Absolute Potassium Cation Affinities (PCAs) in the Gas Phase

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Abstract: The potassium cation affinities (PCAs) of 136 ligands (20 classes) in the gas phase were established by hybrid density functional theory calculations (B3-LYP with the 6-311 + G(3df,2p) basis set). For these 136 ligands, 70 experimental values are available for comparison. Except for five specific PCA values—those of phenylalanine, cytosine, guanine, adenine (kinetic-method measurement), and Me_2SO (by high-pressure mass spectrometric equilibrium measurement)—our theoretical estimates and the experimental affinities are in excellent agreement (mean absolute deviation (MAD) of 4.5 kJ mol^{-1}). Comparisons with previously reported theoretical PCAs are also made. The effect of substituents on the modes of binding and the PCAs of unsubstituted parent ligands are discussed. Linear relations between Li^+/Na^+ and K^+ affinities suggest that for the wide range of ligands studied here, the nature of binding between the cations and a given ligand is similar, and this allows the estimation of PCAs from known Li^+ and/or Na^+ affinities. Furthermore, empirical equations relating the PCAs of ligands with their dipole moments, polarizabilities (or molecular weights), and the number of binding sites were established. Such equations offer a simple method for estimating the PCAs of ligands not included in the present study.

Keywords: alkali metals · binding affinities · cations · density functional calculations · potassium

Introduction

The potassium cation is one of the most abundant metal cations in biological systems. The binding between potassium cation and protein/DNA – RNA/carbohydrate structures underlies many fundamental biological processes and enzymatic functions.[1] Knowledge of the K^+ binding modes and intrinsic binding energies (affinities) of smaller model ligand systems are fundamental to a full understanding of the interaction of K^+ in the more complex and larger biological systems.

A variety of experimental techniques has been employed to determine the alkali metal cation affinities of small model ligands. Absolute affinities were obtained by threshold collisional induced dissociation (threshold CID),[2–13] radiative associative kinetics measurements,[14] and high-pressure mass spectrometric (HPMS) equilibrium measurements,[15–24] while relative affinities were obtained by Fourier transform ion cyclotron resonance (FT-ICR) ligand exchange equilibrium measurements,[25–28] and the mass spectrometric kinetic method.[29–31] Complementing the progress made in experimental measurements, quantum chemical methods have advanced to a stage that not only relative but also absolute alkali metal cation affinities can be obtained in excellent agreement (accuracy: ± 15 kJ mol^{-1}) with experimental values.[7, 10, 24, 26, 27, 32, 33] In many instances, reliable theoretical results have been shown to provide a complementary/alternative route for obtaining and confirming alkali metal cation affinities.[9, 34–37] Also, theoretical findings on the most stable and low-lying binding modes/structures often provide new insights into the interpretation of experimental data. For example, a recent theoretical study on Li^+, Na^+, and K^+ affinity of DNA/RNA nucleobases highlighted the problem of assigning correct binding structures to measured alkali metal affinities when the free ligand exhibits tautomerism.[36, 37] On the other hand, measured experimental affinities are essential for the calibration, validation, and establishment of reliable theoretical protocols.

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While good compilations of intrinsic interaction energies between Li^+/Na^+ and model organic ligands are available,[10, 24–27] far fewer potassium cation affinities (both experimental and theoretical) have been reported in the literature. The present work represents the most comprehensive theoretical study on the potassium cation affinity (PCA) scale reported to date. By comparison with the existing experimental data, the accuracy of the theoretical protocol was established. For the 136 ligands studied here, the K^+ interacts with different atoms (noble gases, carbon, oxygen, nitrogen, sulfur, phosphorus, etc.) in the ligands, and with a wide range of functional groups (alcohol, sulfide, sulfoxide, amine, amide, ether, aldehyde, ketone, nitrile, carboxylic acid, aromatic, heterocyclic, etc.). With such a broad spectrum of ligands, we believe the findings presented here are of general chemical interest and useful in revealing the nature of K^+ binding to organic and biological ligands in the gas phase.

Methods of Calculation

Based on our previous studies on a smaller set of ligands,[38, 39] the interactions between potassium cations and neutral ligands in the gas phase were modeled using the following protocol:

1) Geometry optimization at the HF/6-31G(d) level, followed by frequency calculations to obtain the zero-point energy (ZPE) correction.
2) The effect of electron correlation on structures of ligands and K^+–ligand complexes was obtained by full geometry optimization at the B3-LYP/6-31G(d) level.[40]
3) Energetics were obtained by using the B3-LYP functional with the large and flexible 6-311 + G(3df,2p) basis set, based on geometries determined in step (2), that is, the energetic calculations were carried out at the B3-LYP/6-311 + G(3df,2p)//B3-LYP/6-31G(d) level.

Potassium cation affinities (PCAs) at 0 K, ΔH_0, were obtained by using Equation (1) where E_{K^+}, E_L, and E_{K^+-L} are the electronic energies of the potassium cation, the ligand, and the K^+–ligand complex, respectively, obtained from step (3); ZPE_L and $ZVPE_{K^+-L}$ are the zero-point energy corrections for the ligand and the K^+–ligand complex, respectively, obtained from step (1) with a scaling factor of 0.8929 for the Hartree–Fock frequencies.[32–34] For ease of description, this protocol is abbreviated as energetic protocol for K^+, EP(K^+), in the following. For comparison with experimental values, the EP(K^+) theoretical values at 0 K (ΔH_0) were converted to affinities at 298 K (ΔH_{298}) by standard statistical thermodynamics relations[41] calculated from the scaled HF/6-31G(d) vibrational frequencies.

$$\Delta H_0 = [(E_{K^+} + E_L) - E_{K^+-L}] + [ZPE_L - ZPE_{K^+-L}] \times 0.8929 \quad (1)$$

Results and Discussion

Overview of theoretical and experimental alkali metal cation affinities: In this section, we highlight some recent advances in and issues related to the theoretical and experimental determination of alkali metal cation affinities reported in the literature. Using a density functional based method, Burk et al. recently reported the Li^+ affinity for 63 ligands, calculated at the B3-LYP/6-311 + G(d,p) level.[26] Calibration against experimental data suggested that this level of theory carried an average unsigned error of 15 kJ mol^{-1}, and the accuracy could be improved if systematic errors were taken into account.[26] Several theoretical studies of Na^+ affinities appeared recently.[10, 24, 27, 42] Most of these were conducted at the MP2(full)/6-311 + G(2d,2p)//MP2/6-31G(d) level, with corrections for basis set superposition error (BSSE).[24, 27] Armentrout and Rodgers further compared the performance of this level of theory and other models (DFT, CBS, G2, G3, etc.) with experimental data.[10] Theoretical and experimental sodium affinities were found to be in good general agreement. However, while BSSE-corrected B3-LYP/6-311 + G(2d,2p)//B3-LYP/6-31G(d) sodium affinities are consistently too high (MAD of 8.5 kJ mol^{-1} relative to experiment), the BSSE-corrected B3-P86/6-311 + G(2d,2p)//B3-P86/6-31G(d) values appear to fare better (MAD of 5.5 kJ mol^{-1} in comparison with experiment).[10] Recently, to improve the quality of the basis set for the sodium inner-valence 2s/2p orbitals, Petrie decontracted the standard 6-311 + G(3df) basis for the Na atom. With this more flexible basis set, Na^+ affinities of 38 ligands at the geometry-corrected counterpoise "CPd-G2thaw" level were obtained,[42] and it was suggested that the currently established experimental sodium cation affinities were systematically too low by 3–5 kJ mol^{-1}.

For K^+, far fewer theoretical and experimental values are available. The EP(K^+) theoretical PCAs at 298 K obtained in this study and the available experimental PCAs are compiled in Table 1 and graphically presented in Figure 1, while the geometries of K^+ binding modes for representative class of ligands are shown in Figure 2. Here, we wish to comment on the temperatures reported in the experimental studies. The experimental PCA values were largely obtained by threshold CID, HPMS, and kinetic methods. The threshold CID measurements yielded PCAs at 0 K, and corrections to 298 K (generally less than 2 kJ mol^{-1}) were carried out by theoretical calculations. In HPMS measurements, it is generally assumed that the standard enthalpy of cation binding ΔH is approximately equal to the ion–ligand bond dissociation energy, and is independent of temperature effects. Similarly, in measurements by the kinetic method, the relative affinity measured, $\Delta(\Delta H)$, is also implicitly assumed to be independent of the "effective temperature", even though the $\Delta(\Delta H)$ term may be anchored to a reference ΔH value at a

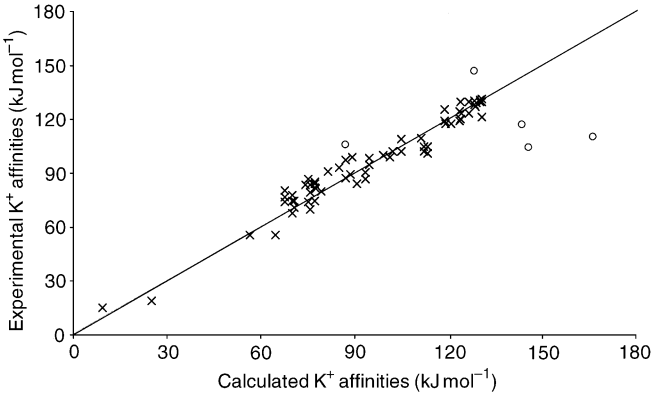

Figure 1. Plot of experimental versus EP(K^+) PCAs: the diagonal line with a slope of 1.0 is drawn for reference purposes. Large differences (> 15 kJ mol^{-1}) are depicted as ○.

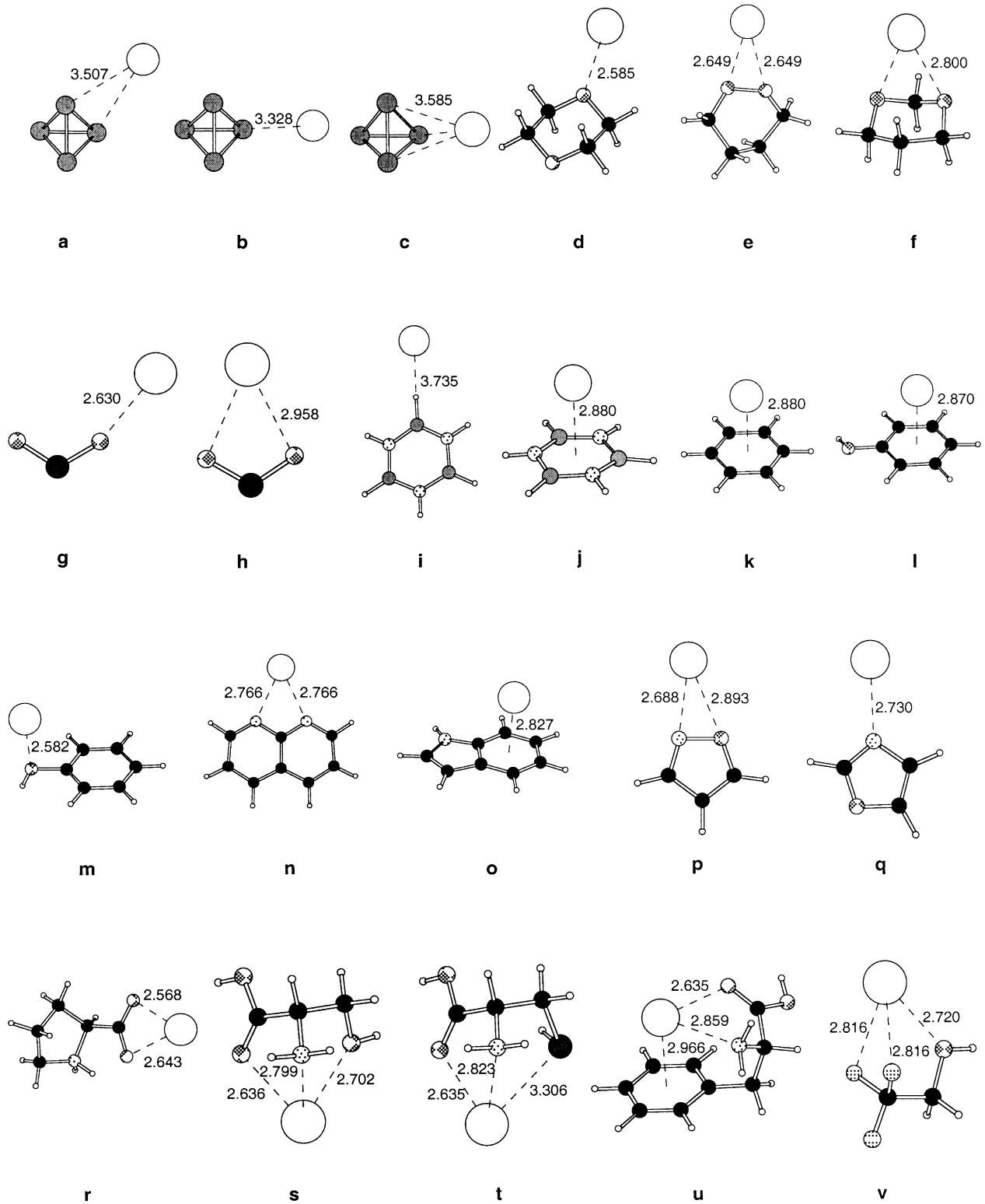

Figure 2. Geometries of selected K^+–ligand complexes, optimized at the B3-LYP/6–31G(d) level of theory. Ligand in **a**–**c** = P_4; **d** = 1,4-dioxane; **e** = 1,2-dioxane; **f** = 1,3-dioxane; **g**, **h** = SO_2; **i**, **j** = borazine; **k** = benzene; **l**, **m** = phenol; **n** = 1,8-naphthyridine; **o** = indole; **p** = isoxazole; **q** = oxazole; **r** = proline; **s** = serine; **t** = cysteine; **u** = phenylalanine; **v** = CF_3CH_2OH

known temperature. Consequently, experimental values obtained by HPMS and the kinetic method are usually not reported at any specific temperature. However, temperature effects on the ΔH or $\Delta(\Delta H)$ term are expected to be small. For the 136 ligands studied, we found general agreement (within $\pm 15\,kJ\,mol^{-1}$) between our EP(K^+) PCA values and experimental values reported in the literature. Only for a few sets of PCA values (phenylalanine, cytosine, guanine, adenine obtained by kinetic method measurements, and Me_2SO obtained by high-pressure mass spectrometric equilibrium measure-

Table 1. Theoretical EP(K^+) PCAs at 298 K and experimental PCAs [kJ mol^{-1}].

Molecule[a]	Theoretical[b]	Experimental[c]	Molecule[a]	Theoretical[b]	Experimental[c]
He	4.1		Ne	4.1	
Ar	9.4	15.4(7)[d]	CO	24.8	19.0(5.0)[d]
HF	51.3		HCl	27.6	
P_4	34.4		PH_3	42.2	
C_2H_2	37.4		C_2H_4	34.7	
H_2S	39.6		MeSH	52.7	
EtSH	57.5		*n*PrSH	59.3	
*i*PrSH	60.2		*n*BuSH	60.6	
*i*BuSH	63.2		*t*BuSH	62.0	
Me_2S	61.8		H_2O	70.4	70.7,[e] 74.9[f,g]
MeOH	75.7	79.5,[h] 83.7[h]	EtOH	81.4	
*n*PrOH	82.2		*i*PrOH	85.2	
*n*BuOH	86.2		*i*BuOH	80.5	
*s*BuOH	87.6		*t*BuOH	88.1	
1,2-propanediol	116.2		1,3-propanediol	122.5	
ethylene glycol	119.3		glycerol	133.9	
CF_3CH_2OH	71.4		CCl_3CH_2OH	76.1	
Me_2O	74.9	87.0,[e] 74.0(4.0)[i]	Et_2O	85.0	93.3[e]
$(MeOCH_2)_2$	123.5	120.0(4.0),[i] 129.7[j]	1,2-dioxane	84.1	
1,3-dioxane	82.9		1,4-dioxane	71.0	
HCHO	77.9		MeCHO	93.7	
EtCHO	95.8		*n*PrCHO	97.3	
*n*BuCHO	98.5		CF_3CHO	59.5	
CCl_3CHO	74.0		Me_2CO	104.6	102.1,[k] 108.8[l]
MeCOEt	105.9		NH_3	77.2	74.9,[e] 84.1,[n] 82(8)[m]
$MeNH_2$	79.2	79.9[e]	Me_2NH	77.5	81.6[e]
Me_3N	74.2	83.7[e]	$EtNH_2$	81.8	
*n*PrNH$_2$	81.3	91.2[e]	HCN	78.4	
MeCN	101.9	102.1(1.7)[o]	EtCN	105.5	
*n*PrCN	107.0		*i*PrCN	108.2	
*t*BuCN	110.3		$PhCH_2CN$	110.3	
CF_3CN	58.6		CCl_3CN	76.4	
HCO_2H	80.4		HCO_2Me	90.2	

[a] Abbreviations: Me = CH_3, Et = C_2H_5, *n*Pr = C_3H_8, *i*Pr = $(CH_3)_2CH$, *n*Bu = C_4H_{11}, *i*Bu = $(CH_3)_2CHCH_2$, *s*Bu = C_2H_5CH, *t*Bu = $(CH_3)_3C$, Ph = C_6H_5. [b] This work, theoretical EP(K^+) affinities at 298 K (ΔH_{298}). [c] Experimental affinities are tabulated at 298 K (ΔH_{298}) or at unspecified temperatures (see text for further discussion). Numbers in parentheses represent reported experimental uncertainties where available. [d] Threshold CID, ΔH_{298}, adjusted from ΔH_0 reported in ref. [4]. [e] HPMS, ref. [17]. [f] HPMS, ref. [15]. [g] HPMS, ref. [20]. [h] Estimated from ligand-exchange HPMS data, ref. [53]; first value anchored to experimental PCA of water reported in ref. [17], and the second to experimental PCA of water reported in refs. [15] and [20]. [i] Threshold CID, ΔH_{298}, ref. [3]. [j] HPMS, ref. [16]. [k] Threshold CID, ΔH_{298}, ref. [2]. [l] HPMS, ref. [21]. [m] Threshold CID, ΔH_{298}, ref. [47]. [n] HPMS, ref. [19]. [o] HPMS, ref. [18].

ment, as indicated by open circles in Figure 1) does the difference between EP(K^+) values and reported experimental values exceed 15 kJ mol^{-1}. These cases of discrepancy are further discussed in the individual sections below.

In addition, we also compiled the theoretical PCAs from the literature (Table 2), corrected to 298 K if required, to facilitate comparison. Different theoretical models were employed in various studies, in which different geometries, electron correlation methods, basis sets, core sizes, and zero-point energies were employed, and BSSE corrections may or may not be included.[3, 5, 6, 8, 9, 11–14, 33, 35, 37, 43–47] Even though direct comparison is difficult, it appears that the PCAs estimated by the EP(K^+) protocol tend to be slightly larger than the affinities estimated by other methods, except when the K^+ binds to the ligand by aromatic π binding (as in the case of benzene, phenol, and pyrrole). Nevertheless, the general agreement is good (within ±5 kJ mol^{-1}) except for a few species (CO, H_2S, NH_3, imidazole, glycine, and the five DNA/RNA nucleobases). Detailed discussions of the discrepancies are given in individual sections below.

Before we discuss the PCAs of individual class of ligands, we would like to comment on our choice of B3-LYP over B3-P86 density functional. To obtain the energetics at the B3-P86/6-311 + G(3df,2p)//B3-LYP/6-31G(d) level for comparison, we replaced the single-point energy calculations (step (3) of the EP(K^+) protocol) with the B3-P86 functionals, and the results are shown in the Supporting Information (Table S1). We found that the affinities obtained by EP(K^+) and B3-P86 functional are both in good agreement with existing experimental affinities, with MADs of 4.5 and 4.3 kJ mol^{-1}, respectively. The EP(K^+) affinities tend to be slightly larger in most cases, except when K^+ interacts with π-type ligands such as C_2H_2, C_2H_4, benzene, and borazine. The largest difference is found for glycerol, for which the EP(K^+) affinity is larger than the B3-P86 affinities by 6 kJ mol^{-1}. For species which show a relatively large difference in EP(K^+) and B3-P86 affinities, we carried out additional calculations at the G2(MP2,SVP) level for benchmarking. We found that the EP(K^+) affinities are marginally more comparable to this benchmark level with a MAD of 3.2 kJ mol^{-1} (as opposed to

Table 1 (cont.).

Molecule[a]	Theoretical[b]	Experimental[c]	Molecule[a]	Theoretical[b]	Experimental[c]
$MeCO_2H$	91.8		HCO_2Et	95.3	
HCO_2nPr	97.0		$MeCO_2Me$	99.5	
$MeCO_2Et$	105.7		$EtCO_2Me$	100.9	
CF_3CO_2Me	82.2		$ClCO_2Me$	80.9	
SO_2	51.9		Me_2SO	128.1	130.1,[k] 146.4(12.6)[l]
PhSOMe	132.2		$HCONH_2$	114.1	
HCONHMe	120.7	117.7[p]	$HCONMe_2$	126.2	123.4,[k] 129.7[l]
$MeCONH_2$	123.2	124.3,[k] 118.9[p]	MeCONHMe	128.4	127.2[k]
$MeCONMe_2$	130.6	121.3,[k] 129.7,[l] 131.2[p]	benzene	67.6	76.6,[g] 74.2(4.1),[q] 80.3[r]
borazine	46.8		phenol	70.0	77.9(12.6),[s] 74.6(3.8)[t]
pyridine	93.3	86.6,[e] 90.6(3.9)[u]	2-methylpyridine	94.6	98.5(3.5)[v]
3-methylpyridine	99.1	100.1(3.5)[v]	4-methylpyridine	101.1	99.0(4.0)[v]
2-fluoropyridine	100.3		3-chloropyridine	81.9	
1,8-naphthyridine	155.6		pyridazine	130.0	130.9(2.6)[u]
pyrimidine	75.7	69.7(4.3)[u]	pyrazine	69.8	67.6(3.6)[u]
1,3,5-triazine	56.5	55.6(3.0)[u]	pyrrole	77.1	85.1(3.6)[w]
indole	89.1	99.0(12.6)[s]	pyrazole	90.5	84.2(3.3)[w]
imidazole	111.1	109.6(5.6)[x]	thiazole	87.1	
isothiazole	86.1		oxazole	83.5	
isoxazole	94.4		1-methylpyrazole	94.5	94.8(3.6)[w]
3-methylpyrazole	92.8		4-methylpyrazole	96.4	
1,4-dimethylpyrazole	100.0		1,5-dimethylpyrazole	101.3	
1,3,5-trimethylpyrazole	103.4		3,4,5-trimethylpyrazole	105.4	
1,3,4,5-tetramethylpyrazole	106.2		1-methylimidazole	118.8	117.7(2.7)[w]
1,2-dimethylimidazole	120.5		2,4,5-trimethylimidazole	122.0	
2*H*-1,2,3-triazole	64.5[y]	55.6(5.5)[x]	1*H*-1,2,4-triazole	87.0[y]	87.5(4.5)[x]
2*H*-tetrazole	88.5[y]	89.6(4.6)[x]	1*H*-tetrazole	109.7[z]	
4*H*-1,2,4-triazole	140.1[z]		1*H*-1,2,3-triazole	118.6[z]	
glycine	118.4	125.5,[k] 119.3[a′]	alanine	124.0	123.6[a′]
valine	128.2	128.0[a′]	leucine	128.8	129.3[a′]
isoleucine	129.8	129.9[a′]	proline	143.0	
serine	137.5		cysteine	123.5	
phenylalanine	145.6	104.2 (20.9)[b′]	adenine	87.1[c′]	106,[d′] 97.4(3.2)[e′]
thymine	112.0[c′]	102,[d′] 104.6(3.8)[e′]	uracil	113.1[c′]	101,[d′] 105.0(2.8)[e′]
cytosine	166.3[c′]	110[d′]	guanine	143.3[c′]	117[d′]

[p] Ref. [54], kinetic-method measurements using theoretical G2(MP2,SVP)-ASC(GCP) K^+ affinity (ΔH_0) values at 0 K of formamide (109.2 kJ mol^{-1})/*N*,*N*′-dimethylformamide (123.9 kJ mol^{-1})/*N*-methylacetamide (125.6 kJ mol^{-1}) as reference values, as reported in ref. [33] and corrected to ΔH_{298}. [q] Threshold CID, ΔH_{298}, ref. [8]. [r] HPMS, ref. [22]. [s] Radiative associative kinetics measurement, ref. [14], reported value reduced by 6.2 kJ mol^{-1}, as described in text, and with thermal correction to 298 K. [t] Threshold CID, ΔH_{298}, ref. [13]. [u] Threshold CID, ΔH_{298}, ref. [6]. [v] Threshold CID, ΔH_{298}, ref. [11]. [w] Threshold CID, ΔH_{298}, ref. [12]. [x] Threshold CID, ΔH_{298}, ref. [5]. [y] EP(K^+) PCA of the most stable tautomer of the free ligands 1*H*-1,2,4-triazole, 2*H*-1,2,3-triazole, and 2*H*-tetrazole kinetically (but not energetically) favored to bind to K^+ in the gas phase, resulting in the formation of K^+–(1*H*-1,2,4-triazole), K^+–(2*H*-1,2,3-triazole), and K^+–(2*H*-tetrazole) complexes proposed as likely to be observed in threshold-CID experiments, as explained in ref. [5]. [z] EP(K^+) PCA of the less stable tautomer of the free ligands 4*H*-1,2,4-triazole, 1*H*-1,2,3-triazole, and 1*H*-tetrazole, energetically (but not kinetically) favored to bind to K^+ in the gas phase, leading to formation of the most stable K^+–(4*H*-1,2,4-triazole), K^+–(1*H*-1,2,3-triazole), and K^+-(1*H*-tetrazole) complexes with the largest PCA, but not likely observed in threshold-CID experiments, as explained in ref. [5]. [a′] Ref. [70], kinetic-method measurements using theoretical G2(MP2,SVP)-ASC(GCP) (see also footnote [p]) K^+ affinity values at 0 K (ΔH_0) of acetamide (118.7 kJ mol^{-1})/*N*-methylacetamide (125.6 kJ mol^{-1})/*N*,*N*′-dimethylacetamide (129.2 kJ mol^{-1}) as reference values, as reported in ref. [33]; the experimentally determined values were corrected to ΔH_{298}. [b′] Kinetic method, ref. [31]. [c′] The PCA is estimated for the most stable tautomer of the free ligands, corresponding to species A1, T1, U1, C1, and G1 in ref. [37]. [d′] Kinetic method, ref. [29]. [e′] Threshold CID, ΔH_{298}, ref. [9].

4.1 kJ mol^{-1} for B3-P86 values). As the performance of both functionals does not differ significantly, the B3-LYP functional was chosen for obtaining PCAs as it is more widely used, and this will possibly allow more direct comparison with other theoretical studies.

For a representative subset of 14 ligands shown in the Supporting Information (Table S2), we further explored the effects of employing B3-LYP geometries and vibrational frequencies on zero-point vibrational energy and thermal correction to 298 K, and the magnitude of the BSSE. Using the B3-LYP frequencies to correct for zero-point energies tends to decrease the theoretical PCA by about 0.5 kJ mol^{-1}, as compared to using the HF frequencies. The thermal correction at 298 K with B3-LYP parameters leads to a further decrease of about 0.3 kJ mol^{-1}. We found that the estimated BSSE obtained by the density functional-based protocol is small (average of 0.7 kJ mol^{-1}), but can be as large as 1.8 kJ mol^{-1} when the cation binds to the ligand by aromatic π interactions. For this subset of ligands, seven experimental PCAs (CO, H_2O, NH_3, benzene, pyridine, pyrrole, and uracil) are available for comparison. For these seven species, inclusion of the above refinement in fact leads to a slight increase in MAD (6.4 kJ mol^{-1}, as opposed to 6.0 kJ mol^{-1} with our EP(K^+) protocol). Therefore, the corrections may not lead to better agreement with experimental data. Given that the magnitude of these corrections (ca. 1–2 kJ mol^{-1}) has

Table 2. Theoretical PCAs (kJ mol^{-1})

Molecule[a]	Theoretical[b]	Literature[c]	Molecule[a]	Theoretical[b]	Literature[c]
CO	24.8	37.1[d]	PH_3	42.2	41.4[e]
H_2S	39.6	31.6[e]	H_2O	70.4	74.7[e], 70.7[f], 68.4[g]
MeOH	75.7	74.9[g]	EtOH	81.4	81.4[g]
*n*PrOH	82.2	81.2[g]	*i*PrOH	85.2	85.2[g]
*n*BuOH	86.2	85.8[g]	*i*BuOH	80.5	83.6[g]
*s*BuOH	87.6	87.4[g]	*t*BuOH	88.1	88.7[g]
1,2-propanediol	116.2	117.9[h]	1,3-propanediol	122.5	122.2[h]
ethylene glycol	119.3	118.2[h]	glycerol	133.9	134.3[h]
Me_2O	74.9	79.0[i]	NH_3	77.2	79.5[e], 77.6[f] 75.1,[g] 75.1,[j] 77.1,[j] 76.1,[j] 64.1,[j] 66.1[j]
$HCONH_2$	114.1	111.2[g]	HCONHMe	120.7	118.9[g]
$HCONMe_2$	126.2	124.5[g]	$MeCONH_2$	123.2	120.2[g]
MeCONHMe	128.4	126.9[g]	$MeCONMe_2$	130.6	129.5[g]
benzene	67.6	72.0[k]	phenol	70.0	74.1[l]
pyridine	93.3	91.3[m], 91.4[n]	2-methylpyridine	94.6	94.5[m]
3-methylpyridine	99.1	97.0[m]	4-methylpyridine	101.1	97.9[m]
pyridazine	130.0	130.5[n]	pyrimidine	75.7	73.2[n]
pyrazine	69.8	68.7[n]	1,3,5-triazine	56.5	53.5[n]
pyrrole	77.1	82.1[o]	indole	89.1	87.2[p]
pyrazole	90.5	86.7[o]	imidazole	111.1	109.3[o], 116.8[q]
1-methylpyrazole	94.5	91.3[o]	1-methylimidazole	118.8	117.2[o]
2*H*-1,2,3-triazole	64.5	65.5[q]	1*H*-1,2,4-triazole	87.0	91.7[q]
2*H*-tetrazole	88.5	90.7[q]	glycine	118.4	110.9[r]
phenylalanine	145.6	146.4[s]	adenine	87.1[t]	78.7[f], 85.2[u]
thymine	112.0[t]	107.1[f], 104.0[u]	uracil	113.1[t]	108.4[f], 104.5[u]
cytosine	166.3[t]	159.0[f]	guanine	143.3[t]	139.7[f]

[a] Abbreviations: Me = CH_3, Et = -C_2H_5, *n*Pr = C_3H_8, *i*Pr = $(CH_3)_2CH$, *n*Bu = C_4H_{11}, *i*Bu = $(CH_3)_2CHCH_2$, *s*Bu = $C_2H_5CH_3CH$, *t*Bu = $(CH_3)_3C$, Ph = -C_6H_5. [b] This work, theoretical EP(K^+) affinities at 298 K (ΔH_{298}). [c] Previously reported PCA at 298 K from literature. For cases where only values at 0 K are reported, thermal corrections to 298 K using HF/6–31G(d) geometries and frequencies were applied. [d] Ref. [43]. [e] Ref. [44]. [f] Ref. [37]. [g] Ref. [33]. [h] Ref. [46]. [i] Ref. [3]. [j] Ref. [47]. [k] Ref. [8]. [l] Ref. [13]. [m] Ref. [11]. [n] Ref. [6]. [o] Ref. [12]. [p] Ref. [14]. [q] Ref. [5]. [r] Ref. [35]. [s] Ref. [45]. [t] The PCA is estimated for the most stable tautomer of the free ligands, corresponding to species A1, T1, U1, C1, and G1 in ref. [37]. [u] Ref. [9].

minimal effect on calculated PCAs, it appears that they could be omitted for computational efficiency.

Noble gas atoms: The strength of K^+ binding to the noble gas atoms is at the lowest end of the PCA scale. While the experimental K^+ affinities for He and Ne are not known, the Ar affinity[4] was determined to be 14(7) kJ mol^{-1} at 0 K (experimental uncertainty in parenthesis). Our calculated K^+ affinity for Ar (8 kJ mol^{-1} at 0 K) is within the error limit of this experimental value.

As the potassium cation is isoelectronic with the argon atom, it is of interest to compare the PCAs of the noble gas atoms with the bond dissociation energy of the corresponding isoelectronic HeAr, NeAr, and Ar_2. The bond dissociation energies for the species are very small (<1 kJ mol^{-1}), as the rare gas atoms are held together by weak dispersion forces.[48] In comparison, the interactions between K^+ and noble gas atoms are much stronger, ranging from 4 to 9 kJ mol^{-1}, and reflect the strength of the inductive forces when a cation interacts with the polarizable noble gas atoms.

Carbon monoxide: In agreement with previous findings on Li^+,[43, 49] Na^+[24, 43] and K^+,[43] the potassium cation prefers to bind to the carbon atom of CO (estimated $K^+\cdots C$ distance of 3.04 Å) with formation of a linear cation–ligand complex. The preferential binding of K^+ to the carbon atom can be explained by the fact that even though oxygen is more electronegative than carbon, the negative end of the CO dipole in fact resides on the carbon atom.[50] Thus, our result highlights the importance of ion–dipole interaction in this complex.

The EP(K^+) PCA is approximately 12 kJ mol^{-1} smaller than that reported previously by Ikuta,[43] and the discrepancy arises presumably from the small basis sets employed in the previous study. We note in passing that although the experimental PCA of CO at 298 K (19(5) kJ mol^{-1})[4] is closer to our theoretical estimate for the $K^+\cdots OC$ (18 kJ mol^{-1}) than for the $K^+\cdots CO$ (25 kJ mol^{-1}) binding mode, both theoretical values are within the error bar of the experimental measurement.

Hydrogen fluoride and hydrogen chloride: K^+ prefers to bind to the halogen atoms in hydrogen halides. While K^+–HF is linear, the K^+–HCl complex is bent ($K^+\cdots$Cl-H angle of 119°). Sodiated hydrogen chloride (Na^+–HCl) has a similar shape to the K^+–HCl complex, with an estimated $Na^+\cdots$Cl-H angle of 114°.[27] Hence, for both Na^+ and K^+, the cation does not bind along the dipole moment vector of HCl; this reflects

a certain degree of covalency when the alkali metal cation binds to second-row elements.[27]

Phosphorus and phosphine: A theoretical study on Li^+-P_4 suggested that Li^+ binds to P_4 in a monodentate fashion, along a threefold axis of the tetrahedron (species **2** in ref. [51]). We found that the larger K^+ prefers to bind in a bidentate manner on an edge of the P_4 tetrahedron, with a $K^+\cdots P$ distance of 3.51 Å (C_{2v}, species **a**, Figure 2) and a PCA of 34 kJ mol^{-1}. The monodentate complex (C_{3v}, species **b**, Figure 2) and the tridentate face-bound K^+-P_4 complex (C_{3v}, species **c**, Figure 2) are approximately 4 kJ mol^{-1} less stable.

The PCA of phosphine (PH_3) is slightly higher than that of P_4. The cation binds to phosphine along the C_{3v} axis of the ligand, with a $K^+\cdots P$ distance of 3.37 Å. Our estimate of K^+-PH_3 affinity at 0 K (41 kJ mol^{-1}) is in excellent agreement with a previous theoretical value of 40 kJ mol^{-1}.[44]

Ethene and ethyne: Hoyau et al.[24] showed that Na^+ binds to the π bonds of C_2H_2 and C_2H_4 at an average distance of 2.65 Å above the plane of the ligand. For K^+, we found that the cation–π binding distance is longer (3.13 Å). The increased distance leads to a decrease in cation affinities by approximately 16 kJ mol^{-1}.

Hydrogen sulfide and thiols: For these sulfur-containing ligands, the cation binds to the sulfur atom at a distance of approximately 3.20 Å. The cation has a tendency to bind to one of the lone pairs of the sulfur atom and is hence rather poorly aligned (ca. 40°) with the molecular dipole moment of the ligand.

The estimated PCAs for ligands of this class studied here range from approximately 40 to 60 kJ mol^{-1}. Our theoretical K^+ affinity of H_2S at 0 K (38 kJ mol^{-1}) is 8 kJ mol^{-1} larger than the value previously reported by Magnusson.[44] This discrepancy may be attributed to two factors: no zero-point energy correction was made and the affinity was calculated with rather small basis sets in that paper. However, no experimental PCAs for this class of compounds are available for comparison.

Water and alcohols: For this class of ligands, K^+ binds to the oxygen atom at a distance of approximately 2.58 Å. For K^+-H_2O, the cation binds along the twofold axis of the ligand, in perfect alignment with its dipole moment. This is in contrast with the preferred mode of K^+ binding in H_2S discussed above, and again reflects the presence and influence of covalency when the cation binds to second-row atoms.

Two sets of experimental PCA for H_2O were determined by Kebarle et al. using the HPMS technique. Our present estimate of 70 kJ mol^{-1} is within ±5 kJ mol^{-1} of both experimental values: 70.7 kJ mol^{-1}[17] and 74.9 kJ mol^{-1}.[15, 20] Three theoretical PCAs for H_2O are available for comparison.[33, 37, 44] The EP(K^+) PCA is in good agreement with all three values, and it is virtually identical to that obtained by Russo et al.[37] at the B3-LYP/6-311+G(2df,2p)//B3-LYP/6-311+G(2df,2p) level with BSSE correction.

For simple alcohols, the cation is in reasonable alignment (ca. 17°) with the dipole moment of the ligands. Previous studies[34, 52] found that when *n*BuOH binds to Li^+, the alkyl chain wraps around so that the terminal carbon atom of the ligand undergoes a secondary interaction with the cation. In the case of K^+, this additional favorable interaction apparently cannot compensate for the unfavorable ligand deformation, so that this cyclic form is slightly less stable than the extended open form (by 5 kJ mol^{-1}).[33]

Direct experimental determination of the absolute PCA of simple alcohols has not been reported. However, the relative enthalpy change when water is exchanged by methanol was determined to be 8.8 kJ mol^{-1},[53] which is in reasonable agreement with the corresponding relative affinity values estimated by various theoretical protocols (i.e., EP(K^+) in Table 1; B3-P86 and G2(MP2,SVP) in the Supporting Information, Table S1) to be in the range of 4.3–6.4 kJ mol^{-1}. We note that using the two experimental PCAs of water and the experimental relative enthalpy change of 8.8 kJ mol^{-1},[53] the absolute PCA for methanol can be estimated to be 79.5[17] or 83.7 kJ mol^{-1}.[15, 20] All theoretical protocols employed here [EP(K^+), B3-P86, G2(MP2,SVP)] yield PCA values that are more consistent with the lower estimate.

Compared with simple aliphatic alcohols, K^+ interactions with polyhydroxyl ligands have been less widely studied. Our results suggested that K^+ bind in a bidentate manner to ethylene glycol (1,2-ethanediol), 1,2-propanediol, and 1,3-propanediol, and in a tridentate fashion with glycerol (1,2,3-propanetriol). Compared with the monodentate binding in simple alcohols, bidentate K^+ interactions with the diols increase the PCA by about 30 kJ mol^{-1}. However, the transition from bidentate (in diols) to tridentate (in glycerol) binding leads to a further enhancement of the PCA by only about 15 kJ mol^{-1}. This suggests that the destabilizing effect of ligand deformation plays an important role in determining the PCA of multidentate complexes.[3, 7, 46]

Ethers and dioxanes: For this class of ligands, K^+ binds to the oxygen atom with a typical $K^+\cdots O$ distance of 2.65 Å, slightly longer than that found in K^+ complexes of aliphatic alcohols, and hence the PCA is smaller than that of the corresponding alcohol analogue.

Dioxanes ($C_4O_2H_8$), which are well-known carcinogens, can be considered as cyclic ethers. For 1,4-dioxane, the cation binds in a monodentate fashion to one of the oxygen atoms in the ligand (C_s, species **d**, Figure 2). In K^+–1,2-dioxane (C_1, species **e**, Figure 2) and K^+–1,3-dioxane (C_s, species **f**, Figure 2), the cation is coordinated in a bidentate manner to the two closely situated oxygen atoms. As a result, the PCA of 1,4-dioxane is lower than those of 1,2- and 1,3-dioxane.

Experimental affinities are available for some ethers. The PCAs at 298 K of Me_2O and $(MeOCH_2)_2$ were determined by Armentrout et al. using the threshold CID method to be 74(4) and 120(4) kJ mol^{-1}, respectively.[3] Both values are in good agreement (within ±4 kJ mol^{-1}) with our theoretical estimates. In contrast, an earlier reported PCA of Me_2O[17] determined by HPMS (87 kJ mol^{-1}) differs more widely from our theoretical estimate of 74.9 kJ mol^{-1}.

Aldehydes and ketones: For this class of ligand, K^+ binds to the carbonyl oxygen atom. Compared to the alcohols and

ethers, the $K^+ \cdots O$ distance is shorter (2.56 Å), with a typical $K^+ \cdots O{=}C$ angle of 165°. Two experimental PCAs of Me_2CO were reported,[2, 21] and both are within ± 4.5 kJ mol^{-1} of our calculated value (105 kJ mol^{-1}).

Ammonia and amines: K^+ binds to the electronegative nitrogen atom in these ligands, with a typical $K^+ \cdots N$ distance of 2.78 Å. A few theoretical PCAs are available for comparison for NH_3.[33, 37, 44, 47] The EP(K^+) PCA is in good agreement with all the reported values based on calculations with all-electron basis sets. In comparison, the two values reported in ref. [47] using pseudopotential are too low by over 10 kJ mol^{-1}. Our EP(K^+) PCA is virtually identical to that obtained at the B3-LYP/6-311 + G(2d,2p)//B3-LYP/6-311 + G(2d,2p)[37] and B3-LYP/6-311 + G(2d,2p)//B3-LYP/6-31G(d) levels,[47] and this indicates that if sufficiently large basis sets are used, the effects of geometry and zero-point corrections on K^+ binding affinities would be minimal. Interestingly, for K^+-$(NH_3)_n$ complexes ($n = 1-5$), the BSSE at the B3-LYP level is small (within ± 1 kJ mol^{-1}) when compared to the BSSE obtained by MP2 calculations (3–4 kJ mol^{-1}) using the same basis set.[47] The rather small BSSE corrections found for these systems at the B3-LYP level are in agreement with our general findings presented in the Supporting Information (Table S2).

Experimental affinities are available for ammonia and four alkylamines.[17, 19, 47] While the experimental PCAs are in good general agreement with our theoretical estimates (within ± 10 kJ mol^{-1}), qualitative differences are found in the order of relative affinities upon successive methyl substitution of ammonia (see section "Effect of substituents" below for further discussion).

Hydrogen cyanide and alkyl nitriles: For HCN and the six alkyl nitriles studied here (including $PhCH_2CN$), K^+ prefers to bind to the nitrogen atom of the ligand. The average $K^+ \cdots N$ distance is 2.68 Å, slightly shorter than that found in potassiated amine complexes. This reflects the fact that the interaction of K^+ with the sp-hybridized nitrogen atom in nitriles is stronger than that with the sp^3-hybridized nitrogen atom in amines. The experimental PCA of MeCN[18] of 102 kJ mol^{-1} at 298 K is in excellent agreement with our calculated value.

Carboxylic acids and esters: Two potential K^+ binding sites are available for this class of ligands (two carboxylic acids and eight esters): the carbonyl and hydroxyl/alkoxyl oxygen atoms. We found that the K^+ prefers to bind to the carbonyl oxygen atom (average $K^+ \cdots O$ distance of 2.51 Å, average $K^+ \cdots O{=}C$ angle of 165°), with a "*trans*" conformation of the $K^+ \cdots O{=}C{-}O$ moiety. In this class of ligand, K^+ is in fairly good alignment with the molecular dipole moment of the ligand (angle of deviation ca. 10°). In general, the PCA of a carboxylic acid is larger than that of the corresponding alcohol; for example, the PCA of acetic acid is 5 kJ mol^{-1} higher than that of methanol. As we are not aware of any experimental and theoretical values in the literature, the PCAs reported here are the first set of estimates available for this class of ligands.

Sulfoxides: For the three sulfoxides studied here, including PhSOMe, K^+ binds exclusively to the oxygen atom, with an average $K^+ \cdots O$ distance of 2.50 Å. It is interesting to compare the structure of the $K^+ - SO_2$ complex with that of the $Na^+ - SO_2$ complex reported previously.[24] Ohanessian et al. found that Na^+ binds to the SO_2 group in a bidentate fashion (with C_{2v} symmetry). We found that the larger K^+ prefers to bind in a monodentate fashion to one of the oxygen atoms (C_s, species **g**, Figure 2), and this mode of binding is about 4 kJ mol^{-1} more stable than the bidentate C_{2v} mode (species **h**, Figure 2). Two experimental values for the PCA of Me_2SO [146 (HPMS)[21] and 130 kJ mol^{-1} (threshold CID][2] were reported by Kebarle et al. However, it was pointed out that the HPMS value was based on the slope of a van′t Hoff plot covering only a narrow temperature range, and hence was subject to a greater experimental error. Thus, the threshold-CID value is considered to be more reliable.[2] Our calculated PCA (128 kJ mol^{-1} at 298 K) is in very good agreement with the threshold-CID value of 130 kJ mol^{-1}, and provides further support for this more recently determined value.

Amides: Amides are perceived as an entry point for understanding the peptide linkage in protein structures, and hence K^+ – amide interactions are of special biological interest. For the amide complexes studied here, K^+ binds in a monodentate fashion to the oxygen atom ($K^+ \cdots O$ distance of 2.45 Å, $K^+ \cdots O{=}C$ angle of 166°), in good alignment with the molecular dipole moment.[2] Kebarle et al. determined PCAs for four of the six amides studied here by HPMS[21] and threshold CID[2]). The reported 298 K PCA of *N*,*N*′-dimethylacetamide ($MeCONMe_2$) deserves special attention. For this species, the PCA determined by threshold CID[2] (121 kJ mol^{-1}) is noticeably lower than that determined by HPMS (130 kJ mol^{-1}).[21] More importantly, the affinity determined by threshold CID is even lower than those of *N*,*N*′-dimethylformamide ($HCONMe_2$, 123 kJ mol^{-1}) and acetamide ($MeCONH_2$, 124 kJ mol^{-1}).[2] This is quite surprising, as the more polarizable $MeCONMe_2$ is expected to have the highest K^+ affinity of these three amides. To resolve this discrepancy, we recently re-measured the PCA of $MeCONMe_2$ using the kinetic method. By anchoring to the ab initio G2(MP2,SVP)-ASC(GCP) theoretical value of $HCONMe_2$ corresponding to 125 kJ mol^{-1} at 298 K[33] (which is consistent with the threshold-CID value[2] of 123 kJ mol^{-1}), we obtained a PCA of $MeCONMe_2$ of 131 kJ mol^{-1}.[54] This indicates that, in contrast to $K^+ - Me_2SO$ (see above), the $K^+ - MeCONMe_2$ affinity determined by the HPMS method[21] is more consistent with available theoretical and experimental values. if the threshold-CID value for $MeCONMe_2$ is excluded, our protocol yields affinities to within ± 3 kJ mol^{-1} for all the six amides studied here.

Benzene, borazine, and phenol: The interaction between cations and aromatic π electrons is a relatively newly discovered type of electrostatic interaction. Such cation – π interaction are implicated in many important biological functions,[55, 56] and benzene is often used as the prototype ligand for understanding them. The most recent experimental dissociation energy of K^+ – benzene (73 kJ mol^{-1} at 0 K),

determined by Amicangelo and Armentrout,[8] is in good agreement with our estimated value of 67 kJ mol^{-1} at 0 K. We note that our 298 K PCA reported in Table 1 (67.6 kJ mol^{-1}) is obtained from the EP(K^+) PCA value at 0 K (67.1 kJ mol^{-1}), with thermal corrections using the HF/6-31G(d) geometry and vibrational frequencies. The experimental PCA (74.2 kJ mol^{-1}, Table 1) is taken directly from ref. [8], with thermal correction at the MP2(full)/6-31G(d) level. The apparent inconsistency (0.7 kJ mol^{-1}) between the two sets of PCA values at 0 K and 298 K probably arises from the level of theory employed for the thermochemical correction.

Even though borazine ($B_3N_3H_6$) is isoelectronic with benzene, its electronic nature has been controversial. Criteria based on magnetic properties and energetic and geometric indices suggested that borazine may not be aromatic.[57] However, recent findings showed that borazine should be aromatic, although its aromaticity is about half of that of benzene.[58] The most stable structure we obtained for borazine has D_{3h} symmetry and is in agreement with previous experimental and theoretical studies.[59] We located two stable minima on the K^+–borazine potential energy surface. The less stable complex is planar and has C_{2v} symmetry (species **i**, Figure 2). The more stable complex has C_{3v} symmetry (species **j**, Figure 2), with the cation 2.88 Å above the ring centroid and $K^+ \cdots N$ and $K^+ \cdots B$ distances of 3.22 and 3.33 Å, respectively.

While the structural features of the most stable K^+–borazine complex (species **j**, Figure 2) are quite comparable to those obtained for K^+–benzene (C_{6v}, species **k**, Figure 2), the estimated PCA of borazine is 21 kJ mol^{-1} lower than that of benzene (68 kJ mol^{-1}). As the quadrupole moment of a ligand is expected to play a key role in determining the strength of the cation–π interaction,[60] we calculated the quadrupole moment of these two ligands. Not only are the calculated values (−3.62 and −7.88 Buckingham for borazine and benzene, respectively) in excellent agreement with experiment (−4.18 and −7.99 Buckingham, respectively),[61] but the increase in quadrupole moment of the ligand also correlates with the increase in PCA from borazine to benzene. Thus, the important contribution of ion–quadrupole interactions in this class of aromatic ligands appears to be confirmed.

Phenol is a prototypical case for competition between π and non-π hydroxyl oxygen binding sites for K^+. For the Na^+–phenol complexes,[24, 62] the binding affinities at 298 K for the aromatic π and non-π complexes are comparable, and differ by about 1–4 kJ mol^{-1}, depending on the computational protocol used to obtain the Na^+ affinities. However, the free energy of binding ΔG_{298} indicates that the non-π complex is the favored form of Na^+–phenol in the gas phase.[24]

For K^+–phenol, two stable minima were again found. In the more stable form (in terms of ΔH_{298}), K^+ is bound to the aromatic π ring (species **l**, Figure 2), while the less stable (by 3 kJ mol^{-1}) non-π mode has a $K^+ \cdots O$ interaction of 2.58 Å (species **m**, Figure 2). Similar to the Na^+–phenol system, the difference in EP(K^+) free energy of binding (ΔG_{298}) suggests that the non-π complex is favored over the π mode (by about 4 kJ mol^{-1}) in K^+–phenol.

We obtained an EP(K^+) PCA for phenol of 70 kJ mol^{-1}. Two experimental values are available for comparison: a recent threshold-CID value of 75 kJ mol^{-1},[13] and an earlier value of 84 kJ mol^{-1} based on results of radiative association kinetics measurements and density functional calculations.[14] We note that the latter value is anchored to the K^+–benzene affinity (at 298 K) of 80 kJ mol^{-1}.[22] However, recent experiments[8] suggested that the PCA at 298 K for benzene might need to be lowered to 74 kJ mol^{-1}. Adopting this lower PCA value of benzene as the anchoring point leads to a revised PCA value of 78 kJ mol^{-1} (corrected to 298 K). With this downward revision of the PCA of K^+–phenol from ref. [14], the two experimental values and our theoretical EP(K^+) affinity are now much more consistent.

Azines: Pyridine (C_5NH_5), pyridazine, pyrimidine, pyrazine (isomers of $C_4N_2H_4$), and 1,3,5-triazine ($C_3N_3H_3$) are six-membered nitrogen heterocycles. The presence of nitrogen atom(s) disturbs the symmetry of the π-electron distribution: charge is localized on the nitrogen atoms, and the resonance stabilization and aromatic character of the molecule are thus decreased.[6] Hence, for this class of ligands, K^+ prefers to bind to the nitrogen lone pair, with an average $K^+ \cdots N$ distance of 2.75 Å, rather than to the π cloud. Our present relative and absolute PCAs are in very good agreement with a combined experimental and theoretical study:[6] the MADs with respect to the reported experimental and BSSE-corrected MP2(full)/6-311+G(2d,2p)//MP2(full)/6-31G(d) values are 2.5 (Table 1) and 1.8 kJ mol^{-1} (Table 2), respectively.

The modes of cation binding in 1,8-naphthyridine ($C_8N_2H_6$) and its PCA have not been reported previously. Our model (C_{2v}, species **n**, Figure 2) suggests that K^+ binds in a bidentate fashion to the two nitrogen atoms of the ligand. Because of the combined effect of polarizability and multidentate interaction, the PCA of 1,8-naphthyridine (156 kJ mol^{-1}) is much higher than those of the other pyridines, and it is at the top end of the PCA scale presented here.

Pyrrole and indole: Pyrrole (C_4NH_5) and indole (C_8NH_7) are important models for understanding the cation–π interactions in tryptophan-containing proteins. Unlike pyridine, the nitrogen atom in pyrrole is electron-deficient,[63] so the pyrrole nitrogen atom is not a favorable site for cation binding. As in the case of Na^+–pyrrole, the potassium cation prefers to bind to the π ring ($K^+ \cdots \pi$ distance of ca. 2.85 Å) of the ligand.

The experimental PCA for pyrrole was recently determined to be 85 kJ mol^{-1},[12] in good agreement with our theoretical PCA (77 kJ mol^{-1}). This is approximately 10 kJ mol^{-1} larger than the theoretical estimate for benzene, and can be attributed to the larger quadrupole and dipole moments of pyrrole.[61]

In the Na^+–indole complex, the cation can bind to either the benzo-π or pyrrolo-π face of the ligand.[64] For the larger potassium cation, only one type of K^+–indole complex is found, in which the cation binds to the benzo-π face, with an estimated PCA of 89 kJ mol^{-1} (species **o**, Figure 2). Thus, even though the PCA of pyrrole is larger than that of benzene, it appears that K^+ binds exclusively to the benzo-π face of indole. This suggests that the distribution of π electrons is sufficiently altered in the polycyclic aromatic ligands that indole should not be regarded as fused benzene and pyrrole rings.[14, 55]

The experimental PCA of indole at 0 K was reported to be 105 kJ mol^{-1} in the study on K^+–phenol by Ryzhov and Dunbar.[14] In view of our discussions in the above section "Benzene, borazine, and phenol", this experimental PCA of indole may need to be lowered (by 6 kJ mol^{-1}) because of the anchoring value of benzene. The revised value is 99 kJ mol^{-1} (at 298 K), which brings it into closer agreement with our estimated PCA at 298 K for indole of 89 kJ mol^{-1}.

Azole: Azoles are building blocks for many antibiotics, anticancer agents, and other drugs.[65] Even though these five-membered heterocycles may be perceived as derivatives of pyrrole, the mode of potassium cation binding is different from that found in pyrrole. For the azoles studied here (except isoxazole), K^+ binds exclusively to the nitrogen lone pair, with an average $K^+ \cdots N$ distance of 2.71 Å, comparable to that found for azines. No cation–π complexes were located, that is, all azoles favor σ binding interaction (except pyrrole).[5, 12] Two theoretical PCAs for imidazole ($C_3N_2H_4$) were reported previously.[5, 12] Our value is in good agreement with the more recent value, calculated at the MP2(full)/6-311 + G(2d,2p)// MP2(full)/6-31G(d) level with BSSE correction.[12] The earlier value,[5] calculated at the HF/6-31G(d,p) level, is about 6 kJ mol^{-1} too large when compared to the EP(K^+) PCA.

In general, the PCA of azoles increases with increasing number of methyl substituent,[12] and with increasing number of ring nitrogen atoms, except for tetrazole.[5] We also estimated the PCAs of oxygen- and sulfur-containing azoles (isomers of C_3ONH_3: oxazole, isoxazole; isomers of C_3SNH_3: thiazole and isothiazole), which have not been reported previously. Isoxazole has a higher PCA (by about 10 kJ mol^{-1}) than oxazole, as K^+ is bound in a bidentate fashion to both N and O atoms in isoxazole (species **p**, Figure 2), but solely to the N atom in oxazole (species **q**, Figure 2). On the other hand, thiazole and isothiazole have similar PCAs, as K^+ binds exclusively to the N atom in both ligands.

Our EP(K^+) PCA values at 0 K for 2*H*-1,2,3-triazole, 1*H*-1,2,4-triazole, and 2*H*-tetrazole are in good agreement (within ±9 kJ mol^{-1}) with the previously reported experimental threshold-CID PCA values (MAD of 4 kJ mol^{-1}). However, our theoretical PCAs for the corresponding 1*H*-1,2,3-triazole, 4*H*-1,2,4-triazole, and 1*H*-tetrazole tautomers are significantly higher by 20–63 kJ mol^{-1}.[5] Our findings here are consistent with the rationalization put forward by Rodgers and Armentrout: in their threshold-CID experiments, binding of K^+ to the most stable tautomers of 2*H*-1,2,3-triazole, 1*H*-1,2,4-triazole, and 2*H*-tetrazole is kinetically favored, even though the resulting K^+ complexes are not the thermodynamically most stable K^+-bound species (see footnotes [y] and [z] to Table 1).[5]

Amino acids: Because of the presence of the acidic carboxyl group and basic amino group, amino acids can exist in two forms: charge-solvated (CS) and zwitterionic (ZW).[35, 66, 67, 68] The ZW form of amino acids is dominant in solution[69] and can be stabilized in the gas phase by binding to cations.[67] Similar to the case of glycine and alanine reported earlier,[68] our calculations show that for other aliphatic amino acids such as valine, leucine, and isoleucine, the potassium cation prefers to bind in a bidentate fashion to the carbonyl and hydroxyl oxygen atoms of the CS form.

Comparing our EP(K^+) PCA of glycine with that estimated by Hoyau and Ohanessian[35] shows their value to be too small by almost 8 kJ mol^{-1}; the difference most likely is due to the different basis sets employed. We are not aware of theoretical and experimental PCAs for the larger aliphatic amino acids in the literature. Using our theoretical G2(MP2,SVP)-ASC-(G-CP) PCAs at 0 K of acetamide (118.7 kJ mol^{-1}), *N*-methylacetamide (125.6 kJ mol^{-1}), and *N*,*N*′-dimethylacetamide (129.2 kJ mol^{-1}) as anchoring reference values,[33] we obtained the experimental PCA of aliphatic amino acids by the kinetic method, as shown in Table 1 (see also footnote [a′] to Table 1). The relative and absolute EP(K^+) PCAs of all five aliphatic amino acids were found to be in very good agreement with the quantitative values determined by the mass spectrometric kinetic method in the order:[70] glycine < alanine < valine ≈ leucine ≈ isoleucine; the absolute PCAs are also within ±1 kJ mol^{-1} of those determined experimentally.[70] We note that the anchoring value of 129.2 kJ mol^{-1} we used for *N*,*N*′-dimethylacetamide is very close to the experimental HPMS value of 129.5 kJ mol^{-1} reported by Kebarle et al.[21] Thus, the experimental set of PCAs for aliphatic amino acids is not only consistent with our EP(K^+) estimates, but it is also consistent with the reported experimental affinity of *N*,*N*′-dimethylacetamide.

We also obtained the PCAs of proline, serine, cysteine, and phenylalanine (species **r**, **s**, **t**, **u**, respectively, in Figure 2). The modes of K^+ binding for these ligands are similar to those of the corresponding Na^+ complexes.[24, 38] No experimental or theoretical PCAs are available in the literature, except for K^+–phenylalanine. The theoretical PCA reported by Ryzhov et al. (Table 2, 146.4 kJ mol^{-1}) is very close to our EP(K^+) PCA of 145.6 kJ mol^{-1}.[31, 45] Using the experimental PCAs of adenine (106 kJ mol^{-1}), cytosine (110 kJ mol^{-1}), and guanine (117 kJ mol^{-1}) as reference values (Table 1),[29] Ryzhov et al. reported a value of 104.2 kJ mol^{-1} (kinetic method) for the PCA of phenylalanine,[31] which is even lower than the threshold-CID value of K^+–glycine (126 kJ mol^{-1} at 298 K) reported by Kebarle et al.[2] This is counterintuitive, because phenylalanine is expected to have a higher PCA than glycine due to its greater polarizability and ion-induced dipole interactions. Hence, it is likely that the kinetic-method value for phenylalanine involves a relatively large margin of experimental uncertainty (>20.9 kJ mol^{-1}/5 kcal mol^{-1}), as estimated by Ryzhov et al. (see section "Nucleobases" below for further discussions on the reference values). We have conducted detailed theoretical and experimental studies on the K^+–phenylalanine system, and our findings will be reported elsewhere.

Nucleobases: Given the biological importance of these ligands as models for cation–RNA/DNA interactions, several experimental[9, 29] and theoretical studies[9, 36, 37, 71] have been reported on the gas-phase alkali metal cation affinities of the five nucleobases adenine (A), thymine (T), uracil (U), cytosine (C), and guanine (G).

Experimental PCAs for all five nucleobases were obtained by Cerda and Wesdemiotis[29] using the extended mass

spectrometric kinetic method, and the PCAs of A, T, and U were determined by Rodgers and Armentrout[9] using the threshold CID method. There have been some concerns regarding the accuracy of the PCAs reported by Cerda and Wesdemiotis.[29] Firstly, Rodgers and Armentrout,[9, 72] noted that the kinetic-method measurements were carried out under only two excitation conditions or effective temperatures. As a result, relative enthalpy (affinity) and entropy changes may not be extractable from the experiment in a statistically meaningful way. Secondly, under the experimental condition of the kinetic-method measurement,[29] several tautomeric forms of the free ligand may co-exist, and this would lead to different K^+-bound structures and affinities.[37] Depending on the energy barrier for interconversion between these tautomeric forms in the free ligand and the K^+-bound form, values determined by the kinetic method may or may not correspond to the PCA of a particular alkali metal cation complex of a nucleobase.[37] Such a complication is suggested to be the case for cytosine and guanine.[37] Moreover, it has also been noted that the values determined by the kinetic method for adenine could not be easily ascribed to the alkali metal cation affinity of any one of the tautomers.[37] Nevertheless, on careful examination, we consider that the PCAs of U and T determined by the kinetic method should be reliable. In the experiment, pyridine, aniline, and *n*-propylamine were used as reference compounds. As noted by Rodgers and Armentrout,[9] these three reference compounds and U/T all bind to K^+ in a monodentate fashion; thus, entropic effects in the kinetic-method measurement would be negligible. Moreover, for these two species, the PCA determined by the kinetic method is comparable to that determined by threshold CID. Taking all the above factors into consideration, we omitted the kinetic-method values for A/C/G, but retained those for U/T in the evaluation of our EP(K^+) protocol. We estimated the EP(K^+) affinities of the most stable K^+-bound structures of these ligands in the most stable free tautomeric forms. When compared to the experimental threshold-CID and selected kinetic-method values,[9] our EP(K^+) affinity is on average about 9.6 kJ mol^{-1} too large.

Comparing the EP(K^+) PCA with previously reported values calculated by ab initio MP2 and DFT methods,[9, 37] our present estimate is approximately 7–9 kJ mol^{-1} too large. In the case of the MP2 values,[9] the difference can be at least partly attributed to BSSE corrections. As an example, for K^+–uracil, the reported BSSE for the MP2-based model is 4 kJ mol^{-1},[9] which accounts for about 50% of the difference. We note here again that our EP(K^+) model does not include the BSSE correction, but for this species, the EP(K^+) BSSE correction is calculated to be small (only 0.8 kJ mol^{-1}; see Supporting Information, Table S2).

However, the differences between our values and the DFT-based estimates by Russo et al.[37] cannot be easily explained. The two DFT protocols, even though not identical, are expected to be comparable, and indeed we found evidence for this in the PCAs of water and ammonia (see discussions in the respective sections above). Using K^+–uracil as an example, we tried to identify the source of the discrepancies. We found that the geometries are similar: for this complex, the calculated $K^+\cdots O$ distance at the B3-LYP/6-31G(d) level (2.465 Å) is only 0.002 Å shorter than that obtained at the B3-LYP/6-311+G(2df,2p) level. The zero-point corrections are also similar: the B3-LYP/6-31G(d) level ZVPE is only 0.4 kJ mol^{-1} larger than that at the B3-LYP/6-311+G(2df,2p) level. To resolve the differences, we attempted to obtain the PCA of uracil using the model reported by Russo et al. (B3-LYP/6-311+G(2df,2p)//B3-LYP/6-311+G(2df,2p) with BSSE correction). A PCA of 113.8 kJ mol^{-1} (without BSSE correction) was obtained, which is very close to our EP(K^+) PCA of 113.1 kJ mol^{-1}. Applying the BSSE correction reduced the estimate from 113.8 to 113.0 kJ mol^{-1}, which still differs from the value reported by Russo et al. (108.1 kJ mol^{-1}, corrected to 298 K) by 4.9 kJ mol^{-1}.[37] In conclusion, it appears that DFT-based protocols could be overestimating the PCAs for the nucleobases. Given these uncertainties, further theoretical studies and experimental measurements on guanine, cytosine, and adenine are clearly required.

Comparison of PCAs with lithium and sodium cation affinity scales: Our theoretical PCA obtained by using the EP(K^+) protocol are plotted against the reported theoretical Li^+ affinities[26] (calculated at the B3-LYP/6-311+G(d,p) level) and Na^+ affinities[6, 10, 11, 24, 27, 42] in Figure 3. The calculations in refs. [6, 10, 11, 24, 27] and related studies were all carried out at the MP2(full)/6-311+G(2d,2p)//MP2/6-31G(d) level, and hence the theoretical Na^+ affinity values from these studies were pooled together as one set and correlated with the EP(K^+) PCAs (denoted Na^+-1 in Figure 3). However, the theoretical Na^+ affinities reported by Petrie[42] were calculated at a different level of theory (CPd-G2thaw),[42] and hence were correlated separately with the EP(K^+) PCAs (denoted Na^+-2 in Figure 3).

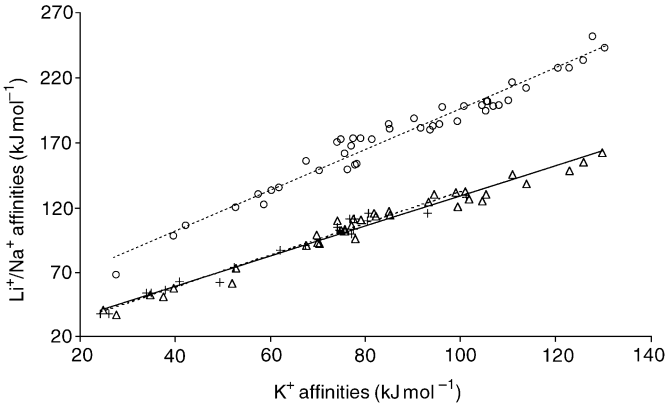

Figure 3. Correlation of PCAs with theoretical Li^+ affinities reported in ref. [26] (298 K, ○) and theoretical Na^+ affinities reported in refs. [6, 10, 11, 24, 27] and related studies (298 K, △, Na^+-1) and ref. [42] (0 K, +, Na^+-2)

The PCAs correlate linearly with Li^+ and Na^+ affinities [Eqs. (2)–(4)].

$$\Delta H_0(Li^+ - L) = 1.55\,PCA + 40.93 \qquad (R^2 = 0.96) \tag{2}$$

$$\Delta H_0(Na^+\text{-}1 - L) = 1.16\,PCA + 12.84 \qquad (R^2 = 0.97) \tag{3}$$

$$\Delta H_0(Na^+\text{-}2-L) = 1.22\,PCA + 10.48 \qquad (R^2 = 0.97) \tag{4}$$

Such good linear correlation indicates that the nature of interactions between Li^+, Na^+, and K^+ and the wide range of ligands studied here are indeed very similar. Furthermore, we note that the correlation relations obtained for Na^+-1 [Eq. (3)] and Na^+-2 [Eq. (4)] differ only in the intercept. In other words, different theoretical models are likely to yield the same relative affinity scale, but the absolute affinities obtained may be different. This highlights the importance of obtaining a set of absolute theoretical PCAs that is consistent with experimental values in order to minimize the presence of systematic errors.

Effect of substituents: We now comment on the effect of substituents on the binding mode and the PCA relative to the unsubstituted parent ligands.

In the case of substituents without electronegative atoms (e.g., alkyl groups), the cation is not bound to these groups. Hence, the presence of these substituents affects the PCA but not the binding site. For aromatic ligands such as pyridine and azoles, methylation increases the PCA. Compared to *o* and *m* substitution, the effect of *p* substitution on PCA is most significant in pyridine, and has been attributed to the larger dipole moment of *p*-methylpyridine.[11]

Using classical electrostatic theory, Davidson and Kebarle suggested that alkyl substitution affects four properties of a ligand: its polarizability, dispersion, intramolecular repulsion (between ligand and ion), and dipole moment.[16] While successive alkyl substituents increase the binding affinity of a ligand by enhancing the polarizability and dispersion component of the cation–ligand interactions, it also increases the repulsion and decreases the dipole moment of the ligand and thus leads to a decrease in binding affinities. Here, we studied the effect of successive methylation at the O/N/S binding sites on the PCAs of water, ammonia, formamide/acetamide, and hydrogen sulfide.

In the $H_2O/MeOH/Me_2O$ series, the first methylation increases the PCA by about 5 kJ mol^{-1}, while slight decrease in PCA is found for the second methylation. In the $H_2S/MeSH/Me_2S$ series, the PCAs are in the order of $H_2S < MeSH < Me_2S$. Similar observations were made for the corresponding theoretical sodium cation affinities for both series,[24, 27] and were rationalized in terms of opposing effects of changes in ligand polarizability (increase) and dipole moment (decrease).[27] While similar rationales can be applied to explain the observed trends in PCAs, we would like to point out that repulsive effects may also play a role here. For the smaller oxygen atom, the repulsive steric effect of successive methylation would be much more strongly felt than for the larger sulfur atom. Thus, it may not be surprising that while the PCA increases with increasing methylation in the H_2S series, it tails off or decreases in the H_2O series.

For the ammonia series, our theoretical results show that the effect of multiple methyl substitutions on the PCA of NH_3 is small, spanning a range of only 5 kJ mol^{-1}. Similar to the H_2O series, the theoretical PCA increases with the first methylation (by 2 kJ mol^{-1} from NH_3 to $MeNH_2$), but decreases on second and third methylations. Interestingly, earlier experimental HPMS results suggest that successive methyl substitution increases the PCA, that is, $NH_3 < MeNH_2 < Me_2NH < Me_3N$.[16] As the difference in PCA for successive methylations is small and can be considered to lie within the expected error limits of theoretical models, we only note here that our EP(K^+) affinities are more in line with the recent reported trends for the experimental (FT-ICR) and theoretical (MP2) sodium cation affinities,[27] and our B3-P86 affinities (Supporting Information, Table S1) differ from the prediction at the G2(MP2,SVP) level (Supporting Information, Table S1). Thus, further calculations and experimental measurements may be needed to resolve the difference in qualitative trends found between experimental and theoretical PCAs of ammonia and its methyl-substituted derivatives.

For electronegative (e.g., fluoro, chloro) or electron-rich substituents (e.g., aromatic π rings), not only are the binding affinities affected, but the presence of these substituents also opens up new modes of binding that are not possible in the parent ligand. We found that the F and Cl substituents are in general not competitive with O or N binding sites already present. Hence, for most classes of ligands (e.g., carboxylic acids, aldehydes, ketones, nitriles), the binding modes remain the same as in the parent ligand on halogenation. In general, the PCA of halogenated ligands decreases, as these electron-withdrawing groups decrease the dipole moment of the ligand. However, in a few cases (e.g., CF_3CH_2OH, species **v**, Figure 2) when the halogen atom is close to the original binding site of of the parent ligand, it offers an additional binding site for K^+. In these cases, the PCA is increased relative to the unsubstituted parent ligands.

For aromatic π substituents, the PCA increases in all cases, as polarizability of the ligand is greatly enhanced by the presence of the highly polarizable phenyl ring. In some cases, the aromatic π substituents (e.g., from alanine to phenylalanine) are also involved in binding, and this leads to a further increase in PCA over that expected solely from the polarizability effect.

Relating PCAs to properties of ligands: In the previous section, the effect of substituents on PCA is discussed in a qualitative manner. Here, we take the discussion one step further by establishing quantitative relations between the PCA of the 136 ligands and their properties. Our aim is to use molecular properties which are readily available and accessible, so that the PCAs can be predicted with relative ease.

As the K^+–ligand interaction is mainly electrostatic in nature, ligand properties such as dipole moment and polarizability are expected to be important. The number of interactions (coordination number or denticity) and to which type of atom(s) K^+ binds should also be important. Based on the goodness of fit (in terms of adjusted R^2) from multiple linear-regression analyses, four parameters were found to be important in governing the PCA of a ligand: the dipole moment μ in Debye and the polarizability α in Å^{-1} of the ligand, the number n_1 of first-row atoms the K^+ ion interacts with, and the number n_2 of second-row atoms the K^+ interacts with. The PCA is related to these four parameters by Equation (5).

$$\mathrm{PCA} = 10.7\mu + 3.6\alpha + 16.1n_1 - 11.8n_2 + 29.6 \qquad \text{adjusted } R^2 = 0.82 \qquad (5)$$

Figure 4 shows the relation between the calculated PCA (Table 1) and the PCA predicted by Equation (5). Clearly, several points show large deviations from the ideal correlation

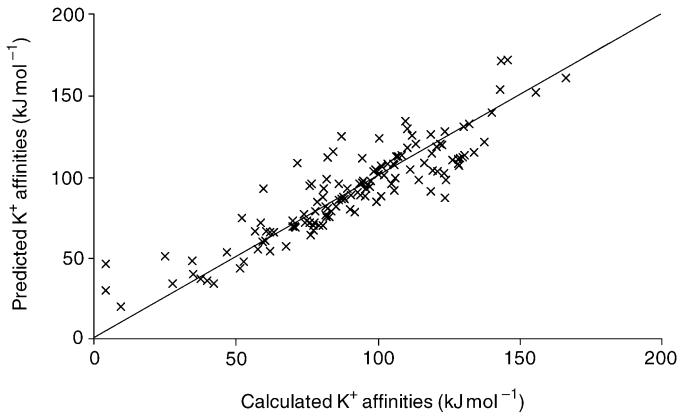

Figure 4. Plot of predicted PCAs [Eq. (5)] against EP(K^+) PCAs: the diagonal line with a slope of 1.0 is drawn for reference purposes.

line with a slope of unity. At the lowest end of the PCA scale, the error can be very large; in the case of Ne, as large as 12-fold (calculated PCA 4 kJ mol^{-1}, predicted PCA 47 kJ mol^{-1}). Such a deviation partly arises from the simplicity of the correlation equation employed, but is also due to the small numerical PCA value for this ligand.

It is clear that our proposed model is quite crude and has neglected other effects such as ion–local dipole interactions.[6] Despite the crudeness of the model, the equation can yield reasonable estimates of PCA. If the four lowest PCA values (He, Ne, Ar, and CO) are ignored, the MAD for the remaining 132 ligands is then reduced to 12 kJ mol^{-1} (error of 10%), with a maximum of 38 kJ mol^{-1} for CF_3CH_2OH (error of 52%). We note that substituting the polarizability by the molecular weight (MW, in g mol^{-1}) of the ligand also yields a reasonably good correlation [Eq. (6)].

$$\mathrm{PCA} = 12.5\mu + 0.1\,\mathrm{MW} + 15.4n_1 - 11.6n_2 + 40.0 \qquad (6)$$

Compared to Equation (5), the adjusted R^2 is somewhat lower (0.74). However, as the molecular weight of a ligand is a parameter that can be more readily obtained than the polarizability, Equation (6) in fact provides a simpler alternative for estimating the PCA of a ligand.

Conclusion

We have reported the theoretical potassium cation affinities (PCA) of 136 ligands, spanning a range from 4 to 166 kJ mol^{-1}. Of these 136 ligands, 70 experimental and 64 theoretical values reported in the literature are available for comparison. We found that our theoretical estimates and most of the experimental affinities are in good general agreement (within ± 10 kJ mol^{-1}). Based on our theoretical EP(K^+) values, we were able to conduct a critical evaluation of the reported values for Me_2SO, $MeCONMe_2$, and phenol obtained by different experimental techniques, for which PCA differences of more than ± 10 kJ mol^{-1} have been reported. Large discrepancies (>26 kJ mol^{-1}) were found in the case of phenylalanine,[31] cytosine,[29] guanine,[29] and adenine.[29] However, in all these cases, the discrepancies likely arise from complications in the experimental measurements. Ignoring these four values and the PCA of Me_2SO determined by HPMS, the mean absolute deviation of our theoretical PCA from the remaining experimental values is 4.5 kJ mol^{-1}. Our EP(K^+) PCA is also consistent with most of the previously reported theoretical values to within ± 5 kJ mol^{-1}. For species with larger differences, we are able to account for the difference in terms of the different basis sets used in the theoretical calculations and/or basis set superposition errors. However, the origin of the rather large difference of 7–9 kJ mol^{-1} found between our values and those reported by Russo et al.[37] for the DNA/RNA nucleobases remains unclear.

The effects of substitution on PCAs of parent ligands are also discussed. For a halogenated ligand, the PCA decreases in general, except when the halogen is close to the original binding site. For aromatic π substituents, the PCA increases in all cases, as the polarizability of the ligand is greatly enhanced by the presence of the highly polarizable phenyl ring. First methylation tends to increase the PCA, while the PCA may decrease upon further methylation.

We have also compared the PCAs with lithium and sodium cation affinities previously reported in the literature. The excellent linear correlation that was found indicates that the nature of the interactions between alkali metal cations (Li^+, Na^+, and K^+) and the wide range of ligands studied here are indeed very similar. Thus, such relations [Eqs. (2)–(4)] allow estimation of PCA for ligands with known Li^+ and/or Na^+ affinities, in particular where the mode of binding for K^+ is not expected to differ from those of the smaller Li^+/Na^+.

Finally, we established two correlation equations [Eqs. (5) and (6)] relating PCAs of ligands with their properties (dipole moment, polarizability, molecular weight, and number of interactions). These two equations offer relatively simple and efficient methods of estimating the PCA of ligands not reported here.

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