13**, for which a similar rationale was suggested.[10]

These findings indirectly provide strong support for the accepted cyclic transition state **12** for hydride transfer in typical MPV/O reactions.[2-4] They are also in harmony with the decisive role recently found for the cation in metal hydride reduction of ketones[11] and α-enones,[12] and in the stereochemical outcome of some aldol condensations,[13,14] but they contrast with the apparent unimportance of cation linking in the Darzens reaction[15] and certain other aldol reactions.[16]

Table I. Pseudo-First-Order Rate Constants for Intra- and Intermolecular Hydride Transfer with **1** in *i*-PrOH at 83 °C[a]

cation	intra ψk_1, s^{-1}	inter ψk_1, s^{-1}
Ba^{2+}	8×10^{-5}	4×10^{-6}
K^+	1×10^{-5}	$<6 \times 10^{-8}$
Na^+	8×10^{-6}	1×10^{-6}
Li^+	4×10^{-6}	2×10^{-5}
Al^{3+}	$<10^{-8}$ [b]	1×10^{-4}

[a] Solutions were 0.58 M in *i*-PrO⁻ and 0.018 M in **1**. [b] Determined from nonreaction in (*t*-BuO)$_3$Al/*t*-BuOH.

Table II. Pseudo-First-Order Rate Constants for Intramolecular Hydride Transfer with **1** in RO⁻K⁺/solvent at 83 °C[a]

RO⁻	solvent	ψk_1, s^{-1}
MeO⁻	MeOH	$<6 \times 10^{-8}$
EtO⁻	EtOH	2×10^{-6}
i-PrO⁻	*i*-PrOH	1×10^{-5}
i-PrO⁻	*i*-PrOH + 0.58 M 18-crown-6	5×10^{-5} [c]
i-PrO⁻	*i*-PrOH + 0.58 M [2.2.2]cryptand	5×10^{-5} [c]
t-AmO⁻	*t*-AmOH	1×10^{-4}
t-AmO⁻	benzene	$>1 \times 10^{-3}$
t-AmO⁻	benzene	1×10^{-4} [b]
t-AmO⁻	benzene + 0.58 M 18-crown-6	5×10^{-4} [b,c]
t-AmO⁻	benzene + 0.58 M [2.2.2]cryptand	1×10^{-3} [b,c]

[a] Solutions were 0.58 M in RO⁻ and 0.018 M in **1**. [b] Determined at 65 °C. [c] The differences in the effect of 18-crown-6 ether vs. [2.2.2]cryptand on the *i*-PrOK/*i*-PrOH and *t*-AmOK/benzene reactions are understandable on the basis of **3** and will be discussed in the full paper.

(5) Lithium occupies an intermediate position. Both intra- and intermolecular hydride transfer in a ratio of 1:6 are observed in *i*-PrOLi/*i*-PrOH. Addition of 12-crown-4 ether changes the ratio to 1:1.

(6) The absence of any intramolecular hydride shift under these vigorous conditions also precludes rationalization of the trend on the basis of rate of exchange of **1** with $[Al(OR)_3]_n$ or rate-limiting rearrangement of $[Al(OR)_3]_n$.[2]

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(9) Although a transition state such as **3** could be imagined as complexed to two Al ions, one bonded to each oxygen atom, the absence of any reaction with (*t*-BuO)$_3$Al/*t*-BuOH must mean that such complexing does not favor hydride shift.

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