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New Chiral Crown Ethers Derived from Camphor and Their Application to Asymmetric Michael Addition. First Attempts to Rationalize Enantioselection by AM1 and AMBER Calculations

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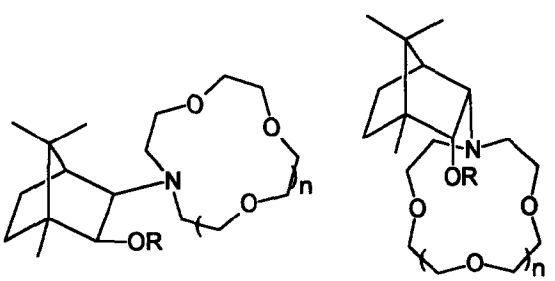
Abstract The synthesis of novel optically active crown ethers derived from (1*R*)-(+)-camphor is described. The mechanism of their catalytic effect upon the Michael addition of phenylacetate to acrylate is discussed in terms of kinetic *vs.* thermodynamic control in the formation of the catalytic ion-pair complexes. The relative basicity of the complexes formed between the alkaline metals and the unprotonated chiral crown ethers plays an important role in the sterochemical outcome. AMBER and AM1 calculations support that the reaction in which the best e.e. (83%) is obtained proceeds under kinetic control.

Introduction

Although many optically active crown ethers have been described in the literature,[1] there have been relatively few attempts to use chiral crown ethers to catalyze asymmetric C-C bond formation reactions.[2] In general, those crown ethers used for the latter purpose were initially envisaged for molecular recognition at the ground state and therefore their structure was not designed from the understanding of the possible shape of the diastereoisomeric complexes and/or transition states involved.[3] In the cases where an explanation to the observed enentioselection was given,[2,4] the relative thermodynamic stability of the diastereomeric transient complexes was only qualitatively evaluated by considering planar structures for the crown ethers. Differences as low as 0.5-1 kcal/mol were accounted for with this approximation. Possible kinetic control of enolate formation was not considered at all and little or nothing was said about the role of the base.

Within a program aimed to understanding the mechanism of these catalytic processes, we present the preparation of novel chiral crown ethers derived from (1*R*)-(+)-camphor (Scheme I).



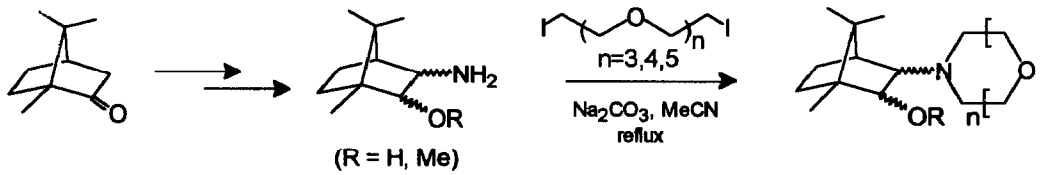
n	R	*exo*	*endo*
1	H	**1x**	**1n**
2	H	**2x**	**2n**
2	Me	**2x-OMe**	**2n-OMe**
3	H	**3x**	**3n**
3	Me	**3x-OMe**	

Scheme I

Upon deprotonation of the hydroxyl group with an alkaline base, a quite stable complex will be formed between the metal and the crown ether with its alkoxide group pointing to the center of the cavity. The efficiency of these complexes as highly asymmetric bases to promote Michael addition of phenylacetate to acrylate is checked. The first attempt to rationalize the reaction mechanism by molecular mechanics (AMBER) and semiempirical calculations (AM1) will be presented.

Synthesis

(1*R*)-(+)-Camphor was transformed into *exo,exo*- and *endo,endo*-3-amino-2-borneol and some of their OMe derivatives, according to literature procedures[5] (Scheme II). These compounds, upon treatment with the corresponding polyethylenedioxadiiodo derivatives,[6] rendered compounds **x** (*exo,exo*) and **n** (*endo,endo*) of Scheme I, respectively, in *ca.* 40% yield.



Scheme II

Michael Addition

The results obtained in the addition of methyl and *tert*-butyl phenylacetate to methyl acrylate catalyzed by the crown ethers of Scheme I, in the presence sodium/potassium *tert*-butoxide (OH and OMe derivatives) or hydride (OH derivatives), are summarized in Table 1. In the reaction with methyl phenylacetate, enantiomeric excesses (e.e.) were directly calculated from the optical rotation of the obtained dimethyl 2-phenylglutarate as compared with that reported for the pure enantiomer.[7] With *tert*-butyl phenylacetate, the resulting mixed *tert*-butyl methyl diester was hydrolyzed with acid and the optical rotation of the so obtained 2-phenylglutaric acid compared with that previously reported.[8]

It may be seen that the e.e.'s were in general moderate although in one case we have obtained a very high enantioselectivity (entry 12), comparable with the best e.e. values reported for this reaction with chiral crown ethers as catalysts. Sources for a low e.e. might be the uncatalyzed reaction and adduct racemization but blank tests demonstrated that these did not appreciably take place at -78°C.

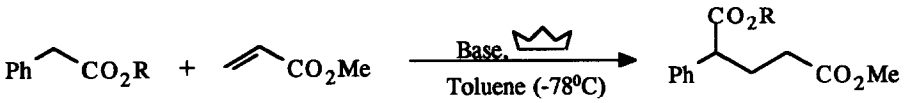
Four facts deduced from Table 1 are specially important as far as the reaction mechanism, not as yet well understood, is concerned:

i) In the case of the studied crown ethers with free OH, similar e.e. values were obtained by using either sodium/potassium hydride or *tert*-butoxide.

ii) Methylation of OH drastically diminished enantioselectivity and chemical yield for **2n**/Na^+ (entries 12 and 15), slightly reduced e.e. for **2x**/K^+ (entries 7 and 11) and did not essentially affect it for **3x**/K^+ (entries 19 and 20). This suggests a crucial role of alkoxide group in the reaction with **2n**/Na^+ but irrelevant for **3x**/K^+, the case of **2x**/K^+ being an intermediate one.

iii) The use of *tert*-butyl instead of methyl phenylacetate impeded the reaction for Na^+ at -78°C (entries 5 and 14) but not for K^+ (entries 10 and 18). In the case of Na^+ the reaction finally proceeded at room temperature but with negligible e.e. (entry 6).

Table 1. Results of the Michael addition of phenylacetate to acrylate catalyzed by crown ethers of Scheme 1.

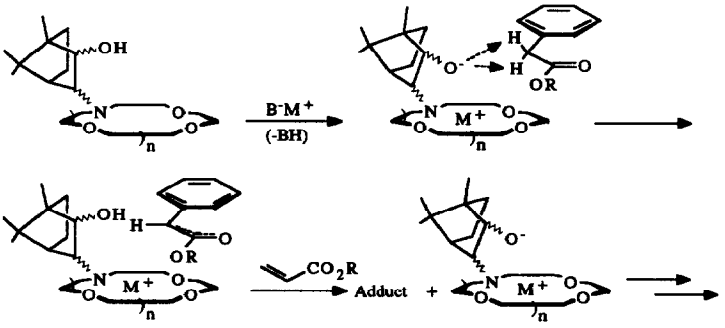


Entry	[a]	R	M^{+b}	time(h)[c]	yield(%)[d]	$[\alpha]_D$[e]	e.e.(%)	config.
1	**1x**(0.2)	Me	Na^+	3.5	70	+5.3	6	S
2	**1n**(0.1)	Me	Na^+	3.5	63	+26.7	34	S
3	**2x**(0.1)	Me	Na^+	3.5	46	+17.0	20	S
4	**2x**(0.2)	Me	Na^+	3.5	73	+10.6	12	S
5	**2x**(0.1)	*t*-Bu	Na^+	12	0	-	-	-
6	**2x**(0.1)	*t*-Bu	Na^+	12(r.t.)	>95	0	0	-
7	**2x**(0.05)	Me	K^+	2.5	85	-37.8	42	R
8	**2x**(0.05)	Me	K^+	0.5(0°C)	96	0	0	-
9	**2x**(0.1)	Me	K^+	3.5	90	-27.8	31	R
10	**2x**(0.1)	*t*-Bu	K^+	5.5	50	+10.0	12	S
11	**2x-OMe**(0.05)	Me	K^+	6.5	82	-15.5	17	R
12	**2n**(0.1)	Me	Na^+	3	65	+73.6	83	S
13	**2n**(0.1)	Me	Na^+	1.5(0°C)	95	+3.5	4	S
14	**2n**(0.1)	*t*-Bu	Na^+	12	0	-	-	-
15	**2n-OMe**(0.1)	Me	Na^+	3	22	+12.4	14	S
16	**2n**(0.05)	Me	K^+	3	72	+38.3	43	S
17	**2n**(0.2)	Me	K^+	3	85	+26.0	29	S
18	**2n**(0.1)	*t*-Bu	K^+	4.5	43	-38.4	45	R
19	**3x**(0.1)	Me	K^+	1.5	85	-33.2	38	R
20	**3x-OMe**(0.1)	Me	K^+	3	40	-40.1	45	R
21	**3n**(0.1)	Me	Na^+	3	15	+16.8	19	S
22	**3n**(0.05)	Me	K^+	2.5	90	+44.0	50	S
23	**3n**(0.05)	Me	K^+	0.75(0°C)	89	0	0	-
24	**3n**(0.1)	Me	K^+	2.5	75	+30.6	35	S

[a] Amount of crown ether relative to acrilate (see experimental part); **-OMe** refers to the corresponding crown ethers with OH methylated. [b] Base used with compounds with free OH group was either *tert*-butoxide or hydride. [c] Reaction temperature -78°C unless otherwise indicated. [d] Isolated product. [e] Dimethyl *(S)*-2-phenylglutarate, $[\alpha]_D$= +88.7 (see ref.); *(S)*-2-phenylglutaric acid $[\alpha]_D$= +85.8 (see ref.).

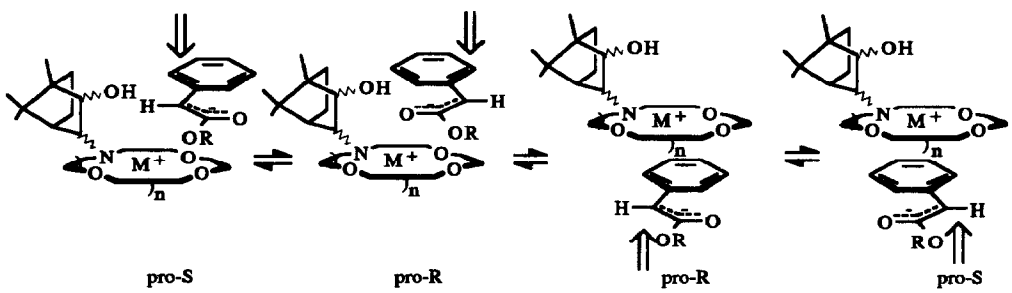
iv) The change of Na^+ by K^+ in the case of **2x** (entries 3 and 7) reversed adduct stereochemistry from *S* to *R*, a phenomenon which has been observed also in another occasion.[9] The cation change also diminished selectivity for *S* adduct in the case of **2n** (entries 12 and 16) but increased it for **3n** (entries 21 and 24).

The mechanism of the reaction can be pictured as follows. In view that identical results were obtained using either sodium/potassium hydride or *tert*-butoxide (fact *i*), one may assume that the base deprotonates the OH group of the crown ether (Scheme III) to form first a strong complex between the crown ether and the alkaline metal. This complex will be specially favorable due to the strong stabilization attained by the interaction between the negatively charged alkoxide group and the metal cation.



Scheme III

The phenylacetate should then approach the face of the crown ether where the O⁻ is placed. Thus, experiencing the highest possible chiral influence of the borneol moiety, the most favorable proton of phenylacetate is abstracted by the alkoxide group and an ion-pair complex is thus formed (Scheme III). If acrylate attacks it before any equilibration can take place, the observed enantioselectivity would be the result of a kinetic control, and therefore proportional to the ability of the borneol moiety to discriminate between benzylic hydrogens in proton abstraction.



Scheme IV

If equilibration does take place (Scheme IV), the stereochemical outcome of the reaction should be controlled by the relative stability of the ion-pair complexes formed by the pro-*R* or pro-*S* enolate, the alkaline metal ion and the crown ether. Although the complex between the crown ether and the alkaline metal ion would get extra stabilization by the quelation of the latter to the oxygen of the OH, the ion-pairing with the enolate could in principle be established by either of the two faces of the crown ether (Scheme IV).

Sterically speaking, the less hindered face and also the "less asymmetry-exerting one" is that below the borneol group. From this point of view, a kinetic control is in principle expected in our case to give higher e.e. values.

Facts *ii-iv* (see above) suggest that the reaction may follow different pathways when Na^+ and K^+ are used: the role of alkoxide group (fact *ii*) and the approach of phenylacetate, impeded by *tert*-butyl group (fact *iii*), appeared to be crucial for Na^+ but not for K^+; on the other hand, e.e. values and even selectivity changed (fact *iv*) when Na^+ was replaced by K^+. From this evidence it may be inferred that the reaction with $\mathbf{2n}^-/Na^+$ follows the kinetic pathway (Scheme III) whereas the reaction with $\mathbf{3x}^-/K^+$ proceeds essentially by thermodynamic control (Scheme IV). The case of $\mathbf{2x}^-/K^+$ may be borderline. Therefore, for $\mathbf{3x}^-/K^+$ and $\mathbf{2x}^-/K^+$ the free energy of activation leading to enolate formation should be lower than for $\mathbf{2n}^-/Na^+$, allowing the rapid equilibration of the formed ion-pairs. A plausible explanation to this different behavior may be found assuming a different basicity of the metal complexes, and therefore a different ease of enolate formation, in the order $\mathbf{3x}^-/K^+ > \mathbf{2x}^-/K^+ > \mathbf{2n}^-/Na^+$. This would also explain why *tert*-butyl phenylacetate reacted at -78°C with $\mathbf{2x}^-/K^+$ and $\mathbf{2n}^-/K^+$ but did not at all with the corresponding Na^+ complexes at the low temperature (fact *iii*).

Finally, a number of additional observations can be made from Table 1. Selectivity was inverted from *R* to *S* adduct when going from $\mathbf{2x}/K^+$ to $\mathbf{2n}/K^+$ (entries 7 and 16) and from $\mathbf{3x}/K^+$ to $\mathbf{3n}/K^+$ (entries 19 and 21), *i.e.* a change in the *exo-exo/endo-endo* stereochemistry of crown ethers led to complementary stereochemical results. On the other hand, it may be seen also that *tert*-butyl phenylacetate gave the opposite stereochemical outcome, compared to the methyl ester, for $\mathbf{2x}/K^+$ (entries 9 and 10) and $\mathbf{2n}/K^+$ (entries 16 and 18), suggesting that the steric bulkiness of the alkoxy group of enolate plays an important role in the relative stability of ion-pair complexes.

Temperature drastically diminished enantioselectivity (entries 7 and 8, 12 and 13, 22 and 23). As mentioned earlier, racemization of the adduct was negligible at -78° during 3 h but we realized it did occur to the extent of 25% at -20° for 1 h.

Increasing the amount of crown ether led in general to an increase in chemical yield but a diminution of enantioselectivity (compare entries 3 and 4, 7 and 9, 16 and 17, 22 and 24).

Calculations

From data in Table 1 we suggested the existence of a dichotomy of kinetic and thermodynamic control (*vide supra*) which depended on the catalyst and alkaline cation. But, the transition states and/or intermediate ion-pair complexes involved (Schemes III and IV) should contain such number of conformational uncertainties that we do not dare predict or explain the observed enantioselectivity by simple visual inspection of models, as it has been done in previous papers. In similar situations, previous authors accounted for the observed e.e values (up to *ca.* 85%, which corresponds to differences lower than 1 kcal/mol at -78°C between transition states or intermediate complexes) by a crude qualitative estimation of steric and/or polar interactions between the enolate and *planarly* depicted crown ether rings. Moreover, the aforementioned kinetic/thermodynamic dichotomy or the role of the base were not considered.

With the aim of making a somewhat more rigorous approach to the problem, it was challenging to explore whether relatively simple calculations[10] might be able to explain the stereochemistry of the reaction.

We have calculated the energy minima of possible ion-pair complexes (Table 2) and transition states (Table 3) for the reaction of methyl phenylacetate with Na^+ and/or K^+ complexes of **2x**, **2n**, **3x** and **3n**, by using molecular mechanics AMBER[11] and semiempirical AM1[12] calculations within the HYPERCHEM package.[13] Details of how calculations were performed are given in the experimental part.

Table 2 shows that the most stable pro-*R* or pro-*S* arrangement of the ion-pair complexes predicted by the calculations, despite their relative simplicity, coincided in all cases with the experimental configuration of the adduct. It should be noted that the ion-pair complexes of Table 2 were calculated with the *Z-syn* enolate. Calculations performed with *E* enolate led in all instances to the wrong stereochemical outcome and have been omitted in Table 2 for the sake of simplicity. Experimental ir data are in agreement with this finding since they have shown that potassium methyl phenylacetate enolate exists only in *Z-syn* configuration when the ion pairs are cryptand separated,[14] a situation which is quite similar to ours.

Calculated[15] e.e. values agreed fairly well with the observed ones for **2x**/K^+, **2n**/Na^+ and **2n**/K^+ but were exagerated in the case of **2nOMe**/Na^+, **3x**/K^+ and **3n**/K^+, suggesting that the calculations are in fact too simple to be considered in a strictly quantitative viewpoint. In addition, it should be noted that e.e values were computed assuming that both pro-*R* and pro-*S* ion-pair complexes would react at the same rate with methyl acrylate, which of course might not necessarily be the case.

On the other hand, we found it impossible to extract a clear pattern from AMBER energy partition in order to understand why an ion-pair complex was favored upon the other.

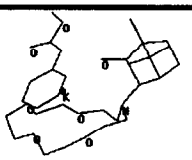
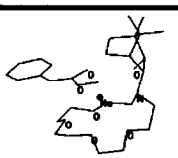
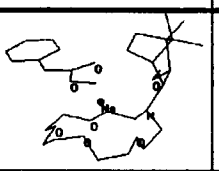
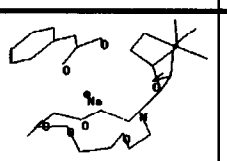
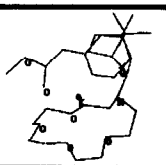
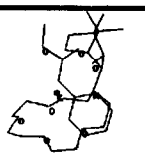
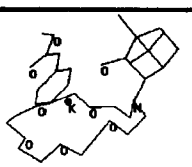
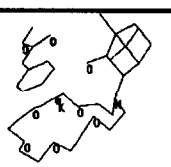
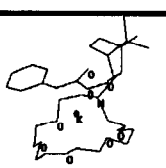
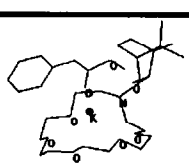
For **2x**/K^+, the pro-*R* arrangement was predicted to be more stable due to stabilizing electrostatic interactions ($\Delta_{R\text{-}S}$ = -0.9 kcal/mol) and hydrogen bonding ($\Delta_{R\text{-}S}$ = -0.5 kcal/mol; established between OH group of aminoborneol moiety and carbonyl oxygen of phenylacetate enolate), which compensate for its less favorable van der Waals interactions ($\Delta_{R\text{-}S}$ = 1.0 kcal/mol). We should remark that it was possible to find a pro-*S* arrangement bearing hydrogen-bonding but resulted to be a local minimum 1.6 kcal/mol less stable than the structure shown in Table 2.

For **2n**/Na^+, a much lower value of van der Waals interactions of pro-*S* ion-pair complex ($\Delta_{S\text{-}R}$ = -2.1 kcal/mol) was responsible of its higher stability. Therefore, OH group was not predicted to play any significant role in this case, in contrast to what the experimental results suggested (*vide supra*). Moreover, calculations failed in predicting the observed decrease in *S* selectivity when the OH was replaced by OMe (83% to 14%). In turn, an increase (72% to 96%) was calculated in going from **2n**/Na^+ to **2nOMe**/Na^+.

Comparing **2n**/Na^+ and **2n**/K^+, the experimental decrease in *S* selectivity when changing cations (Na^+, 83% to K^+ 43%) is relatively well reproduced (Na^+, 72% to K^+ 56%), but it should be noted that cation exchange, which as far as the calculations are concerned simply involves a change in metal atomic radius, varied the reasons by which the pro-*S* arrangement resulted more stable: instead of favorable van der Waals interactions as in **2n**/Na^+, electrostatic interactions ($\Delta_{S\text{-}R}$ = -1.3 kcal/mol) were the major factor for **2n**/K^+, which were even able to overcome the stabilization of its pro-*R* isomer gained by hydrogen-bonding.

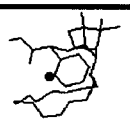
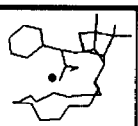
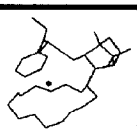
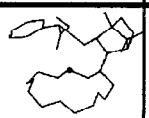
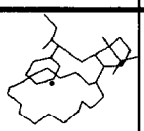
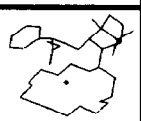
For the K^+ complexes of **3x** and **3n**, calculations predicted both electrostatic and hydrogen-bonding interactions to stabilize their pro-*S* and pro-*R* ion-pair complexes, respectively, albeit in these cases the expected total energy differences resulted too high leading to exagerated e.e. values.

Table 2.- AMBER energy partition, total energy and structure of the calculated minimum for the indicated pro-*S* and pro-*R* ion-pair complexes with methyl phenylacetate enolate *Z*.[a]

Compl.	Energy	pro-*S*		pro-*R*		calc. e.e.[b]	obs. e.e.[c]
2x/K+	Bond		1.9		1.9	36(*R*)	42(*R*)
	Angle		19.9		19.7		
	Dihedral		15.0		15.2		
	VdW		8.3		9.3		
	Electr.		-55.6		-56.5		
	H-Bond		0.0		-0.5		
	E_{total}		**-10.5**		**-10.7**		
2n/Na+	Bond		1.4		1.6	74(*S*)	83(*S*)
	Angle		18.2		18.6		
	Dihedral		15.1		14.0		
	VdW		4.1		6.2		
	Electr.		-60.8		-61.7		
	H-Bond		0.0		0.0		
	E_{total}		**-21.9**		**-21.2**		
2nOMe/ Na+	Bond		1.6		1.6	96(*S*)	14(S)
	Angle		18.8		18.9		
	Dihedral		15.6		15.4		
	VdW		3.9		3.3		
	Electr.		-58.7		-56.5		
	H-Bond		-		-		
	E_{total}		**-18.8**		**-17.3**		
2n/K+	Bond		1.7		1.7	60(*S*)	43(*S*)
	Angle		19.1		18.8		
	Dihedral		13.2		13.5		
	VdW		6.5		6.2		
	Electr.		-53.6		-52.3		
	H-Bond		0.0		-0.4		
	E_{total}		**-13.1**		**-12.6**		
3x/K+	Bond		1.7		1.7	90(*R*)	38(*R*)
	Angle		19.4		19.1		
	Dihedral		14.6		14.7		
	VdW		4.2		4.4		
	Electr.		-53.6		-54.4		
	H-Bond		0.0		-0.4		
	E_{total}		**-13.7**		**-14.8**		
3n/K+	Bond		1.8		1.7	90(*S*)	50(*S*)
	Angle		19.4		19.1		
	Dihedral		14.6		14.8		
	VdW		4.8		4.2		
	Electr.		-55.2		-53.9		
	H-Bond		-0.5		0.0		
	E_{total}		**-15.2**		**-14.1**		

[a] All energy values in kcal/mol. [b] Calculated % at -78°C. [c] See Table 1.

Table 3.- Calculated energy for pro-*S* and pro-*R* transition states (TS) in the approach of methyl phenylacetate to the complexes **2n**$^-$/Na$^+$ and **2x**$^-$/M$^+$

	M$^+$	TS pro-*S*		TS pro-*R*		calc. e.e.[a]	obs. e.e.[b]
2n$^-$	Na$^+$		-1.3		0.3	98(*S*)	83(*S*)
2x$^-$	K$^+$		10.7		11.9	92(*S*)	42(*R*)
3x$^-$	K$^+$		13.4		14.3	84(S)	20(*S*)

[a] Calculated % at -78°C. [b] See Table 1.

Finally, Table 3 summarizes the calculations performed on possible transition states for the reaction with **2n**/Na$^+$, **2x**/K$^+$ and **3x**/K$^+$, complexes upon which we based the dichotomy of kinetic *vs.* thermodynamic control (*vide supra*). Although Table 2 already explained the observed stereoselectivity for **2n**/Na$^+$, it is highly signifficant that calculations of Table 3 only agreed fairly well for this complex, whose experimental data strongly suggested a kinetically controlled ion-pair complex formation, and led to the wrong or an exagerated isomer preference for **2x**/K$^+$ and **3x**/K$^+$, respectively, for which thermodynamic control was proposed. Consequently, despite the inherent esotery of transition-state calculations, these calculations are in reasonable accord with the suggested kinetic/thermodynamic control problem.

Conclusion

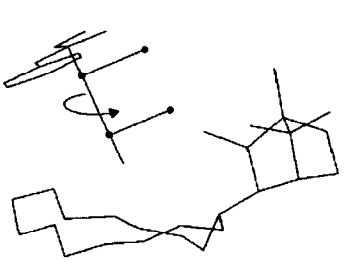
Evidence has been presented which indicates that the mechanism of ionic reactions catalyzed by chiral crown ethers is far more complex than anticipated in previous papers. It has been demonstrated that slight variations in the structure of the base or the reactants and the nature of the cation produce important changes in the mechanism of the reaction and in its stereochemical outcome which are impossible to predict on elementary grounds. However, even simple calculations as those presented in this work appear to be very valuable in predicting the stereochemistry of the adduct, although more accurate methods have to be developed to be able to make quantitative predictions.

Experimental Part

Calculations

Molecules were built and calculated within the HYPERCHEM package run on a PC 486DX33 computer with 8Mb of memory. Complexes of crown ethers **2x**, **2n**, **3x** and **3n** with Na^+ or K^+ were first pre-calculated with molecular mechanics AMBER program, using internal parameters except for the cations (Na^+, $r^*= 1.600$, $\varepsilon = 0.120$; K^+, $r^*= 1.925$, $\varepsilon = 0.120$). Once the minumum was reached, a single-point semiempirical AM1 calculation was performed, in order to get atomic charges, and then another AMBER minimization carried out considering electrostatic interactions. This process was repeated twice. The shape of the final structures looked quite reasonable and contained metal-heteroatom distances ($\overline{d_{NaIN}} = 2.81$ Å; $\overline{d_{KIN}} = 3.20$ Å; $\overline{d_{NaIO}} = 2.59$ Å; $\overline{d_{KIO}} = 2.88$ Å) which are similar to other found by x-ray diffraction analysis in Na^+ or K^+ complexes of related azacrown ethers.[16]

The most stable conformations of methyl phenylacetate enolate were obtained by AM1 minimization, resulting the *Z-syn* configuration 1.4 kcal/mol more stable than the corresponding *E* enolate. To calculate the ion-pair complexes of Table 2 we placed phenylacetate and the complexes as shown in Scheme V.

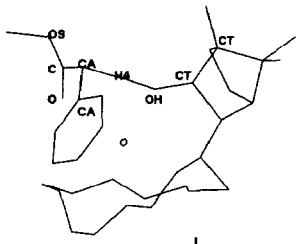


Scheme V

Rotation in 30^0 steps of phenylacetate with respect to the corresponding complex, by means of four dummy atoms (marked with ● in Scheme V) which were removed before minimization, led to twelve different starting structures. Only the atoms belonging to the complex between the crown ether and the metal were selected to be minimized. Therefore, phenylacetate was kept frozen while the minimization routine docked the complex freely towards it. The fact that the same minimized structure was found from several different starting arrangements assured the finding of a true minimum.

Table 4 summarizes the changes in AMBER atom types and parameters introduced in the calculations of transition states listed in Table 3. The hydrogen to be abstracted was taken as H4 type and the benzylic carbon as CA type. The equilibrium distances to the abstracted hydrogen of borneol oxygen and benzylic carbon (H4-OH and H4-CA in Table 4, respectively) were estimated from a model study performed with phenylacetate and methoxide: the bonds C_{Bn}-H-O were kept linear by means of a high bending constant (OH-H4-CA in Table 4) and for various C_{Bn}-O distances, several positions of H were tried until AM1 single-point calculation gave an energy maximum. Force constants for these 'imaginary' bonds, H4-OH and H4-CA, are small to allow their deformation at low energy cost. To assure the location of a true minimun, phenylacetate was placed in 84 different starting arrangements by means of the combined rotation of two dihedral angles (CT-CT-OH-H4 and CT-OH-H4-CA in Figure of Table 4). The resulting structure of the phenylacetate moiety of calculted TS was very close in all cases to that of *Z*-enolate (see Table 3).

Table 4. Atom types and parameters necessary for AMBER calculations of transition states of Table 3.



AMBER Atom types			K	r or θ
H4	OH		5.0	1.225
H4	CA		2.5	1.900
CT	OH	H4	15.0	108.5
C	CA	H4	30.0	109.5
CA	CA	H4	30.0	109.5
OH	H4	CA	100.0	180.0
HC	CA	H4	30.0	109.5
CA	C	O	80.0	120.4
CA	C	OS	80.0	120.4

General. Aminoborneols and polyethylendioxadiiodo derivatives were prepared as previously described. Methyl phenylacetate and acrylate were purchased from Aldrich and distilled prior to their use. *tert*-Butyl phenylacetate was prepared from phenylacetyl chloride and *tert*-butanol following usual procedures. ^{1}H (200 MHz) and ^{13}C NMR (50.3 MHz) spectra were recorded on a Bruker AC-200 instrument. IR spectra were measured on a Philips PU 9165 instrument. Low resolution mass spectra (EI, 70 eV or CI, NH_3 as indicated) were obtained on a Hewlett-Packard 5985 spectrometer. High resolution mass spectra (HRMS, LSIMS technique) were recorded on a VG Autospec spectrometer located at the *Servicio Interdepartamental de Investigación* (SIdI) of the *Universidad Autónoma de Madrid*. Optical rotation was measured on a spectropolarimeter Perkin-Elmer M-50.

General procedure for *O*-methylation of aminoborneol: A solution of 2g (0.12 mmol) of aminoborneol in 20 mL of dry THF was slowly added to a suspension of 2.25 g (0.13 mmol) of 25% potassium hydride in oil, previously washed twice with dry hexane, in 10 mL of dry THF at room temperature under argon. The reaction mixture was stirred for 30 min, then a solution of 0.72 mL of methyl iodide (0.12 mmol) in dry THF was slowly added and the resulting mixture was stirred for 1 h at room temperature. After filtering out the salts, the filtrate was concentrated at reduced pressure and 20 mL of ethyl ether were added. The organic layer was washed with brine, dried over calcium carbonate and the solvent removed *in vacuo*. The oily residue was purified by Kugelrhor destillation.

(*1R,2R,3S,4S*)-3-Amino-2-methoxy-1,7,7-trimethylbicyclo[2.2.1]heptane (4). It was obtained from *endo-endo*-aminoborneol [(*1R,2S,3R,4S*)-3-amino-2-hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptane] as a yellowish oil in 65% yield after distillation (b.p. 65°C/0.5 mm Hg). $[\alpha]_D$ +58.1 (*c* 2.6, C_6H_6). IR (film, cm^{-1}): υ 3600, 3419, 2953, 2339, 1607, 1464, 1369, 1125, 1105, 1008. ^1H NMR ($CDCl_3$): δ 3.4 (s, 3H, OMe), 3.5-3.15 (m, 2H), 1.8-1.0 (m, 5H), 0.89 (s, 3H), 0.86 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 60.1 (C2), 84.8 (OMe), 51.2 (C3), 49.8 (C4), 45.9 (C1, C7), 18.3 (C5, C6), 19.6 (Me, Me), 14.7 (Me). MS (EI) *m/z*: 183 (M^+, 10), 168 (11), 147 (15), 136 (17), 98 (34), 84 (100).

***1R,2S,3R,4S*)-3-Amino-2-methoxy-1,7,7-trimethylbicyclo[2.2.1]heptane (5).** It was obtained from *exo-exo*-aminoborneol [(*1R,2S,3R,4S*)-3-amino-2-hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptane] as a colorless oil in 73% yield after distillation (b.p. 75°C/1 mm Hg). $[\alpha]_D$ -72.1 (*c* 3.2, C_6H_6). IR (film, cm^{-1}): υ 3400, 2900, 1600, 1480, 1375, 1115, 1080. ^1H NMR ($CDCl_3$): δ 3.4 (s, 3H, OMe), 3.0 (s, 2H), 1.8-0.7 (m, 5H), 1.2 (s, 3H), 0.9 (s, 3H), 0.8 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 91.1 (C2), 60.5 (OMe), 59.2 (C3), 53.4 (C4), 49.3 (C1), 46.1 (C7), 33.4 (C6), 26.4 (C5), 21.3 (Me), 21.0 (Me), 11.4 (Me). MS (EI) *m/z*: 183 (M^+, 20), 168 (32), 151 (25), 136 (46), 98 (54), 84 (100).

General method for preparation of crown ethers. To a refluxed suspension of 2.96 mmol of aminoborneol or its OMe derivative and 13.5 mmol of sodium or potassium carbonate in 100 ml of dry acetonitrile under argon, a solution of 2.8 mmol of the corresponding polyethylenedioxadiiodo in 50 ml of dry acetonitrile was added at a rate of 3 mL/h by means of a syringe pump. The reaction mixture was refluxed for 3-7 days and its progress checked by the disappearance of the diiodo derivative (TLC). The mixture was allowed to cool at room temperature and the salts filtered out. The filtrate was concentrated at reduced pressure and then treated with 50 mL of a 1:1 mixture of diethyl ether/water. The organic layer was dried over sodium sulfate and the solvent evaporated at reduced pressure. The remaining oil was treated with 5 mL of 10% hydrochloric acid and the mixture washed with 10 mL of dichloromethane. The aqueous layer was carefully neutralized with 10% sodium hydroxide in an ice bath and extracted with 3x10 mL of ethyl ether. The combined organic extracts were washed with 10 mL of a saturated solution of sodium or potassium chloride, depending on the alkaline metal to be used in the catalytic reaction, dried over sodium sulfate and concentrated at reduced pressure. The resulting oil was used without further purification.

***N*-[(*1R,2R,3S,4S*)-2-Hydroxy-1,7,7-trimethylbicyclo[2.2.1]hep-3-yl]-1-aza-4,7,10-trioxacyclododecane (1n).** It was prepared from 1,11-diiodo-3,6,9-trioxaundecane using sodium carbonate. Yield 51%. $[\alpha]_D$ +21.3 (*c* 1, $CHCl_3$). IR (film, cm^{-1}): υ 3400-3200, 2870, 1750, 1650, 1440, 1370, 1170-1080. ^1H NMR ($CDCl_3$): δ 3.9-3.6 (m, 13H, CH_2O crown, CHO), 2.9 (dd, 1H, CHN, J=11.3 and 1.6 Hz), 2.8-2.4 (m, 4H, CH_2N crown), 1.8-1.7 (m, 1H), 1.76 (t, 1H), 1.5-1.3 (m, 1H), 1.15-0.85 (m, 2H), 0.88 (s, 6H), 0.85 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 73.9 (C2), 70.6 (C6', C8'), 69.5 (C5', C9'), 69.3 (C3', C11'), 64.8 (C3), 54.5 (C2', C12'), 50.2 (C4), 48.1 (C7), 45.4 (C1), 26.4 (C6), 20.1 (C5), 19.0 (Me, Me), 14.4 (Me). MS (CI) *m/z*: 329 (M^++2, 21.2), 328 (M^++1, 100). HRMS calcd. for $C_{22}H_{42}NO_6$, 328.2488, found 328.2499.

***N*-[(*1R,2R,3S,4S*)-2-Hydroxy-1,7,7-trimethylbicyclo[2.2.1]hep-3-yl]-1-aza-4,7,10,13-tetraoxacyclopentadecane (2n).** It was prepared from 1,14-diiodo-3,6,9,12-tetraoxatetradecane using sodium carbonate. Yield 45%. $[\alpha]_D$ +22.8 (*c* 1, $CHCl_3$) IR (film, cm^{-1}): υ 3500-3300, 2970, 2880, 1470, 1450, 1350, 1300, 1260, 1130, 1070. ^1H NMR ($CDCl_3$): δ 3.9-3.6 (m, 17H, CH_2O crown, CHO), 2.9 (dd, 1H, CHN, J=11.3 and 1.6 Hz), 2.8-2.4 (m, 4H, CH_2N crown), 1.8-1.7 (m, 1H), 1.76 (t, 1H), 1.5-1.3 (m, 1H), 1.15-0.85 (m, 2H), 0.88 (s, 6H), 0.85 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 73.6 (C2), 70.9 (C8', C9'), 70.3 (C6', C11'), 69.9 (C5', C12'), 69.2 (C3', C14'), 63.7 (C3), 53.6 (C2', C15'), 50.2 (C4), 48.2 (C7), 45.2 (C1), 26.1 (C6), 19.9 (C5), 18.9 (Me, Me), 14.3 (Me). MS (CI) *m/z*: 374 (M^++3, 3.8), 373 (M^++2, 22.7), 372 (M^++1, 100). HRMS calcd. for $C_{20}H_{38}NO_5$, 372.2750, found 372.2764.

***N*-[(*1R,2R,3S,4S*)-2-Hydroxy-1,7,7-trimethylbicyclo[2.2.1]hep-3-yl]-1-aza-4,7,10,13,16-pentaoxacyclooctadecane (3n).** It was prepared from 1,17-diiodo-3,6,9,12,15-pentaoxaheptadecane using potassium carbonate. Yield 39%. $[\alpha]_D$ +26.5 (*c* 1, $CHCl_3$) IR (film, cm^{-1}): υ 3500-3300, 2970, 2880, 1470, 1450, 1350, 1300, 1260, 1130, 1070. ^1H NMR ($CDCl_3$): δ 3.9-3.6 (m, 21H, CH_2O crown, CHO), 2.9 (dd, 1H, CHN, J=11.3 and 1.6 Hz), 2.8-2.4 (m, 4H, CH_2N crown), 1.8-1.7 (m, 1H), 1.76 (t, 1H), 1.5-1.3 (m, 1H), 1.15-0.85 (m, 2H), 0.88 (s, 6H), 0.85 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 73.2 (C2), 70.4 (C8', C9', C11', C12'), 70.2 (C6', C14'), 70.1 (C5', C15'), 69.8 (C3', C17'), 62.1 (C3), 51.6 (C2', C18'), 49.8 (C4), 47.8 (C7), 44.7 (C1), 26.3 (C6), 19.5 (C5), 18.5 (Me, Me), 14.0 (Me). MS (CI) *m/z*: 418 (M^++3, 4.3), 417 (M^++2, 24.5), 416 (M^++1, 100). HRMS calcd. for $C_{22}H_{42}NO_6$, 416.3012, found 416.3019.

***N*-[(*1R,2S,3R,4S*)-2-Hydroxy-1,7,7-trimethylbicyclo[2.2.1]hep-3-yl]-1-aza-4,7,10-trioxacyclododecane (1x).** It was prepared from 1,11-diiodo-3,6,9-trioxaundecane using sodium carbonate. Yield 45%. $[\alpha]_D$ +12.1 (*c* 1, $CHCl_3$) IR (film, cm^{-1}): υ 3400-3200, 2870, 1750, 1650, 1440, 1370, 1170-1080. ^1H NMR ($CDCl_3$): δ 3.7-3.4 (m, 12H, CH_2O crown), 3.3 (d, 1H, CHO, J=6.9 Hz), 2.8 (m, 4H, CH_2N), 2.5 (d, 1H, CHN, J=6.9 Hz), 1.9 (d, 1H, CH bridgehead, J=4.9 Hz), 1.7-1.4 (m, 2H), 1.4 (m, 2H), 1.1 (s, 3H), 0.9 (s, 3H), 0.7 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 79.4 (C2), 73.2 (C3), 71.2 (C6', C8'), 70.1 (C5', C9'), 69.2 (C3', C11'), 54.1 (C2', C12'), 47.2 (C4), 46.1 (C1, C7), 32.0 (C6), 28.2 (C5), 22.1 (Me), 21.9 (Me), 11.5 (Me). MS (CI) *m/z*: 329 (M^++2, 21.5), 328 (M^++1, 100).

***N*-[(*1R,2S,3R,4S*)-2-Hydroxy-1,7,7-trimethylbicyclo[2.2.1]hep-3-yl]-1-aza-4,7,10,13-tetraoxacyclopentadecane (2x).** It was prepared from 1,14-diiodo-3,6,9,12-tetraoxatetradecane using sodium carbonate. Yield 42%. $[\alpha]_D$ +10.4 (*c* 1, $CHCl_3$) IR (film, cm^{-1}): υ 3400-3200, 2950, 2860, 1750, 1640, 1350, 1120. ^1H NMR ($CDCl_3$): δ 3.7-3.4 (m, 16H, CH_2O crown), 3.3 (d, 1H, CHO, J=6.9 Hz), 2.9-2.6 (m, 4H, CH_2N), 2.5 (d, 1H, CHN, J=6.9 Hz), 1.9 (d, 1H, CH bridgehead, J=4.9 Hz), 1.7-1.4 (m, 2H), 1.4 (m, 2H), 1.1 (s, 3H), 0.9 (s, 3H), 0.7 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 78.8 (C2), 70.8 (C8', C9'), 71.5 (C3), 70.2 (C6', C11'), 69.8 (C5', C12'), 68.5 (C3', C14'), 52.1 (C2', C15'), 46.5 (C4, C7), 46.3 (C1), 31.8 (C6), 27.8 (C5), 21.3 (Me), 21.2 (Me), 11.3 (Me). MS (CI) *m/z*: 374 (M^++3, 3.7), 373 (M^++2, 22), 372 (M^++1, 100). HRMS calcd. for $C_{20}H_{38}NO_5$, 372.2750, found 372.2754.

***N*-[(*1R,2S,3R,4S*)-2-Hydroxy-1,7,7-trimethylbicyclo[2.2.1]hep-3-yl]-1-aza-4,7,10,13,16-pentaoxacyclooctadecane (3x).** It was prepared from 1,17-diiodo-3,6,9,12,15-pentaoxaheptadecane using potassium carbonate. Yield 38%. $[\alpha]_D$ +5.9 (*c* 1, $CHCl_3$) IR (film, cm^{-1}): υ 3300-3100, 2870, 1750, 1630, 1450, 1360, 1110. ^1H NMR ($CDCl_3$): δ 3.7-3.4 (m, 20H, CH_2O crown), 3.3 (d, 1H, CHO, J=6.9 Hz), 2.9-2.6 (m, 4H, CH_2N), 2.5 (d, 1H, CHN, J=6.9 Hz), 1.9 (d, 1H, CH bridgehead, J=4.9 Hz), 1.7-1.4 (m, 2H), 1.4 (m, 2H), 1.1 (s, 3H), 0.9 (s, 3H), 0.7 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 79.0 (C2), 71.1 (C3), 70.7 (C8', C9', C11', C12'), 70.5 (C6', C14'), 70.1 (C5', C15'), 68.4 (C3', C17'), 51.3 (C2', C18'), 46.8 (C7), 46.5 (C1, C4), 31.8 (C6), 27.6 (C5), 21.8 (Me), 21.1 (Me), 11.3 (Me). MS (CI) *m/z*: 418 (M^++3, 4.1), 417 (M^++2, 23), 416 (M^++1, 100). HRMS calcd. for $C_{22}H_{42}NO_6$, 416.3012, found 416.3024.

***N*-[(*1R,2R,3S,4S*)-2-Methoxy-1,7,7-trimethylbicyclo[2.2.1]hep-3-yl]-1-aza-4,7,10,13-tetraoxacyclopentadecane (2nOMe).** It was prepared from **4** and 1,14-diiodo-3,6,9,12-tetraoxatetradecane using sodium carbonate. Yield 35%. $[\alpha]_D$ +20.5 (*c* 1, $CHCl_3$) IR (film, cm^{-1}): υ 2970, 1760, 1640, 1460, 1360, 1270, 1120, 1030. ^1H NMR ($CDCl_3$): δ 3.8-3.6 (m, 17H, CH_2O crown, CHO), 3.41 (s, 3H, OMe), 3.3 (d, 1H, CHN, J=3.3 Hz), 2.9-2.6 (m, 4H, CH_2N crown), 2.0-1.3 (m, 5H), 0.94 (s, 3H), 0.89 (s, 3H), 0.86 (s, 3H). ^{13}C NMR DEPT135 ($CDCl_3$): δ 85.9 (C2), 70.8 (C8', C9'), 70.2 (C6', C11'), 69.7 (C5', C12'), 68.5 (C3', C14'), 62.7 (C3), 60.3 (OMe), 52.5 (C2', C15'), 48.9 (C4,), 26.7 (C6), 19.5 (Me), 19.0 (C5), 18.9 (Me), 15.5 (Me). HRMS calcd. for $C_{21}H_{40}NO_5$, 386.2906, found 386.2925.

***N*-[(*1R,2S,3R,4S*)-2-Methoxy-1,7,7-trimethylbicyclo[2.2.1]hep-3-yl]-1-aza-4,7,10,13,16-pentaoxacyclooctadecane (3xOMe).** It was prepared from **5** and 1,17-diiodo-3,6,9,12,15-pentaoxaheptadecane using potassium carbonate. Yield 34%. $[\alpha]_D$ +4.3 (*c* 1, $CHCl_3$) IR (film, cm^{-1}): υ 2980, 2950, 1730, 1640, 1450, 1350, 1260, 1100, 1030. ^1H NMR ($CDCl_3$): δ 3.8-3.6 (m, 21H, CH_2O crown, CHO), 3.3 (s, 3H, OMe), 2.91 (d, 1H, CHN, J=7.1 Hz) 2.85-2.5 (m, 4H, CH_2N), 1.8-1.3 (m, 4H), 1.75 (d, 1H), 1.1 (s, 3H), 0.9 (s, 3H), 0.7 (s, 3H). ^{13}C NMR DEPT135 ($CDCl_3$): δ 92.7 (C2), 72.7 (C3), 70.8 (C8', C11'), 70.6 (C9', C12'), 70.5 (C6', C14'), 70.4 (C5', C15'), 69.7 (C3', C17'), 61.1 (OMe), 53.4 (C2', C18'), 47.0 (C4), 33.2 (C6), 27.4 (C5), 21.4 (Me), 20.5 (Me), 11.9 (Me). HRMS calcd. for $C_{23}H_{44}NO_6$, 430.3169, found 430.3180.

Michael addition. A suspension of 0.1, 0.2 or 0.4 eq of sodium or potassium *tert*-butoxide or hydride (20% in mineral oil, washed twice with dry hexane) and 0.05, 0.1 or 0.2 eq, respectively, of crown ether in 3 mL of dry toluene was placed at room temperature under argon for 15 min in an ultrasound bath. The homogeneous mixture was cooled down to -78°C and it was added 2 eq (2.7 mmol) of methyl or *tert*-butyl phenylacetate. The reaction mixture was stirred for 30 min at the low temperature and 1 eq (0.13 g, 1.4 mmol) of methyl acrylate was slowly added by means of a syringe. After stirring for several minutes, the reaction was monitored by TLC (hexane/ethyl acetate 6:1). When completed, it was allowed to warm at room temperature and quenched with 10 mL of saturated ammonium chloride. The mixture was extracted with 3x10 mL of ethyl ether, the combined organic extracts dried over sodium sulfate and the solvent evaporated at reduced pressure. The resulting adduct was purified by flash chromatography (hexane/ethyl acetate 6:1). In the case of using *tert*-butyl phenylacetate, the resulting methyl *tert*-butyl 2-phenylglutarate

was hydrolyzed following standard method. Spectroscopic data of the resulting 2-phenylglutaric acid were identical to those previously reported.

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References and notes

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